Optimisation of the production process of patient-specific parenteral medication

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Optimisation of the Production Process of Patient-specific Parenteral Medication

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Introduction

This research is conducted at ZGT Pharmacy. ZGT is a hospital group in Twente and consists of two hospitals. Within ZGT Pharmacy, patient-specific medication is produced. An example of patient-specific medication is chemotherapy. The prescribed dosage is determined based on characteristics of the patient, the patient's disease, and the well-being of the patient.

The production of patient-specific medication is a complex process. It requires expensive resources and materials and international guidelines must be followed. Within hospital pharmacies, various production systems are used, however it is currently unknown which method performs best.

Three important planning characteristics of the patient-specific medication production process are:

- After producing medication with a certain active substance, the remaining volume in the vial should be thrown away. Therefore you want to use as much content of the vials as possible, as the remaining volume leads to spillage costs.
- The production can only be executed shortly in advance of the administration since the shelf life of the medication is short.
- Patient orders can be cancelled before, during, or after production. Cancellation of already produced medication results in disposal costs since only administered medication will be reimbursed by health-insurers. Currently, to avoid disposal of end-products, checks on the continuation of the administration are executed.

Problem statement

The production of patient-specific medication within ZGT Pharmacy is experienced to be inefficient by the management since they belief that too many resources are used for the current output. To be able to solve this problem we use the Management Problem Solving Approach (Heerkens & Winden, 2012). Based on the developed problem cluster we identified that seven of the eleven problem causes are due to the current way of planning.

Therefore we define the following problem statement:

The current way of planning the production of patient-specific medication at ZGT Pharmacy does not correspond to the current way of working and is therefore resulting in a waste of manpower, raw material and end-products.

This leads to the following research objective:

The goal of this research is to find a production system that minimises spillage and disposal and thereby the necessity to perform checks, while maintaining the current production quantity.

Within this research, we focus on cytostatic medication. The current production of cytostatic patient-specific medication at ZGT Pharmacy costs €XX per year.

Approach

Production systems

In order to fulfil the research objective, we first identify four production systems:

- One-stop-shop: As soon as the patient arrives at the hospital, examinations are carried out and the dosage of the medication is determined. The production follows this process. When an order arrives at the production, this order is produced on a first-come-first-serve basis. Once production is complete, the medication is brought to the patient and administered. In this scenario, there is never unnecessary production and therefore no disposal of end-products. However, each medication is produced separately, which causes spillage as the requested dose does often not correspond to the bottle size of vials. This production process is currently used in Hospital X.
- Clustering: The production order is placed after an examination appointment within a week before the administration appointment. The medication that is expected to be produced within a certain time horizon is clustered so that there is less spillage in the use of vials. However, production must be done in advance, causing that the produced end-product must be thrown away when administration is postponed or cancelled, or when a dosage changes. This production process is currently used in ZGT, with a time horizon of one day to cluster requests.
- Hybrid form: This production system combines the one-stop-shop and clustering approaches. In the hybrid form, it is predetermined for each product which production system is used. This division can be done per category or per medication (for example based on price or probability of cancellation). This production process is currently used in Hospital Y.
- Central production and distribution: Within this production system, the production of medication is organised centrally. One hospital pharmacy produces medication for a large number of hospitals and therefore more orders are produced per day and less spillage occurs. However, within this production system there is more disposal since medication is produced further in advance.

The advantages and disadvantages of the production systems are displayed in Table 1.

Table 1 - Advantage and disadvantages of the production systems

Production system	Spillage	Disposal	Checks
One-stop-shop	- -	++	++
Clustering	+	- -	- -
Hybrid	-	+	+
Central production and distribution	++	- -	- -

Since central production and distribution system cannot achieved by ZGT Pharmacy, we do not include this in our research.

Production system optimization

These production systems can be optimised to work even better in practise. We describe two general improvements, applicable to all three production systems, and some system specific improvements.

The first general improvement concerns the storage of vials in the clean room. Within the clean room, only a limited number of storage places are available for vials. To minimize the costs of spillage and disposal, it is very important to determine which vials must be present in the clean room. This can differ per production system.

Furthermore, phaseals can affect the spillage costs. These are special caps that extent the shelf life of an opened vial. However, these caps come at a cost, and cannot be placed on every vial. We include these phaseal in our research to show whether it is a promising method to reduce spillage.

One system specific improvement is the time window in which production orders are clustered. The moment an order is produced has effect on both the spillage and disposal costs. Per order, the best

moment to produce the order can be determined, so costs of waste of raw material and end-products can be minimized.

Finally, the decision in which production system an order is produced must be made within the hybrid production system. This is influenced by the cancellation probability and whether spillage will decrease when orders are clustered, and therefore also has effect on both the spillage and disposal costs. Per order, the optimal system should be determined in order to reduce costs.

Models

In order to analyse the costs of the different production systems, we build three MILP models, one for each production system. These models minimize the total costs while taking into account the various factors of the production systems. Table 2 displays the optimisation possibilities of each production system, together with which costs are taken into account in the models.

Furthermore, we provide a model extension to include the use of phaseals in the models.

Table 2 – Optimisation possibilities per production systems

	Characteristics			Objective	
Production system	Vial volume	How to cluster	Production system trade-off	Costs of spillage	Costs of disposal
One-stop-shop	X			X	
Clustering	X	X		X	X
Hybrid	X	X	X	X	X

AHP

The costs resulting from the MILP models are an important KPI for ZGT Pharmacy. However, both quantitative and qualitative KPIs are relevant when deciding on a production system. To determine the most suitable production system for ZGT Pharmacy, an Analytic Hierarchy Process (AHP) is used. We will analyse the impact of these methods by four Key Performance Indicators (KPIs), which represent the stakeholders. The KPIs are:

- Waste of raw material and end-products in terms of costs.
- Employee deployment in terms of number of employees needed.
- Patient experience in terms of both waiting time for the patient and number of appointments per treatment and score this on a scale of 1 to 10, the higher the better.
- The magnitude of change for the hospital on a scale of 1 to 10, the higher the bigger the change.

Results

The costs of waste of raw material and end-products are calculated via the models. The results are shown in Figure 1. The scores of the production systems on the KPIs are shown in

Table 3.

Based on the insights gained during this research and the AHP, clustering is determined to be the best production system for ZGT Pharmacy. This is the same production system as currently used, however some improvements can be made to reduce the costs of the production of patient-specific medication. The current production costs are €XX, while the optimal way of clustering, in terms of costs, would only cost €XX. This is a costs reduction of €XX.

Table 3 - Scores of the production systems on the KPIs

KPI	One-stop-shop	Clustering	Hybrid
Waste of raw-material and end-products	€XX	€XX	€XX
Employee deployment	8.5	8	8
Patient experience	8	6	4
The magnitude of the change for the hospital	8	2	6

Figure 1 - Results for the models for ZGT Pharmacy

Besides this, there are additional improvement opportunities that could be implemented to reduce waste of raw material and end-products. Dose banding provides a cost reduction between 24% and 47%, depending on the type of dose banding. Furthermore, implementing phaseals in the production process can lead to a cost reduction of 75% and is therefore a very promising method to prevent spillage and improve the current performance of ZGT Pharmacy.

Conclusion

Our results show that the clustering production system is optimal for ZGT Pharmacy. This system is currently already in use by ZGT, and therefore requires a small amount of change. We do recommend to change the vials in the clean rooms to reduce costs.

Furthermore, we recommend implement dose banding in the production protocol. Besides this, further research is required in the use of phaseals.

Preface

Dear reader,

In front of you is the master thesis: “Optimisation of the production process of patient-specific medication”. This research is conducted as final assignment of my master Industrial Engineering & Management at the University of Twente.

This research is conducted at ZGT Pharmacy and I want to thank them for the opportunity and their guidance, especially Suzanne Selles and Eddy Hogt. Besides learning more within the work field of Industrial Engineering & Management, I also learned a lot by applying this in the complex environment of a healthcare organisation.

Furthermore, I want to thank Gréanne Leeftink and Aleida Braaksma for the feedback and valuable input during the research. They helped me constructing the research in the right way and lift the research to a higher level.

Lastly, I want to thank everyone else who was willing to listen to my endless stories and help me brainstorming during the project, especially those in my inner circle.

I hope you enjoy reading this thesis.

Laura Medendorp

Juni 2021, Enschede

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1. Introduction

This chapter introduces the research and in which way this will be conducted. We will first provide background information on the company and the department where this research focuses on (Section 1.1). Subsequently, we will discuss the problem statement (Section 1.2), followed by the research goal which will contain the research objective and the research questions (Section 1.3). At last, we will provide information on the approach of this research (section 1.4).

1.1 Research context

1.1.1 Ziekenhuisgroep Twente

Ziekenhuisgroep Twente (ZGT) is a hospital group that provides care to about 390,000 residents of Twente and its surroundings. It is established in 1998 when two hospitals were united. The 'Streekziekenhuis Midden-Twente', which lays in Hengelo, and the 'Twenteborg', which is located in Almelo (Ziekenhuisgroep Twente, 2020).

In 2014, they followed the nationwide development of a smaller number of hospitals for complex care and a larger number of hospitals for simple elective interventions and more chronic care. Acute and high-risk care is situated in Almelo and Hengelo has become a service-oriented centre for diagnostics, outpatient care, day treatment, and short stay with various expertise centres. The goal is to provide a wide care package of good quality (Ziekenhuisgroep Twente, 2020). In Figure 2, an overview of information about ZGT is given.

Figure 2 - Infographic ZGT (based on information of Ziekenhuisgroep Twente (2020))

1.1.2 ZGT Pharmacy

This research will focus on the pharmacy department of ZGT. This department takes care of the pharmaceutical supply of ZGT. Besides this, they also provide medication for various care institutions outside the hospital, other hospitals, and community pharmacies.

The ZGT Pharmacy has an important advisory role in the use of medication and provides information to doctors, nurses, and patients for this purpose. In addition, the ZGT Pharmacy has a controlling and coordinating role in the transfer of information regarding admission and discharge medication.

The main tasks of the ZGT Pharmacy are:

- Purchasing of medication
- Production of medication
- Delivery of medication
- Logistics and quality control
- Analysis of medication

The ZGT Pharmacy consists of hospital pharmacies in Almelo and Hengelo and an outpatient pharmacy in Almelo and Hengelo (Ziekenhuisgroep Twente, 2020).

In the hospital pharmacy there work pharmacists, pharmacy assistants, pharmacy practitioners, and pharmaceutical consultants. They have, among their other occupations, a monitoring, informing, and advising role towards the other specialists and nurses. They also carry out checks in the nursing wards and, if necessary, consult with nurses, doctors, or patients about medication and methods of administration. In addition, research is being carried out into new medication and therapies, which are called trails, in collaboration with the specialists of ZGT. The pharmacy is responsible for coordinating logistics (Ziekenhuisgroep Twente, 2020).

1.1.3 ZGT Pharmacy – VTGM

The production of medication is executed in the hospital pharmacy department in Hengelo. They produce a large number of medications. This mainly concerns medications that are not for sale or that have to be tailor-made for a patient. The latter category of medication is called '*voor toediening gereed maken*' (VTGM), which translates to '*prepare for administration*'. This concerns, for example, cytostatic treatments (chemotherapy) for patients with cancer, special nutritional infusions, morphine cassettes, and radioactive medication. All these types can be roughly divided into two categories: cytostatic and aseptic medication. These are parenteral medication, which means that the medication will be injected. In the remainder of this report, we refer to these parenteral medication as patient-specific medication.

In Figure 3, an overview of more information about the VTGM department is shown.

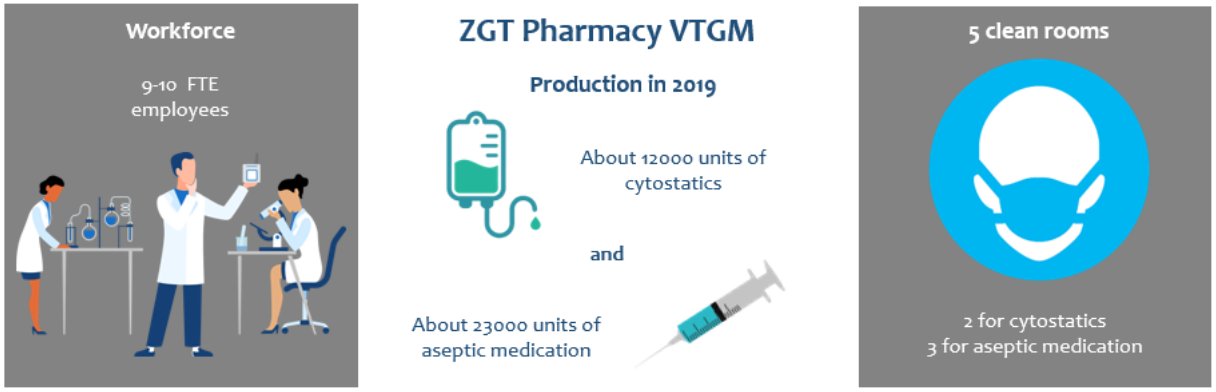

Figure 3 - Infographic ZGT Pharmacy VTGM ZGT (based on information of Ziekenhuisgroep Twente (2020))

1.1.4 Production process of patient-specific medication

The production of patient-specific medication consists of two types of requests: planned requests and short-term requests. The first category includes medication such as chemotherapy, also called cytostatic. The second category consists of, for example, requests for patients who are about to leave the hospital and who need to take a certain medication home. These requests are known only 24 hours before they must be fulfilled.

During the production of the medication, the GMP-Z guideline must be observed. GMP-Z stands for "Good Manufacturing Practice Hospital Pharmacy". These guidelines are aimed at preventing the medication from being contaminated, interchanged, or damaged, and have effect on the production process of the medication. For example, the production process must be done in clean rooms, which have a controlled environment, and a hygiene protocol must be followed at all times. This protocol includes, among other things, special clothing, cleaning the room, and checking for microorganisms present in the room afterwards. The produced medication may also be stored for a limited time. The exact time depends on the kind of medication, but is mostly between 24 and 96 hours.

Figure 4 - Production of medication in a clean room

Production methods

The production of patient-specific medication is a complex process. It requires expensive resources and materials and international guidelines must be followed. Within the production planning, a trade-off between spillage of raw material and disposal of end-products must be made. Looking at hospital pharmacies of various hospitals, we see that various production systems are used. However, it is not known (yet) which method performs best.

We roughly distinguish three systems of producing patient-specific medication. These are the following:

- One-stop-shop: As soon as the patient arrives at the hospital, examinations are carried out and the dosage of the medication is determined. The production follows this process. When an order arrives at the production, this order is produced on a first come first serve basis. Once production is complete, the medication is brought to the patient and administered. In this scenario, there is never unnecessary production and therefore no disposal of end-products. However, each medication is produced separately, which causes spillage as the requested dose does often not correspond to the bottle size of vials. This production process is currently used in Hospital X.
- Clustering: The production order is placed after an examination appointment within a week before the administration appointment. The medication that is expected to be produced within a certain time horizon is clustered so that there is less spillage in the use of vials. However, production must be done in advance, causing that the produced end-product must be thrown away when administration is postponed or cancelled, or when a dosage changes. This production process is currently used in ZGT, with a time horizon of one day to cluster requests.
- Hybrid form: This production system combines the one-stop-shop and clustering approaches. In the hybrid form, it is predetermined for each products which production system is used. This division can be done per category or per medication (for example based on price or probability of cancellation). This production process is currently used in Hospital Y.

1.2 Problem statement

In this section, we discuss the problems that occur within the production process of patient-specific medication in ZGT. This information is gained through conversations with stakeholders like the management of ZGT pharmacy and employees, such as hospital pharmacists and pharmacy assistants. The information is also verified with them before including it in this report.

1.2.1 The action problem of ZGT Pharmacy

After conversations with the management and the employees of this production process, we defined the following action problem of ZGT Pharmacy:

The production of patient-specific parenteral medication within ZGT Pharmacy is inefficient since the resources are used excessively for the current output.

We will analyse the problem with the use of the Management Problem Solving Approach (MPSM) of H. Heerkens and A. van Winden (2012). This approach is a systematic approach to solve business problems. To be able to solve this problem and make the production process more efficient, we developed a problem cluster. In this problem cluster, the causes of the problem are traced back to their original core problem. The problem cluster is displayed in Figure 5.

1.2.2 The causes of the problem

We divide the causes of inefficiency during production into three categories. Excessive use of material, an excessive number of actions taken by the personnel during the process, and the inefficient use of assets.

Excessive use of material

The excessive use of material during the process is caused by two things. First, vials are partly used, and second, produced medication is not administered. These two causes are related to each other. Recall that the current production planning of the ZGT Pharmacy clusters orders to reduce the number of vials that are partly used. However, clustering results in a chance that produced medication will not be used due to cancellation or a change in dosages. Despite the clustering, the vials are still not always used efficiently, as the volume of the vials does not always match the required dosages.

Furthermore, not all orders can be clustered at all times, due to late approval by pharmacists and emergency requests. Moreover, the current planning horizon in which they cluster is only 24 hours. This is mainly due to two reasons. Firstly doctors and pharmacists do not want that medication is produced far in advance, due to possible cancellation or changes. Secondly, whether the treatment will take place is confirmed late. For these reasons, the current way of planning does not enable ZGT Pharmacy to efficiently use all its resources.

An excessive number of actions by personnel

The excessive number of actions taken by the personnel during the process is caused by three things. First of all, to make it possible to cluster production and to prevent waste of materials via partly used vials and producing medication that is not used, a lot of checks are performed. It is checked multiple times whether a treatment will be executed and whether there are factors that will discourage this. Examples of this are appointments before the treatment in which the continuation of the treatment is discussed, notes in the patient file about the condition of the patient, and whether there is an appointment for the treatment. So, due to the current planning system, clustering the production, there is a high number of checks needed.

Besides the checks, not all needed information is always retrievable, such as medication recipe. Sometimes an appointment for administration is planned, but there is no recipe for the medication in the patient file yet. To be able to produce the medication and to prevent waste, the missing information should be searched for. At last, when a dosage changes, medication has to be reproduced. Reproducing medication takes extra manpower too.

Inefficient use of assets

The inefficiency in the use of assets is primarily caused by three things. First, as described before, the production of patient-specific medication must be performed in clean rooms. Production in clean rooms is expensive since these rooms need to be in a good condition, according to the GMP-Z guidelines, when in service. However, these clean rooms are only used for a part of the day which means the asset is not used efficiently.

Furthermore, a hygiene protocol must be followed when medication is produced. Additionally, every time another kind of medication is produced, new equipment is required, to avoid contamination. This is more costly when the production is not clustered and every produced medication requires new equipment instead of multiple medications produced in a row.

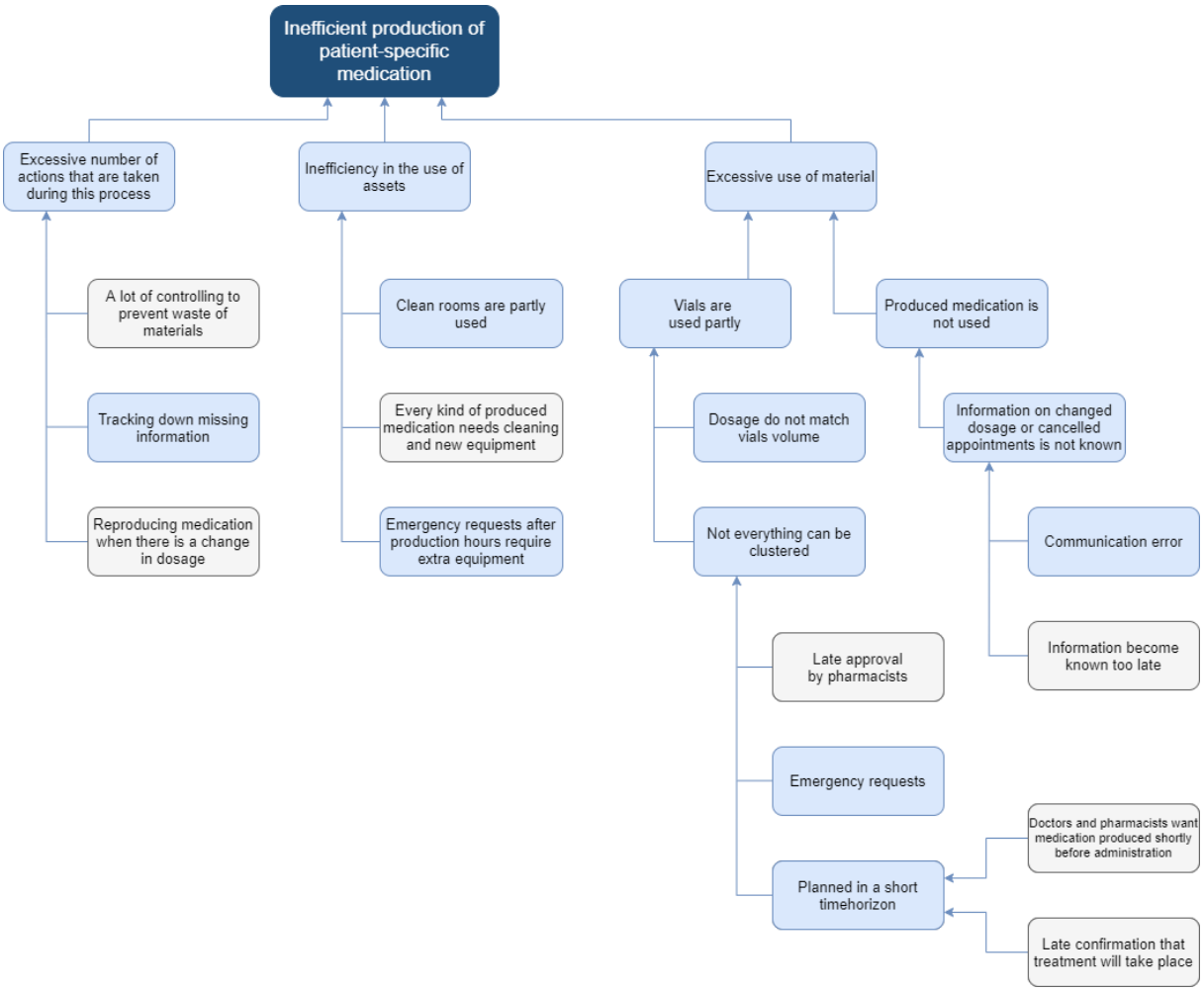

Figure 5 - Problem cluster

1.2.3 Problem statement

The next step in the MPSM is to find the core problem. The core problem is a problem that is last in the chain of problems, displayed at the bottom of the problem cluster. As shown, we have multiple core problems. Therefore we have to choose which problems we address during this research. We select the core problem based on the extent to which we can influence it and whether it is related to the study field of Industrial Engineering & Management. In the problem cluster, seven core problems are displayed grey. These problems can be solved by a better way of planning. We do not have a direct influence on the other core problems. Therefore we chose to focus on the core problems related to planning the production.

Current wastes in manpower, raw material, or end-products are not the result of the “clusterable” orders, but of the unexpected changes (by doctors or cancellation). That is why there must be a production planning method that can handle these changes and ensures that fewer orders have to be disposed and re-made. As a consequence, fewer checks will be required around production, because there is less uncertainty, which, in addition to saving on production manpower, also means saving on the required "support manpower". The problem statement of this research will therefore be:

The current way of planning the production of patient-specific parenteral medication at ZGT Pharmacy does not correspond to the current way of working and is therefore resulting in a waste of manpower, raw material and end-products.

1.3 Research goal

In this section, we explain the goal of this research and provide the research objective. In order to fulfil the research objective, we have developed sub-questions. These are also stated and explained in this chapter. The research design to answer these questions is discussed in Section 1.4.

1.3.1 Research objective

As described in Section 1.2, the current way of planning the production of patient-specific medication at ZGT Pharmacy does not fit the current way of working. To make the production more efficient, less resources should provide the same output. Within the described problem, we will mainly focus on reducing the use of manpower and material by changing the planning of the production. As described in Section 1.1, there are currently three different methods known from practice to plan the production of patient-specific medication. In our research, we will analyse and improve the working of these production systems in order to find the best suitable production system for ZGT.

The research objective will be as follows:

The goal of this research is to find a production system that minimises spillage and disposal and thereby the necessity to perform checks, while maintaining the current production quantity.

Efficiency is defined as ‘doing something in a good, careful and complete way with no waste of time, money or energy’ (Oxford Dictionaries, 2020). So referring to this research, efficiency will mean producing all required medication with no waste of manpower, raw material, and end-products. With manpower, we address the time that employees of ZGT are working on the production of medication and the secondary processes that came along with this. Raw materials are the substances necessary for the production of the medication. End-products are the produced patient-specific medications.

1.3.2 Research questions

To fulfil the research objective, we have developed several sub-questions. These are needed to be able to provide and achieve the research objective and thereby solve the problem of ZGT pharmacy. We will now present the sub-questions and why these are relevant.

1. ***What is the current way of producing patient-specific medication within ZGT?***

- *What does the production process of patient-specific medication within ZGT currently look like?*
- *What are the most important KPIs for ZGT?*
- *What is the current performance of the production of patient-specific medication within ZGT?*
- *Which restrictions must be met when adjusting the production process of patient-specific medication?*

To be able to improve the production process of patient-specific medication within ZGT, we first have to understand how the process is currently executed. Therefore we will first map the process and explain the current way of working. Subsequently, we will measure the performance of the current process. In this way, we will be able to see how other methods perform in comparison with the current method. Besides this, in order to make the process more efficient, we have to understand which restrictions hold concerning the production process of patient-specific medication.

2. ***What are the possible production systems for patient-specific medication for ZGT and how can these be modelled?***

- *What systems are available in literature and practice?*
- *How can these systems be improved and which are suitable for ZGT?*
- *How can the production system be modelled?*

To gain insight into the different methods to design a production process of patient-specific medication, we will therefore look into processes that are executed within companies, as well as into literature that analyses these processes. This will help us with understanding the process and will inform us about the performance of the processes.

Additionally, we search for improvement techniques of the different systems to improve the systems even further. To make sure that the systems are applicable to the situation of ZGT, we will analyse them and select the suitable ones.

When we have insight in the various production system and the way they can be improved, we model these production system in order to gain insight in how the production system perform in terms of costs. Furthermore, we perform experiments with these models to analyse the working.

3. ***How do the various methods perform?***

- *What is the performance of the various production systems on the KPIs?*
- *Which method performs best for ZGT?*

We develop a model for each of the selected production systems and determine performance on the aforementioned KPIs. To choose the best method for ZGT, we will perform an AHP. This will help us make this complex decision. These analyses are important to take a well-considered decision.

4. ***How should the current way of working be adjusted to achieve the chosen model?***

- *What adjustments must be made to change to the chosen method of production?*
- *How can these adjustments be made?*

When the suitable production system for ZGT is chosen, we provide recommendations on what should be adjusted to the current state of affairs to achieve this production system. Besides this, we also provide an explanation about how this can be done.

When all these questions are answered, we could provide a conclusion on the research and transfer our recommendations in the last chapter of the research.

1.3.3 Scope of the research

As mentioned before, the production of patient-specific medication consists of cytostatic medication and aseptic medication. These are produced in different clean rooms and require different raw materials and production protocols.

Within this research we will focus on the production of cytostatic medication. We made this decision based on the fact that cytostatic medication is produced in lower amounts. The question whether clustering is the best production system to reduce spillage is uncertain. Furthermore the probability that an administration appointment is postponed or cancelled is higher, since the treatment has a great impact on the body of the patients. As well as the probability that a dosage will change due to the working of the previous cytostatic treatment.

The results of this research are therefore based on the production of cytostatic medication. However, fortunately, the research design is in such a way that it can easily duplicated for the aseptic medication. The same models can be used for this type of medication without much modifications.

1.4 Research approach

This section focuses on how the sub-questions will be answered to fulfil the research objective. Along, an overview of the structure of this research will be given.

The current situation

The first research question will provide insight into the current production process of patient-specific medication at ZGT. This will be done by a process map and explanation of the clustering of the production of medication. This insight will be gained via interviews with involved employees and via observations of the process. Besides this, we will decide what the most important performance indicators are through conversations with stakeholders. The current value of these performance indicators will be determined via the use of historical data of ZGT Pharmacy. The last part of this research question contains information about restrictions that need to be followed in the production process. These will also be established through conversations with involved employees and stakeholders.

Literature

The second research question involves a review of the current literature relevant to the problem of ZGT. Each sub-question will be answered independently of the others. We will be searching for answers to these questions in scientific articles and study books.

Models

Based on the findings in the literature and the production processes in other companies, we will provide more insight into the alternatives in research questions 2 and 3. This will be done via observing and interviewing the involved employees at the different companies. Via this, we can map the process to get a good overview. Furthermore, when there are other methods described in the literature, we will include these in our research too. We will determine a process map for these methods and describe the way they work. When we have described the most important models in literature and practice, we will make a model for each method that determines the costs of production of the patient-specific

medication. This will be done by information found in literature and the analysis that is made of these methods.

Case study

When the models for each method are made, we can now perform a case study to provide an answer to research question 4. To determine the costs of production in each method, we will use historical data of ZGT as input for our models. Furthermore, we will describe the impact on the patients, company, and employees. This information will be gained via literature, interviews, and observations. To be able to conclude which production system is best for ZGT Pharmacy, we will use an Analytic Hierarchy Process (AHP). We determine the importance of the aspects via conversations with the stakeholders.

Adjusting the process

Based on the outcome of question 4, we can determine what should be changed to develop the current production system into the chosen production system. We will do this by analysing the current and new production process. Furthermore, we give recommendations on how this adjustment process could be organised.

2. Current situation

In this chapter, we provide more information about the current way the production of patient-specific medication at ZGT Pharmacy is executed. In Section 1.1.4 we already explained the production process of patient-specific medication briefly. In Section 2.1, we will explain the production process in more detail. Then, we go further into the KPIs (Section 2.2) and the current performance on these KPIs (Section 2.3). At last, we discuss the restrictions that hold during this research.

2.1 Production process

In this section we explain the production process within ZGT Pharmacy with the help of a process map which is displayed in Figure 6. Besides this, we discussed clustering in more detail and tell more about special caps that extending the shelf life of an opened vial, called phaseals.

2.1.1 Before production

In the production process of patient-specific medication are six departments involved. The production process of patient-specific medication starts when a doctor or assistant plans a treatment of a patient. They have to provide a recipe and an appointment for administration in the electronic patient file named HiX. When this is done, the front-office checks whether there is a probability that the administration will not take place. This is checked based on information in the patient file. For example, whether there is an appointment with the doctor before the administration appointment, in which a change in dosage or cancelation of the treatment can be discussed. When there is no sign that the treatment will not take place, there is a check if all required information, such as appointment details and recipe, is provided.

When all information can be found, the next step is that a pharmacist approves the recipe. During the process, pharmacists are legally obligated to check whether the prescription is right and that it is not harmful to administrate the medication in conjunction with other medication the patient uses. The pharmacist also checks again whether there is a probability that the administration will not take place. The last check is the same as the one the front-office executes.

The process continues at the back-office of VTGM. During the production of patient-specific medication, ZGT Pharmacy uses a program called CATO. Since the recipe is currently stored in HiX, it should be transferred to CATO. Therefore they print the recipe and file the recipe in in CATO. Because mistakes can be made here, the recipe in CATO has to be checked again by a pharmacist. When this is approved, the process continues in one of the clean rooms.

In CATO, the to be produced medication is clustered based on the active substance. This is explained later in this section.

2.1.2 Production

In the clean room, two pharmacist assistants are working. One of them in the production room and the other in the preparation room. The latter is picking the raw materials and needed equipment for every cluster, based on the protocol in CATO. The pharmacist assistant in the production room cleans the workplace and prepares the supplies. Preparing the supplies includes among others cleaning the vials and placing raw materials and equipment in an orderly manner. Before the medication can be produced, both pharmacist assistants check if the active substance in the vials and their batch number corresponds with the protocol in CATO. When the information is correct, the medication is produced. After producing, the medication is labelled and checked by both pharmacists assistants again. When the labels

are correct too, the medication will be packed and delivered to the back-office of VTGM via a sluice in the wall.

2.1.3 After production

The produced medication will now be checked at the back-office and the front-office. The latter also makes sure the produced medication will be delivered to the right administration location. This can be in a ZGT hospital or in a different hospital.

Before administration of the medication, there is a final check by a pharmacist on the production protocol. When the production is performed correctly, the medication can be administered.

The production process of patient-specific medication is displayed in Figure 6. The steps in which checks are performed are displayed in orange and the other actions are displayed in blue. A more detailed picture can be found in Appendix A.

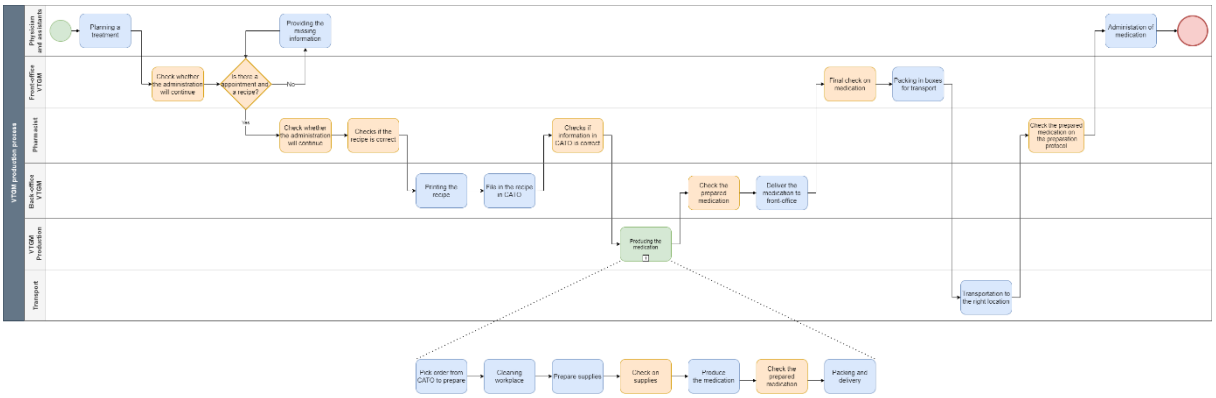

Figure 6 - Process map of the production process of patient-specific medication

2.1.4 Clustering

As explained in the previous section, the production of medication at ZGT Pharmacy is currently clustered. When the probability is high that a treatment will take place, the order is added to CATO one day before the treatment. When a pharmacist confirms the recipe of the order in CATO, the order moves to the production section in CATO. The pharmacist assistants that are producing the medication see a list of all medication that has to be produced. They select all orders with the same active substance to produce sequentially. Via the production protocol in CATO they receive a list of materials that should be gather to produce this cluster.

When a new order is moved to the production section in CATO, it can directly be produced. Hereby it is possible to produce emergency requests quickly. However, it can occur that a newly added order contains an active substance that is clustered shortly before. This order will then be produced on its own.

The most medication have only one active substance which have to be combined with water or NaCl solution. Because of this, clustering is possible. When medication has more than one active substance, it is usually produced more often according to the same recipe, therefore it is also possible to cluster these orders.

2.1.5 Phaseal

There are already proceedings in the process to prevent spillage of vials. This is done by the use of phaseals. Phaseals are special caps that can be used on vials. An example of a phaseal is shown in Figure 7. These phaseals can be used only once and cost approximately seven euros per piece. When a vial is only partly used, a phaseal can be installed on it and can be stored longer to prevent spillage. However, phaseals are only being used when there is enough evidence that the substance in the vial is stable enough to keep for a week. Besides this, a phaseal is an expensive tool. Therefore a trade-off between the costs of the phaseals and the savings on spillage must be made.

Figure 7 - Phaseal

Currently, phaseals are only used for aseptic medication. Before phaseals can be used for cytostatic medication, there must be pharmaceutical evidence that keeping open vials with phaseals will not do any harm and is in line with the GMP-Z guidelines.

2.2 Case mix ZGT Pharmacy

To give a good overview of the situation within ZGT Pharmacy, we provide a Case mix of ZGT Pharmacy in this section. In Figure 8, an overview of the cytostatic production orders is given. A more detailed picture can be found in Appendix B. These histograms give a representation of the production orders of one year (between 01-02-2020 and 31-01-2021). Within this time window, 13429 orders are produced, of which 335 were cancelled. These orders consist of 38 different active substances. Almost the entire period analysed took place during the COVID-19 pandemic. This had minimal effect on the data. However, we will be slightly more cancellations than in a 'normal' year. We do not have precise information on this, but it is important to keep this in mind.

The graphs shows the price per mg, the number of orders of an active substance per year, the percentage of orders of an active substance that is cancelled per year, the time between a cancellation and the administration appointment and the shelf life of an active substance. More detailed information about the orders per active substance can be found in Appendix D.

Based on this Case mix, other hospitals can decide whether their situation is comparable to the situation of ZGT Pharmacy.

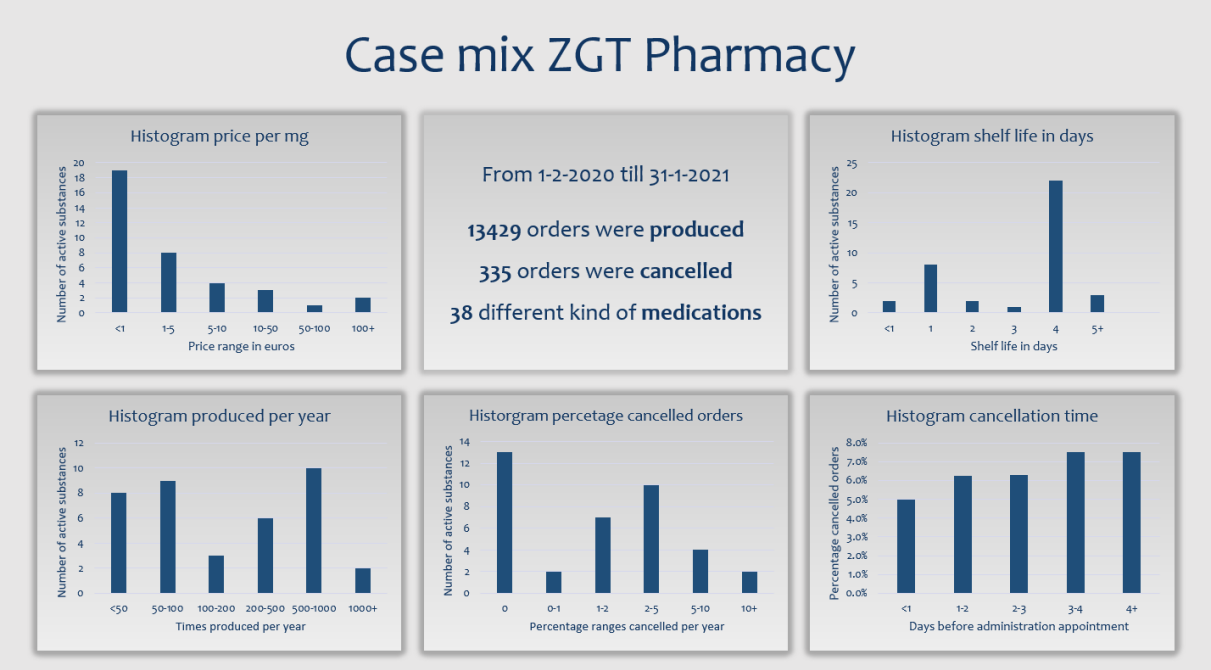

Figure 8 - Case mix ZGT Pharmacy

2.3 Key Performance Indicators

In this research, we aim to determine which production system is most suitable for ZGT. Currently, some problems occur during the production process of patient-specific medication, these are described in Section 1.2. We want to investigate which (improved) production system is best to prevent these problems and make the production process more efficient.

We will analyse the impact of these methods by five different Key Performance Indicators (KPIs). These KPIs are chosen based on conversations with the stakeholders. The most important stakeholders in this process are pharmacists, assistants, the management and patients. These KPIs represent the stakeholders.

Waste of raw material and end-products

As stated, a part of the raw material from vials is thrown away when producing medication. Besides, sometimes also end-products are disposed when the treatment will not continue with the produced medication, due to cancelation or a change in dosage. Only medication that is administered to a patient can be declared to the health insurance and therefore reducing the spillage and disposal is important.

To measure the cost of spillage and disposal, we make models for the different production systems. The output of these models will be the cost of waste of raw-material and end-products.

Employee deployment

Within each system, the deployment of employees varies, which results in a required number of employees per method. For example checking whether a treatment will continue is not necessary when a one-stop-shop production system is used.

We want to complete the production process with as few employees as possible to make it more efficient. We measure this KPI in terms of number of employees needed to fulfil all process steps.

Patient experience

Patients are one of the stakeholders and their satisfaction during the different production systems is relatively hard to measure. Almost all aspects stay the same when the production system changes. We assume that the quality of the medication will not differ among the different production systems since all GMP-Z guidelines, that ensure quality of the medication, have to be followed in all different production systems. There are two aspects that will change when practicing the different production systems.

Waiting time for patients

First, the waiting times for receiving medication. The patient experience must be good and therefore the waiting time for the patient is an important performance indicator. We are not able to determine exact numbers of waiting time, therefore we provide an estimation in minutes.

Number of appointments

Second, the number of appointments. Multiple appointments at the hospital for one treatment is not favourable in terms of patient experience. Therefore, the number of appointments per treatment is an important performance indicator for the patient experience too. Since this can differ per treatment, we will make an estimation for this KPI.

The patient experience as a whole will be expressed on a scale from 1 to 10. The higher the number, the better the patient experience.

The magnitude of the change for the hospital

Changing the current process will result in changes for ZGT Pharmacy and working procedures. While determining the best production system for ZGT Pharmacy, we will take into account the size of the change to compare the advantages of the method to the effort the company has to put in it. A small change in waste of material in terms of money and slightly less workforce needed should not result in an immense change in the process. Changing the process will cost money and effort and should therefore only be considered when it results in a significant increase in efficiency.

This KPI is not expressible in an exact number, therefore we will score the different production systems on a scale from 1 to 10. 1 means no change and 10 means a major difference and thus change needed.

2.4 The current performance

To compare the different (improved) production systems, we also want to know the performance of the current production system to define whether there is an improvement and how big this improvement is. In this section we provide the current performance on the chosen KPIs.

Waste of raw material and end-products

As mentioned in Section 2.4, this KPI will be measure in terms of costs. The costs of waste of raw material and end-products per year are determined and amount to €XX.

Employee deployment

As displayed in the process map, there are four categories of employees working on the production of patient-specific medication. We do not take into account the doctors, their assistants and the transportation employees.

As stated earlier, production takes place on weekdays. At the front-office of VTGM there are two employees working on their tasks per day. Furthermore, there is one pharmacist checking the information on both HiX and CATO for approximately half of the day. The back-office employees are working with one-and-a-half employee on entering information in CATO, checking the medication an

delivering it to the front-office. At last, the production of medication is performed by two employees per clean room and there is production in two clean rooms, so four employees. In total this makes eight employees per day needed to produce the current output.

Patient experience

Waiting time for the patient

There is currently no waiting time for patients. The medication is already produced in advanced and is therefore directly available at the department where it will be administered.

Number of appointments

Besides the administration appointment, there is for some kind of treatments, an extra appointment necessary. These appointment concern checks of the patients health. Based on these measurements, there will be decided on the continuation of the treatment and the dosage of the next treatment. Approximately 1.5 till 2 number of appointments are needed per treatment.

The magnitude of the change for the hospital

Since this is the current situation, the change for the hospital is zero and therefore will receive a score of 1 on the scale.

2.5 Restrictions

An important aspect to consider while determining the best production system for ZGT Pharmacy is the restrictions which must comply with the system. In consultation with the stakeholders, we established three restrictions.

GMP-Z guidelines

As mentioned before, it is important and even obligated to follow the guidelines that are drawn up to prevent the medication from being contaminated, interchanged, or damaged, the GMP-Z guidelines. Within each production system it is important to make sure that it will always be possible to follow these guidelines.

Limited storage capacity

A solution to prevent a high amount of spillage are different sizes vials. However, there is a limited storage place for these vials in the clean rooms. It is possible to change the volume of the vials or make some small adjustments in the current product range available, but it is not possible to store an unlimited amount of vials.

Employee deployment

There could be a change in working time for the employees when a different production system is used. However, the collective labour agreement (CLA) should be taken into account. This has among others effect on the number of hours that may be worked in a row and which hours of the day the employees may be deployed.

2.6 Conclusion

In this chapter, the current way of producing patient-specific medication within ZGT pharmacy is discussed. In this process, six different departments are involved. The doctors and their assistants are making requests and are responsible for the administration of the medication. The transportation department makes sure that the medication and resources end up in the right place. Pharmacists perform checks on the right dosage and substance several times in the process. The front office primarily checks whether administration will surely take place. The back office makes the link between the two

systems, HiX and CATO, and checks the produced medication. In the clean rooms, two employees produce the medication. Various checks are also carried out during the production.

The VTGM production in ZGT's pharmacy is clustered. Medication with the same active substance is produced in a row, so less spillage of raw material occurs. The clustering can easily be done with the use of CATO. To avoid expensive raw material vials to only be used partly, phaseals are being used. These are special caps that extend the shelf life of a material.

To determine which production system is best for ZGT Pharmacy, five KPIs are taken into account. These KPIs and their current performance can be found in Table 4.

Table 4 - Current performance on the KPIs

KPI	Current value
Waste of raw-material and end-products	€XX
Employee deployment	8 employees
Waiting time for patients	0
Number of appointments	1.5 till 2
The magnitude of the change for the hospital	1

During this research there are three restrictions that should be met. First, the GMP-Z guidelines must always be followed. Second, we should take into account that there is only limited storage capacity for vials in the clean rooms and at third, employee deployment must be in line with the CLA.

3. Production systems

This chapter gives an overview of literature that is useful for this thesis. We start by describing the planning characteristics of the problem (Section 3.1). Hereafter, we give an overview of the already known production systems for practice and the production systems we find in literature (Section 3.2). We explain them in more depth and substantiate this with, when possible, findings in literature. Afterwards, we discuss how these production systems can be improved (Section 3.3). We conclude by discussing which production systems are suitable for ZGT (Section 3.4).

3.1 Planning characteristics of the problem

Before we describe the production systems in practice and literature, we first define the production situation. The production problem has three important characteristics. First of all, the remaining content of the vials has to be thrown away when they are opened. Therefore you want to use as much content of the vials as possible. This can be seen as a cutting stock problem. The cutting stock problem (CSP) addresses the issue of how to cut out required pieces of (a) certain size(s) from stock-material with minimum loss. There are many fields of application of CSP, such as the manufacturing industry of clothing, aerospace, and steel (Cheng et al., 1994). An example of the one-dimensional CSP is cutting out a certain number of rods of a certain length. One wants to use as much of the length of the original rod. In our case, we want to use as much volume of a vial as possible.

The second characteristic of the problem is that the production must be done within a limited time before the product is used, as the medication has a short shelf life. We can compare this in a certain extent with the production of food. Producing food to keep it in stock and sell at a later time is risky since there is a probability the food will not be sold before expiring. Therefore the consideration about the right moment of production has to be made. This can be seen as Just In Time (JIT) production. JIT is a logistic method for inventory management belonging to Lean Manufacturing (Theisens, 2016).

The third characteristic is that a produced order can be cancelled before, during, or after production. Planning orders with (time-dependent) cancellations is related to statistics, as you need to take into account how big the probability is that an order will not be used and therefore will not be paid for and thus results in costs of disposal. This can also be compared to a food context. For example, a company that sells prepared sandwiches during lunchtime. When a sandwich is prepared it cannot be used longer than a day. There is a certain expectation about the number of sandwiches that will be sold. However, no exact number can be determined. The amount of sandwiches that will be sold on a day depends on a number of characteristics, for example, the day of the week or the weather. This can be the same with the probability of cancellation of a treatment. Several factors can influence the probability that a treatment will not continue. However, we do not (yet) know which factors and to which extent they influence the continuation of the treatments. This can also be seen as the newsvendor problem. In the newsvendor problem, a decision maker is facing random demand for a perishable product and has to decide how much of it to stock for a single selling period (Petruzzi, 1999).

3.2 Production systems in practice and literature

In this section, we discuss the different production systems that are found in literature and practice. In the existing literature, production systems of patient-specific medication are marginally discussed. To gain information about the currently used systems, we have conducted interviews at hospital pharmacies to be able to describe and analyse these production systems. We distinguish five different production systems.

3.2.1 One-stop-shop

A one-stop-shop concept is an organizational model that is characterized by providing all services or goods at the same location. This can be applied in many different areas. Within the scope of healthcare, it is explained as a single appointment in one location where a patient may receive tests, diagnostics, and in some cases treatments, reducing the total number of appointments required (National Health Service England, 2016).

The underlying idea behind a one-stop service in diagnosis is that carrying out all tests in a single appointment and having the results reviewed immediately is more efficient and results in less waiting time for patients (Friedemann Smith et al., 2018). Besides the use of the one-stop-shop approach in the production of medication, it is used in hospitals for example by skin cancer treatments. Implementing a one-stop-shop concept for the treatment of newly diagnosed patients reduces the waiting time between diagnosis and treatment significantly (Romero et al., 2021). Furthermore, when the time from referral to diagnosis to treatment is reduced, the patient outcome can be improved (Drevets et al., 2019).

Within Hospital X, the one-stop-shop concept is used by the administration of medication of for example expensive chemotherapy. Instead of having an appointment where the current status of the patient is discussed and measured several days before the administration appointment, these appointments are all scheduled on the same day. When the patient arrives at the hospital, several tests are taken to determine the condition of the patient. When the condition is sufficient to undergo the treatment, the medication recipe is sent to the pharmacy department. The pharmacy department will start producing the order as quickly as possible. Meanwhile, the patient has to wait until the medication is ready, which takes approximately between one and one-and-a-half hour(s). When the medication is produced, the medication is transported to the location of the patient, and the medication is administered.

The production of patient-specific medication via a one-stop-shop system prevents that the medication that is produced will not be used due to a change in dosage or cancellation in the administration appointment. So, no disposal of end-products will occur. However, since every medication is produced separately, the spillage of raw material is higher.

As stated in the research goal, we want to minimize spillage and disposal and thereby the necessity to perform checks. When the one-stop-shop approach is used, no checks have to be executed anymore. This is due to the fact that an order will only arise when it will also be administered and the probability of cancelation and thus disposal of end-products is zero. This is an advantage of the one-stop-shop production system.

3.2.2 Single-unit production in advance

Hospital Y is using a mix of production systems, which will be explained in more detail in Section 3.2.4. One of the production systems they use focuses on single-unit production of patient-specific medication in advance. The confirmation of the recipe of the medication arrives about two days before the administration appointment. Each medication is produced separately. No clustering is done in this production system.

The difference with the one-stop-shop production system is that there is still a probability that the administration will not occur and therefore result in costs of disposal. Thus, a one-stop-shop system is already an improved production system since there are no disposal costs in this system.

3.2.3 Clustering

A clustering concept is an organizational model that combines individual orders into groups. The aim of clustering is to produce more (of the same) products in a row to reduce costs and time. Production clustering can take multiple forms, as from a logistical perspective it reduces to batch production. Batch production entails that each time you produce, you produce more than one item. A review on batch processes in written by D. Rippin (1993).

In the existing literature, no research exists on clustering the production of patient-specific medication. However, it is frequently used in other application areas, such as in food production and for producing component parts of automobiles (Slack & Brandon-Jones, 2013). In our case, the production of patient-specific medication, production in batches will result in a lower amount of needed resources such as syringes and cleaning material. Besides this, batch production requires less set-up time. In our case, preparing the supplies and cleaning the workplace is reduced, which reduces the total time of production.

The current production system within ZGT Pharmacy is clustering. Medication with the same active substance is produced in a row. Medication is produced one day in advance. Recipes with the same active ingredient are produced consecutively. For a detailed description of ZGT's clustering processes, please refer to Chapter 2.

The advantage of a clustering production system is mainly the reduction of spillage of raw material. When more than one recipe is produced in a row, more volume of the vials will be used and less spillage occurs. Besides this, the medication is produced in advance, which ensures that there is no waiting time for the patient since the medication is already produced before the patient enters the hospital.

3.2.4 Hybrid

A hybrid concept is an organizational model that combines two production systems. We define the hybrid production system as a combination between one-stop-shop and clustering. Part of the medication is produced via a one-stop-shop approach, while the other orders are produced in clusters, as described in Sections 3.2.1 and 3.2.3.

The main reason to use a combination of two production systems is to create a better production system that takes advantage of the strength of production systems. The working of the hybrid production system depends on the division of orders over the different production systems. In other words, which medication is produced via which production system.

In the existing literature, no research exists on using a mixture of more than one production system when producing patient-specific medication. However, at Hospital Y they use a hybrid production system. They either use clustering or single-unit production, depending on the requested medication.

The production orders at Hospital Pharmacy Y arrive around two days before they have to be administered. Before the medication is produced, there will be checks done to make sure that the treatment will take place. When there is a probability that the treatment is cancelled, production will be postponed until there is more certainty.

Most medication is produced per unit and only some expensive substances are clustered. Half of the time, the production of both the individual medication and the clustered medication takes place a day in advance and the other half of the time on the day itself. The medication that is produced a day in advance mainly goes to another hospital or are products that have a longer shelf life. Very expensive substances are produced when there is confirmation that the patient is able to undergo the treatment.

These patients then have to wait while the medication is produced. This looks the same as the one-stop-shop approach.

In order to reduce the costs of waste, they are looking into clustering more medication, so spillage of raw material is reduced.

3.2.5 Central production and distribution

The Dutch patient-specific medication production system is decentralized, however, production systems in other parts of the world are centrally organized. As described in the article of Reinhardt et al. (2017), in the United Kingdom there are only a few hospital pharmacies with a manufacturing license, so medication is typically obtained from commercial suppliers. This means that the production is done in a few locations and these products are distributed over the country. Logically this results in more production per day and thus less spillage of raw material. However, this could result in more disposal of end-products because medication needs to be produced further in advance. After all, it also needs to be transported. Note that, since there is more production in this production system, the probability that a medication that is cancelled can be used for another patient is quite high. This could result in a reduction in the disposal of end-products.

3.2.6 Conclusion

We have found five different production systems in literature and practice. Based on the descriptions and analyses of the spillage of raw-material and disposal of end-products, we can leave the single unit production out of consideration. This production system produces more waste since there is as much spillage as in the one-stop-shop system, but also a probability that the end-product will not be administered. Besides this, the probability of disposal is the same as with the clustering system, although there will be more spillage of raw material. Therefore it will be useless to further analyse this production system and we choose to focus on one-stop-shop and clustering.

Furthermore, we choose for the same reasons to analyse a hybrid production system that contains a mix of the one-stop-shop system and the cluster system. Since this will result in the best results in terms of costs of spillage and disposal.

Finally, the central production and distribution system is not a feasible solution for now. This production system requires a nationwide change in the production of patient-specific medication, which is not in the scope of this project.

Therefore we continue with three production systems, the one-stop-shop system, the cluster system, and the hybrid production system consisting of a one-stop-shop as well as a cluster system.

3.3 Improving the production systems

The appointed production systems are explained as they are currently used in hospital pharmacies or described in literature. However, these systems can be improved to even work better in practice. In this section, we discuss how these production systems can be improved. This information is partly acquired from literature and partly from discussions and findings during the analysis of the current situation. There are more possibilities to improve the current production systems, but we pointed the most promising in terms of improvement.

3.3.1 Improving the one-stop-shop production system

The one-stop-shop production system is hard to optimize. It is a rather straightforward method that cannot be designed more efficiently while keeping the same structural idea of the production. However,

there are some aspects that affect the costs of this production system in terms of spillage, like the volume of the vials and the use of phaseals. These improvements can be found later on in this chapter.

Production planning

The article of Mazier et al. (2009) described the optimisation of the planning of the production in a production system that is similar to the one-stop-shop system. Using this method while planning the production of the one-stop-shop could decrease the waiting time. However, it is difficult to say anything about the difference this approach will make because this production system is less extensively analysed and it is not known how this production method will result in terms of waiting time for ZGT Pharmacy.

Mazier et al. (2009) propose a one-stop-shop in which they aim to minimize the tardiness on the target service time of delivering the medication. They distinguish two approaches: an off-line approach, which they solve with an integer linear programming model (ILP model) to minimize tardiness, and a real-time approach, which they solve with a combination between the ILP model and a greedy algorithm.

Robbes et al. (2020) describe an extended model in which not only the production but also the delivery of chemotherapy is taken into account. They state that: “The preparation of the order can only start after this validation in order to avoid the losses of drugs” (Robbes et al., 2020, p.2). This characterises the one-stop-shop approach. This article describes a multi-heuristic to optimize the production and delivery of chemotherapy. The advantage of combining the one-stop-shop with chemotherapy treatment planning is that in the planning of the patient appointments, drug requirements can be matched, to still use the advantages of clustering.

3.3.2 Improving the cluster production system

The cluster production systems produce medication with the same active substance in a row to reduce spillage of raw material. The production takes place in advance. To further improve the production system we state improvement possibilities in this section. We first focus on the clustering time horizon and hereafter on possible process improvements. Besides this, there are generic improvements that could also be used in a cluster production system. These are described in Section 3.3.4.

(Rolling) time horizon

In healthcare organisations, the horizon in which production is clustered is historically decided. For example, in ZGT a static horizon of one day is used, which means production is clustered for one day in advance. However, clustering the production within a different timeframe could lead to a different ratio between spillage of raw material in vials and disposal of end-products and it may even lead to a reduction of cost of spillage and disposal. Therefore it would be good to have insight into the time window in which clustering is executed and make a choice based on costs instead of logic in order to reduce the spillage and disposal.

First, it is important to define what we mean by clustering the production. As mentioned before, we define clustering as producing medication with the same active substance in a row, so less spillage of raw material occurs.

This can be done in two ways. First, a static time window, similar to what is currently used. An analysis of the costs of spillage and disposal could result in the best time window to cluster. Since medication only has a short shelf life, the maximum time to produce in advance is four days. So, an analysis of a time window between one and four days could be done.

Furthermore, a rolling time horizon can be used. A rolling time horizon approach does not only include the production orders for this day but also takes into account the orders for the days after tomorrow. The model considers whether it is useful to also produce an extra order to use more material of an

already opened vial. Referring back to the cutting stock problem as we explained in Section 3.1, more of the stock-material is used then which results in less spillage of raw material.

A rolling time horizon method solves an integrated planning and scheduling optimisation problem by a sequence of iterations. In each iteration, only a part of the planning horizon is taken into account, while the rest of the horizon is represented in an aggregate manner. The rolling time horizon approach successively solves each scheduling sub-horizon and carries any unsatisfied demand over to the following sub-horizon. This approach produces feasible planning and scheduling solutions (Li, 2010).

The rolling time horizon approach has two major benefits. First of all, solving the planning problem over the entire horizon results in a problem of unrealistic size, while the rolling time horizon approach significantly reduces the computational requirements by cutting it into smaller problems. Besides this, planning decisions for the far future could not be accurate enough due to uncertainty, which is a critical factor of our problem. The rolling time horizon approach considers only a relatively rough model for far future planning periods in the aggregate planning model (Li, 2010).

Li (2010) presents a general multiperiod linear programming-based planning model and a continuous-time representation-based process scheduling model to solve this problem.

Process improvements

Besides changes in the way the clustering is currently executed, some other steps could be taken to improve the clustering production system. When analysing the process map of the system, some steps seem to be non-value adding. According to the Lean philosophy, which is a management philosophy that focuses on delivering the highest possible quality at the lowest possible cost, actions that do not add value for the customer should be eliminated to reduce costs. Within Lean, there are eight types of waste: defects, overproduction, waiting, unused talent, transportation, inventory, motion, and extra-processing (Bicheno & Holweg, 2009).

Within processes, three categories of activities could be distinguished (Theisens, 2016):

- Value-added activities: the customer finds this activity of value and is, therefore, willing to pay for it.
- Non-value-adding activities: the customer does not consider this activity of value and therefore does not want to pay for it. It is imperative that these steps are removed from the process as they cost money but yield nothing.
- Necessary activities: these steps do not add value for the customer. However, they are essential to run the process and cannot be removed from the process.

3.3.3 Improving the hybrid production system

In the hybrid production system, a part of the medication is produced via a one-stop-shop approach and the other part via clustering. The improvements as stated in section 3.3.2, can also be useful in a hybrid production system with clustering. Furthermore, we discuss the trade-off between the production systems in this section. Besides this, there are generic improvements that could also be used in a hybrid production system. These are described in Section 3.3.4.

Division of order between production systems

In the hybrid production system, for each production order the decision must be made via which production system it is produced. The question is whether it is optimal to have a fixed assignment of medication types to both systems, and how to assign medication to a system. Hospital Y uses a hybrid production system and bases the decision on the price of the medication. However, this does not have to be optimal. In this section, we suggest different approaches to make this trade-off.

Price

The trade-off can be influenced by different points, for example by expensive and non-expensive medication. ZGT has labelled a number of medications as expensive. These are currently already produced less far in advance. However, they are still cancelled sometimes and could thereby result in a high amount of disposal costs. Furthermore, not clustering the production could result in a high amount of spillage of raw material. Therefore it is important to gain insight on the best way to produce expensive and non-expensive medication for ZGT Pharmacy.

Production rate

Furthermore, insight can be gained on the usefulness of clustering medication that is often or rarely produced. When a medication is rarely produced, it may be hard to cluster and therefore be better to not be produced in advance. This lowers the probability of disposal and will not result in more spillage since it already was not clustered.

Shelf life

Moreover, the trade-off can be made based on the shelf life of medication. When a medication can only be stored a short time after production, the production of this kind of medication should be executed often in order to serve the patients. In this case, the probability the orders can be clustered is smaller and these orders can better be produced via the one-stop-shop system. On the other hand, medication that can be stored for a couple of days is very suitable for clustering since more orders of the same kind of medication probably arrive and spillage of raw material can be reduced.

Cancelation probability

In addition, a trade-off can be made based on the probability that a kind of medication is cancelled. Based on historical data, we can determine the probability that a kind of medication is cancelled and result in the disposal of the end-product. The higher the probability of disposal, the better to produce via the one-stop-shop production system to prevent the disposal.

Statistical analyses

Statistical analyses can help us decide which medication to cluster and which not. By the use of regression, we are able to predict whether a treatment will take place by analysing various characteristics. When we predict a treatment has a high probability of continuation, this can be produced in advance and be clustered, while medication with a low probability can be produced via a one-stop-shop. Regression analysis is a statistical method to estimate the relationship between variables and to model and analyse these relationships. The relationship between the dependent variable (y) and the independent variables (x_i's) will be estimated (Theisens, 2016). Which characteristic has an impact on the continuation of the treatment and in which amount is not known yet. However, determining this could help to find a good trade-off between the different production systems. This brings us back to the third characteristic of this production problem, as described in Section 3.1.

A benefit of a good trade-off between the different production systems for each kind of medication is that the probability of high costs of cancellation is small and therefore the necessity to perform checks on the continuation of the treatment becomes less. These checks are performed by pharmacy assistants and take a lot of time. When a good trade-off between production systems is made, there should also be made an analysis between the labour costs of performing these checks and the savings that could be made by performing them.

There are two ways in which we can analyse the best trade-off for ZGT Pharmacy. First, we can evaluate the working of the different trade-offs by programming them and determining the costs of spillage and disposal. This will not provide us an optimal solution. However, it will be easy to implement since there are clear rules on which medication is produced via which production system. Second, we can make a

mathematical model that determines for every order how it should be produced. This will result in an optimal solution, but to be implemented, it should be ran about every day. Instead of having clear rules, it will differ per order. Based on this, rules can be determined to make it easier to work with.

3.3.4 Generic improvement techniques

Besides the aforementioned system-specific improvement techniques, some elements of the production process of patient-specific medication can be improved independently of the system in place. In this section, we state the most promising ideas derived from literate and conversations with involved stakeholders.

Vial volume

The volume of vials could have a major impact on the costs of a production system. When medication is produced per unit, vials with high volume could result in high costs of spillage. Besides this, when a cluster production system is used, small volumes in vials could result in higher costs than necessary because vials with smaller volumes are more expensive than vials with a bigger volume. Therefore it can be very important to take into account sets with vials of different volumes as input when testing the working of a production system. As stated in the restrictions in Section 2.5, the storage place for vials is limited. Therefore not all vials can be stored and a decision between different sets of vials should be made.

This can be compared to the cutting stock problem as described in Section 3.1. One wants to use as much of the raw material as possible. Via an LP model, we can determine which vials we want to use. The objective will be to minimize spillage while taking into account the limited storage capacity as a constraint.

Dose Banding

Another way in which costs of spillage and disposal could be reduced is dose banding. Currently, the dosages are calculated based on individual patient information like body weight or body surface area. With dose banding, doses within a defined range, usually ±5% of the calculated dose, are rounded to an agreed standard midpoint dose (Plumridge & Sewell, 2001).

Using dose banding allows the preproduction of frequently used doses. Besides this, there are a number of advantages when this method is used. The intended benefits of chemotherapy dose standardisation are, among others, fewer dose calculation errors, reduced waiting time for patients, and reduced costs through reduced wastage. The latter can be achieved because cancelled doses can be reused easier and it is easier to avoid incomplete usage of vials during production (National Institute for Health and Care Excellence, 2018).

In the Dutch Cancer Institute, Antoni van Leeuwenhoek, fixed-dosing has been implemented for monoclonal antibodies. They analysed two scenarios and calculated the savings that were made when using dose banding. First, clustering orders from a day, resulted in a saving of €0.8 million per year. Second, single-unit production, resulted in a saving of €3.1 million per year. This leads to the conclusion that fixed-dosing, or dose banding, results in substantial savings in health care costs (Heinhuis et al., 2020).

Phaseals

As mentioned in Section 2.1.5, phaseals are used to prevent spillage of raw material in vials. The decision which substances receive a phaseal depends currently on a previously made decision based on stability and the costs of the substance. However, this decision could also be made based on a calculation. One

can determine for which vials and with which remaining volume it is most efficient to use a phaseal. This could result in even less spillage than is currently prevented.

This calculation should result in a yes or no decision. When the costs of a phaseal are lower than the expected gain when using a phaseal, it is worth using it. This results in the following calculation:

$$Remaining\ vial\ volume\ in\ mg\ \times price\ per\ mg \times probability\ that\ the\ remaining\ volume\ will\ be\ used\ within\ the\ shelf\ life$$

when the calculation is greater than the *price of a phaseal*, the phaseal must be used. In other words, the calculation must exceed the threshold of the price of a phaseal to be used.

Employee deployment

Currently, the productions at ZGT start at 7:30 AM every weekday. They produce medication until 4:00 PM or earlier if all orders are fulfilled. However, a change in the working hours could have an effect on the costs of spillage and disposal since orders can be changes or added till 1:00PM. When more orders are entered into the IT system CATO, which is used during production, more orders can be clustered. This could result in less spillage of raw-material. Furthermore, cancellations and changes in the prescribed medication occur during the day. When the production started later, a part of these cancellations and changes could be taken into account and therefore results in less disposal of end-products. Therefore it can be useful to take a critical look at the production hours to reduce the costs of waste.

Active control on continuation of the treatment

In order to decrease the disposal of end-products, some hospitals perform an active control on the continuation of the treatment. This can be seen as a mitigation strategy that provides more insight into the probability that cancellations occur and thus provides better information to take into account when planning (the production of) the treatment. Via a phone call, which is executed before production, the condition of the patient is checked via some questions. When the condition is sufficient the medication is produced. In this way, the probability of cancellation of the treatment decreases a lot, and costs on disposal of end-products can be saved. However, the downside of this approach is that it takes a lot of time to make all these phone calls.

3.4 Suitable production systems for ZGT

3.4.1 Suitability criteria

To determine if the different production systems and their improvement methods are suitable for ZGT, we first appoint some criteria that should be met by the different systems. We discussed these criteria and then describe the improvement approaches we choose.

The first criterium is that a production system must be feasible within the situation of ZGT. This means that the changes that have to be made must be in line with the GMP-Z guidelines and that methods that change the dosage or the administration process must be scientifically proven to be responsible. Besides this, it must be possible to achieve this system with the possibilities that ZGT has itself. ZGT is unable to change factors that are beyond its control, it can only change its own situation.

It is important that the changes are feasible for the staff and that the work situation remains pleasant. The processes should not suddenly become much more complicated or require more time, money or effort.

The third criterium is that the changes that a different production system brings along should have a reasonable ratio between required effort and increase in efficiency. We are not able to completely

valuate the impact of an improvement or different production system. However, based on the information we found, we can evaluate how significant the change will be and whether it is worth the effort.

3.4.2 Decision

Based on the aforementioned criteria, we decided on which improvement methods we focus. An overview of all improvement methods is shown in Table 5. For every production system, we determine the optimal settings of vial volumes. We do this because this has a major impact on the working of these systems and can already improve them while no fundamental changes need to take place.

Furthermore, we improve the working of the clustering production system by determining the best time window to cluster in. Within the models, we optimise the production day for each production order while keeping in mind the administration day and the shelf life of the medication. This approach could reduce the spillage of raw-material and is easy to implement.

To improve the hybrid production system, it is important to know which medication is produced in which way. Therefore, we analyse which trade-off approach works best and implement this in the hybrid production system.

Furthermore, we will analyse the effect of dose banding and phaseals on the models, to investigate whether this are promising method to reduce costs.

Besides the improvement methods we chose to implement during this research, we also strongly recommend that ZGT Pharmacy further investigates the two improvement methods and tries to implement them in the production systems. These are the process improvements of the one-stop-shop and clustering, of which a first intent is presented in Appendix C.

Last, we decided not to take into account the other methods since we have no influence on them or because these steps are more appropriate as further research instead of directly using them to improve the production systems.

Table 5 - Optimisation methods

Category	Improvement focus	Included	Explanation
One-stop-shop	Production planning	No	We have no evidence that this will improve the current situation and therefore we do not take it into account but appoint it as further research
	Process optimisation	Recommend	We recommend to further investigate this, but will not focus on this during this research
Clustering	Rolling time horizon	Yes	This could decrease the costs of the production system considerably, so we take this into account.
	Time window	Yes	This can have a significant impact on the costs of the production system and thus should be taken into account
	Process optimisation	Recommend	We recommend to further investigate this, but will not focus on this during this research
Hybrid	Trade-off	Yes	It is important to determine a good trade-off when this production system is used.
Other	Vial volumes	Yes	Can make a significant difference between the different production systems and can improve them a lot
	Dose Banding	Yes	This can have a significant impact of spillage and disposal costs.
	Phaseals	Yes	Can make a significant difference between the different production systems and can improve them a lot
	Employee deployment	No	We will not directly focus on this, but appoint it as further research
	Active checks	No	We do not have an influence on this, so we do not include this in our research

4. Models

In this chapter, we describe the models we use to determine the costs of the different production systems. First, we describe the structure of determining these costs (Section 4.1), followed by a description of the assumptions we made (Section 4.2). Then, we introduce the notation we use in the models (Section 4.3) and we describe the three MILP models to optimize the production systems (Section 4.4 till 4.6). Finally, we provide a model extension for using phaseals in Section 4.7.

4.1 Structure

Within this chapter, we describe the models we build to analyse the costs of spillage and disposal of the different production systems while optimizing their situation. We determine the costs of the production system with the use of historical data of orders. More information about the input data is given in Chapter 5. Furthermore, the assumptions relating to these models are described in Section 4.2. Before we described the working of the models, we explain the approach of this analysis.

4.1.1 Costs of spillage and disposal

To determine the best production system for ZGT Pharmacy, we analyse the performance of the production systems on chosen KPIs. One of these KPIs is the waste of raw material and end-products. We express this KPI in terms of money, the costs of spillage of raw material and disposal of end-products.

As written in Section 3.4, the volume of the vials may have an impact on the costs, therefore we make an optimization model that chooses the best settings in terms of vials in the clean rooms while minimizing the costs of spillage and disposal.

For the three production systems, we provide Mixed Linear Programming models (MILP-models). These models differ on some points. For the one-stop-shop system, we only have to take into account the vials, while for the cluster system we also have to take into account how to cluster the orders. Besides this, for the hybrid production system, we also have to determine which product to produce via which production system. In Table 6, we give an overview of the decisions we include in the models.

Besides the characteristics of the production systems, also the objective function differs. Within the one-stop-shop production system, no disposal of end-products will occur, since the medication is only produced when the administration will take place. This is also the case for the part of the production of the hybrid production system that is produced via the one-stop-shop approach. Within the other part of the hybrid production system and the cluster production system disposal of end-products can take place. We add stochasticity to the models by including the probability of cancelling an order and the costs involved with cancelling.

In order to provide a clear overview of the models, we first specify the notation we use. Then we provide a model description, model, and model explanation for every production system.

Table 6 - Characteristics production systems

	Characteristics			Objective	
Production system	Vial volume	How to cluster	Production system trade-off	Costs of spillage	Costs of disposal
One-stop-shop	X			X	
Clustering	X	X		X	X
Hybrid	X	X	X	X	X

4.1.3 Phaseals

Besides determining the costs of the production system and optimising them, we also want to investigate the impact of phaseals on the production systems. In order to see the impact of phaseals on the costs of spillage and disposal, a model extension is needed. In section 4.7, the extension is described.

4.2 Assumptions

During this research, we mainly focus on the situation within ZGT Pharmacy. This means that there are several assumptions made, based on the case. The situation of ZGT Pharmacy is already explained in the Case mix in Section 2.2. Besides this, we described in this section the assumptions within ZGT that do not directly apply to other hospital pharmacies.

Production for external locations

A part of the production orders that ZGT Pharmacy produces are transported to other locations. Based on order data of a year we conclude that about 18% of the orders will go to the ZGT hospital in Almelo and 20% of the orders will go to a hospital in Hardenberg. The remaining 62% percentage will be administered in Hengelo. Since the production takes place in Hengelo and transportation of medication to Almelo and Hardenberg takes extra time and results in transportation costs, it is not possible to perform a one-stop-shop production system with these external orders. Therefore, a complete one-stop-shop system is not an option for ZGT Pharmacy. However, we will determine the costs of this system to get a broad view of the different production systems and their performance.

Storage capacity

As described earlier, there are only limited storage places for vials within the clean rooms. Therefore, not all available vials on the market can be stored. To be able to produce all orders, the number of storage places must exceed the number of different raw materials or extra storage outside the clean rooms must be available. Within the cytostatic clean room there are 48 places available.

Emergency orders

Some orders are not prescribed on forehand but have to be produced within a short time frame since these are emergency orders. The active substances needed for these resources should be available within ZGT Pharmacy at all times. Although the frequency of these orders may be low, they must be accessible directly. Since this comprises a small percentage of the total orders, these are not further included in our analysis of the production systems.

Characteristics of the orders

The input data of our models contain historical orders of ZGT Pharmacy. Therefore it would not provide the same output and thereby the corresponding choice of the best system for other hospitals. The demand, the frequency of demand, number of cancellations, and prices of raw material can differ between hospitals. To get a good overview of the characteristics of ZGT Pharmacy one can compare their characteristics with the ones of ZGT through the Case mix in Section 2.2.

Production on weekdays

The production of patient-specific medication only takes place on weekdays. Orders with a long shelf life can be produced before the weekend when they are administered on Monday. Although this does not apply to all orders, orders with a short shelf life should be produced on Monday.

Allowance health insurers

The costs of the production of patient-specific medication can be declared at the health insurers. The health insurance covers only the costs of the medication that is administered and not the spillage that

occurs or disposal of an end-product. Therefore only the spillage and disposal costs are taken into account.

Clustering orders

As explained earlier, orders are clustered based on the active substance of the medication. ZGT Pharmacy works with a clustering horizon of whole days. So medication can be produced on the same day of administration or one, two, three, etc. days in advance.

4.3 Notation

In this section, we introduce the notation we use in the MILP models that follow in the coming sections. Not all sets, parameters, and decision variables are used in every model, and also some parameters and decision variables include fewer indices in certain models.

Sets

Orders i ;	i = 1, 2, …, n
RawMaterials j ;	j = 1, 2, …, m
Vials k ;	k = 1, 2, …, p
Day d ;	d = 1, 2, …, q
ProductionSystem s ;	s = OSS, Clust (which refers to one-stop-shop and clustering)

Parameters

$Required_{i,j}$	The amount (mg) from raw material j that is needed to produce order i.
$VialCombination_{j,k}$	Whether vial k contains raw material j (binary).
$VialPrice_{j,k}$	Price of vial k of raw material j per mg.
$VialSize_{k}$	Size of vial of type k in mg
StorageCapacity	Number of places in clean rooms for vials.
BigM	A very large number that (un)restricts the variables.
$ProducePossibility_{i,d}$	Whether order i can be produced at day d (binary).
$CancellationProb_{i,d}$	The probability that order i will be cancelled when produced on day d.
$ObligatedProdSys_{i}$	Obligated production system for order i (binary, 0 = all systems possible, 1 = clustering).

Decision Variables

$Produce_{i,j,k,d,s}$	The ml of raw material j of vial k that is used to produce order i on day d via production system s.
$VialStored_{j,k}$	Whether vial k of raw material j is used (binary).
$NrVialsOSS_{i,j,k}$	Number of opened vials of raw material j and size k to produce order i via OSS approach.
$NrVialsClust_{j,k,d}$	Number of opened vials of raw material j and size k on day d to produce cluster orders.
$ProductionDay_{i,d}$	Whether order i is produced on day d (binary).
$ProductionSystem_{i}$	Which production system is used for order i (binary, 0 = OSS, 1 = clustering)

4.4 One-stop-shop MILP model

4.4.1 Model description

The one-stop-shop model minimizes the costs of spillage. The model represents single-unit production. A new vial is used for every production order. We optimise the decision which vials are available within the clean rooms. Not all indices, parameters, and decision variables are necessary for this model. As

input for the model we only use information about the active substance and the amount of active substance needed per order. Besides this, the vials are input to the model. The vials also have characteristics as the active substance, volume, and price. The goal of the model is to minimize the spillage costs while producing all orders and taking into account the limited available places for vials within the clean room.

4.4.2 MILP model

Objective

$$Min\ z = \sum_{i=1}^{n}\sum_{j=1}^{m}\sum_{k=1}^{p}[(NrVialsOSS_{i,j,k} \times VialSize_k - Produce_{i,j,k}) \times VialPrice_{j,k}]$$

Constraints

1. $\sum_{j=1}^{m}\sum_{k=1}^{p} VialStored_{j,k} \leq StorageCapacity$
2. $\sum_{i=1}^{n} NrVialsOSS_{i,j,k} \leq VialStored_{j,k} \times BigM \qquad \forall j,k$
3. $\sum_{i=1}^{n} NrVialsOSS_{i,j,k} \leq VialCombination_{j,k} \times BigM \qquad \forall j,k$
4. $\sum_{k=1}^{p} NrVialsOSS_{i,j,k} \times VialSize_k \geq Required_{i,j} \qquad \forall i,j$
5. $\sum_{k=1}^{p} Produce_{i,j,k} = Required_{i,j} \qquad \forall i,j$
6. $Produce_{i,j,k} \leq NrVialsOSS_{i,j,k} \times VialSize_k \qquad \forall i,j,k$

4.4.3 Model explanation

The model aims on minimizing the spillage costs, which are calculated through the price of the volume of the opened vials minus the price of the volume that is needed for the orders.

The first constraint makes sure that the storage capacity of vials is not exceeded. This can be done because, the second constraint makes sure that when a vial is used, the VialStored variable turns to one. An order can only be produced with vials that really exist, therefore, the third constraint makes sure the orders are produced with available vials. The fourth constraint makes sure the orders are fulfilled by determining the number of vials needed to produce the required amount. The fifth constraint makes sure that the required amount for every order is produced via one of the vials. When an order is produced, it is important that there is enough volume available to produce this order. Therefore, the sixth constraint assures that the volume is greater or equal to the produced amount. An important note here is that constraints five and six are not strictly necessary, but since we extend the models this provides a more logical overview.

4.5 Clustering MILP model

4.5.1 Model description

The clustering model minimizes the costs of spillage and disposal while determining the optimal way of clustering. For every day, it will be determined which orders will be produced and how many vials will be needed to produce all these orders. The spillage is the remaining volume of the vials that will not be used anymore. The model determines the most efficient way in which the orders can be clustered, so for each order the best production day is determined. The model takes into account the shelf life of the medication after production. Furthermore, it takes into account the probability of cancelation of an order when it is produced a certain number of days in advance and thus the expected disposal costs. Besides this, the model also decides which vials should be placed in the clean rooms, while taking into account the limited storage places.

4.5.2 MILP model

Objective

$$\min z = \sum_{d=1}^{q}\sum_{j=1}^{m}\sum_{k=1}^{p}[(NrVialsClust_{j,k,d} \times VialSize_k - \sum_{i=1}^{n} Produce_{i,j,k,d}) \times VialPrice_{j,k}] + \sum_{i=1}^{n}\sum_{j=1}^{m}\sum_{k=1}^{p}\sum_{d=1}^{q} DisposalCosts_{i,j,k,d}$$

Constraints

1. $\sum_{j=1}^{m}\sum_{k=1}^{p} VialStored_{j,k} \leq StorageCapacity$
2. $\sum_{d=1}^{q} NrVialsClust_{j,k,d} \leq VialStored_{j,k} \times BigM \qquad \forall j,k$
3. $\sum_{d=1}^{q} NrVialsClust_{j,k,d} \leq VialCombination_{j,k} \times BigM \qquad \forall j,k$
4. $\sum_{k=1}^{p}\sum_{d=1}^{q} Produce_{i,j,k,d} = Required_{i,j} \qquad \forall i,j$
5. $\sum_{d=1}^{q} ProductionDay_{i,d} = 1 \qquad \forall i$
6. $Produce_{i,j,k,d} \leq Required_{i,j} \times ProductionDay_{i,d} \times ProducePossibility_{i,d} \qquad \forall i,j,k,d$
7. $\sum_{i=1}^{n} Produce_{i,j,k,d} \leq NrVialsClust_{j,k,d} \times VialSize_k \qquad \forall j,k,d$
8. $[Produce_{i,j,k,d} - BigM \times (1 - ProducionDay_{i.d})] \times CancellationProb_{i,d} \times VialPrice_{j,k} \leq DisposalCosts_{i,j,k,d} \qquad \forall i,j,k,d$
9. $DisposalCosts_{i,j,k,d} \geq 0 \qquad \forall i,j,k,d$

4.5.3 Model explanation

The model aims on minimizing the spillage and disposal costs. The spillage costs are calculated through the price of the volume of the opened vials minus the price of the volume that is needed for the orders for every day. The disposal costs are calculated by the probability of cancellation multiplied by the production costs of this order.

The first constraint makes sure that the storage capacity of vials is not exceeded. This can be done because, the second constraint makes sure that when a vial is used, the VialStored variable turns to one. An order can only be produced with vials that really exist, therefore, the third constraint makes sure the orders are produced with available vials. The fourth constraint makes sure that the required amount of raw material for an order is produced. An order has to be produced in one go, the fifth constrain makes sure that an order is produced in one go and only once. To produce the orders, for every order a production day must be determined out of the possible days to produce this order. The sixth constraint makes sure that a production day is chosen and that this is a day at which it is possible to produce this order. When orders are clustered on a day, it is important that enough volume for all these orders is taken into account. Therefore, the seventh constraint assures that the volume is greater or equal to the produced amount. When an order is produced on a certain day, disposal costs should be taken into account. These disposal costs are determined via the eighth and nineth constraints. When production takes place on a certain day, the expected disposal costs are the product of the cancellation probability of the order, the vial price, and the volume that is produced. When the order is not produced on a certain day, the disposal costs are set to zero for this day.

4.6 Hybrid MILP model

4.6.1 Model description

The hybrid production model also aims to minimize the costs while determining which vials should be stored within the clean rooms. This is done by combining the two production systems. For every order,

it should be decided how this order is produced. Therefore not only spillage costs but also disposal costs are taken into account in this model. Because some orders cannot be produced via the one-stop-shop approach due to transportation to another location, this is taken into account in the model.

4.6.2 MILP model

Objective

$$\min z = \sum_{i=1}^{n}\sum_{j=1}^{m}\sum_{k=1}^{p}[(NrVialsOSS_{i,j,k} \times VialSize_k - Produce_{i,j,k,d,OSS}) \times VialPrice_{j,k}] + \sum_{d=1}^{q}\sum_{j=1}^{m}\sum_{k=1}^{p}[(NrVialsClust_{j,k,d} \times VialSize_k - \sum_{i=1}^{n} Produce_{i,j,k,d,clust}) \times VialPrice_{j,k}] + \sum_{i=1}^{n}\sum_{j=1}^{m}\sum_{k=1}^{p}\sum_{d=1}^{q} DisposalCosts_{i,j,k,d}$$

Constraints

1. $\sum_{j=1}^{m}\sum_{k=1}^{p} VialStored_{j,k} \leq StorageCapacity$
2. $\sum_{i=1}^{n} NrVialsOSS_{i,j,k} + \sum_{d=1}^{q} NrVialsClust_{j,k,d} \leq VialStored_{j,k} \times BigM \quad \forall j,k$
3. $\sum_{i=1}^{n} NrVialsOSS_{i,j,k} + \sum_{d=1}^{q} NrVialsClust_{j,k,d} \leq VialCombination_{j,k} \times BigM \quad \forall j,k$
4. $\sum_{k=1}^{p}\sum_{d=1}^{q}\sum_{s=1}^{t} Produce_{i,j,k,d,s} = Required_{i,j} \quad \forall i,j$
5. $\sum_{d=1}^{q} ProductionDay_{i,d} = 1 \quad \forall i$
6. $Produce_{i,j,k,d,s} \leq Required_{i,j} \times ProductionDay_{i,d} \quad \forall i,j,k,d,s$
7. $Produce_{i,j,k,d,Clust} \leq ProducePossibility_{i,d} \times BigM \quad \forall i,j,k,d$
8. $\sum_{d=1}^{q} Produce_{i,j,k,d,OSS} \leq NrVialsOSS_{i,j,k} \times VialSize_k \quad \forall i,j,k$
9. $\sum_{i=1}^{n} Produce_{i,j,k,d,Clust} \leq NrVialsClust_{j,k,d} \times VialSize_k \quad \forall j,k,d$
10. $Produce_{i,j,k,d,OSS} \leq ProductionSystem_i \times BigM \quad \forall i,j,k,d$
11. $Produce_{i,j,k,d,Clust} \leq (1 - ProductionSystem_i) \times BigM \quad \forall i,j,k,d$
12. $ProductionSystem_i \leq ObligatedProductionSystem_i \quad \forall i$
13. $[Produce_{i,j,k,d,Clust} - BigM \times (1 - ProducionDay_{i.d})] \times CancellationProb_{i,d} \times VialPrice_{j,k} \leq DisposalCosts_{i,j,k,d} \quad \forall i,j,k,d$
14. $DisposalCosts_{i,j,k,d} \geq 0 \quad \forall i,j,k,d$

4.6.3 Model explanation

The model aims on minimizing the spillage and disposal costs. The objective function consists of three parts, the spillage costs of the one-stop-shop production, the spillage costs of clustered production and the disposal costs of the clustered production.

The first constraint makes sure that the storage capacity of vials is not exceeded. This can be done because, the second constraint makes sure that when a vial is used, the VialStored variable turns to one. An order can only be produced with vials that really exist, therefore, the third constraint makes sure the orders are produced with available vials. The fourth constraint makes sure that the required amount of raw material for an order is produced. An order has to be produced in one go, the fifth constrain makes sure that an order is produced in one go and only once. To produce the orders, for every day a production day must be determined. The sixth constraint makes sure that a production day is chosen. An order can be produced some days in advance, depending on the kind of active substance. Constraint seven makes sure that an order is not produced too far in advance or after administration, but only at the possible production days. When orders are clustered on a day, it is important that enough volume for all these orders is taken into account. Therefore, the eighth and ninth constraint assures that the volume is greater or equal to the produced amount. When a production system is chosen, the order needs to be produced in this way. The tenth and eleventh constraints assure that only production can

take place when this production system is chosen. Some orders can only be produced via one of the production systems. For example, because it is an external order and one-stop-shop is not possible. The twelfth constraint makes sure that an order is produced in an obligated way when necessary. When an order is produced via the clustering production system on a certain day, disposal costs should be taken into account. These disposal costs are determined via the ninth and tenth constraints. When production takes place on a certain day, the disposal costs are the product of the cancellation probability of the order, the vial price, and the volume that is produced. When the order is not produced on a certain day, the disposal costs are set to zero for this day.

4.7 Phaseal model extension

As described earlier, phaseals can help by reducing the spillage costs. Phaseals are special caps that ensure that vials can be preserved after opening. In order to see the impact of phaseals on the costs of spillage and disposal, a model extension is needed. In this section, the extension is described.

4.7.1 Model description

The phaseal model extension focus on choosing on which vials a phaseal is needed. The model still aims to minimize the costs, although an extra factor is included namely the phaseal costs. The model extension differs for one-stop-shop and clustering since with the one-stop-shop model, whether a phaseal will be used should be decided after the production of each order, while for the clustering model this has to be decided after every day. In order to let the model process the orders in the right way, the order numbers must be in chronological order.

There are three situations to distinguish with regard to phaseals:

1) No vials are opened. This case appears when the current inventory is sufficient to serve the orders or when no order of the active substance arise. In this case there is no phaseal needed, there are no spillage costs and the inventory in equal to the inventory of the previous order or day minus the used volume to produce the orders.
2) There are vials opened, but no phaseal is used. The model determines that although new vial(s) is/are opened, a phaseal is not needed. This results in no inventory, since the remaining volume will not be kept. The spillage costs are calculated by the inventory before this order or day plus the remaining volume of the vial multiplied by the price per mg.
3) There are vials opened and a phaseal is used. The inventory is calculated by inventory before this day or order plus the remaining volume in of the vial multiplied by the probability that this volume will be used. The spillage costs are calculated by the inventory times the probability the volume will not be used times the price per mg.

4.7.2 MILP extension

Parameters

PhasealPrice	The price of one phaseal.
$PhasealProssibility_{j,k}$	Whether it is possible to put a phaseal on this vial (binary).
$ProbVolumeUsed_j$	The probability that the remaining volume in the vial will be used before expiring.

Variables

$PhasealOnVial_{i,j,k}$ / $PhasealOnVial_{j,k,d}$	Whether a phaseal is places on vial j of size k after order i or day d.
$Inventory_{i,j,k}$ / $Inventory_{j,k,d}$	Inventory of vial j of size k after order i or day d.
$OpenedVials_{i,j,k}$ / $OpenedVials_{j,k,d}$	Whether there is a / are vial(s) j opened of size k for order i or at day d.

Besides these variables, also four auxiliary variables are used: Inventory1, Inventory2, SpillageCosts1 and SpillageCosts2.

Objective

$$\min z = \sum_{j=1}^{m}\sum_{k=1}^{p}\sum_{d=1}^{q} SpillageCosts_{j,k,d} + \sum_{i=1}^{n}\sum_{j=1}^{m}\sum_{k=1}^{p}\sum_{d=1}^{q} DisposalCosts_{i,j,k,d} + \sum_{j=1}^{m}\sum_{k=1}^{p}\sum_{d=1}^{q} PhasealOnVial_{j,k,d} \times PhasealPrice$$

Constraints

The constrains are given for the clustering model and will only differ in terms of indices for the one-stop-shop model.

1. $Inventory_{j,k,0} = 0 \qquad \forall\, j,k,d$
2. $PhasealOnVial_{j,k,d} \leq PhasealPossibility_{j,k,d} \qquad \forall j,k,d$
3. $OpenedVial_{j,k,d} \leq NrVialsClust_{j,k,d} \qquad \forall j,k,d$
4. $OpenedVial_{j,k,d} \times BigM \geq NrVialsClust_{j,k,d} \qquad \forall j,k,d$
5. $Inventory_{j,k,d} \geq 0 \qquad \forall j,k,d$
6. $Inventory1_{j,k,d} \geq 0 \qquad \forall j,k,d$
7. $Inventory2_{j,k,d} \geq 0 \qquad \forall j,k,d$
8. $Inventory_{j,k,d} = Inventory1_{j,k,d} + Inventory2_{j,k,d} \qquad \forall j,k,d$
9. $Inventory1_{j,k,d} \geq \left[\left(Inventory_{j,k,d-1} - \sum_i Produce_{i,j,k,d}\right) - NrVialsClust_{j,k,d} \times BigM\right] - \left[PhasealOnVial_{j,k,d} \times BigM\right] \qquad \forall j,k,d$
10. $Inventory2_{j,k,d} \geq \left[Inventory_{j,k,d-1} + \left(NrVialsClust_{j,k,d} \times VialSize_k - \sum_i Produce_{i,j,k,d}\right) \times ProbVolumeUsed_j\right] - [BigM \times (1 - PhasealOnVial)] \qquad \forall j,k,d$
11. $SpillageCosts_{j,k,d} \geq 0 \qquad \forall j,k,d$
12. $SpilliageCosts1_{j,k,d} \geq 0 \qquad \forall j,k,d$
13. $SpillageCosts2_{j,k,d} \geq 0 \qquad \forall j,k,d$
14. $SpillageCosts_{j,k,d} = SpillageCosts1_{j,k,d} + SpillageCosts2_{j,k,d} \qquad \forall j,k,d$
15. $SpillageCosts1_{j,k,d} \geq \left[\left[\left(Inventory_{j,k,d-1} + NrVialsClust_{j,k,d} \times VialSize_k - \sum_i Produce_{i,j,k,d}\right) \times VialPrice_{j,k}\right] - \left(1 - OpenedVials_{j,k,d}\right) \times BigM\right] - \left[PhasealOnVial_{j,k,d} \times BigM\right] \qquad \forall j,k,d$
16. $SpillageCosts2_{j,k,d} \geq \left[\left[Inventory_{j,k,d} \times \left(1 - ProbVolumeUsed_j\right) \times VialPrice_{j,k}\right] - OpenedVials_{j,k,d} \times BigM\right] - (1 - PhasealOnVial_{j,k,d}) \times BigM \qquad \forall j,k,d$

4.7.3 Model explanation

The model consists of some general constraints and some constraints that are related to the different situations. The general constraints are number one till four. The first constraint makes sure that the start inventory for all different vials is zero. The second constrain makes sure that phaseals are only used on vials at which this is possible. The third and fourth constraint make sure that the binary variable OpenedVial is 1 when a vial is opened and is 0 when no vial is opened.

Constraint five till sixteen are related to the different situations, as mentioned in Section 4.7.1. More information on these constraints are displayed in Table 7. The constraints make sure that the right inventory and spillage costs are calculated, given the situation.

Table 7 - Different situation regarding phaseals

Situation 1		Situation 2		Situation 3	
NrVials = 0	OpenedVials = 0	NrVials > 0	OpenedVials = 1	NrVials > 0	OpenedVials = 1
PhasealonVial = 0		PhasealonVial = 0		PhasealonVial = 1	
$Inventory_{j,k,d} = inventory_{j,k,d-1} - \sum produce_{i,j,k,d}$		$Inventory_{j,k,d} = 0$		$Inventory_{j,k,d} = Inventory_{j,k,d-1} + [NrVials_{j,k,d} * VialSize_k - \sum produce_{i,j,k,d}] * ProbVolumeUsed_j$	
$SpillageCosts_{j,k,d} = 0$		$SpillageCosts_{j,k,d} = [Inventory_{j,k,d-1} + [NrVials_{j,k,d} * VialSize_k - \sum produce_{i,j,k,d}]] * VialPricej,k$		$SpillageCosts_{j,k,d} = Inventory_{j,k,d} * (1-ProbVolumeUsed_j) * VialPrice_{j,k}$	

4.8 Conclusion

In order to analyse the costs of the different production systems, we build three MILP models, one for each production system. These models minimize the total costs while taking into account the various factors of the production systems. Table 8 displays the optimisation possibilities of each production system, together with which costs are taken into account in the models.

Furthermore, we provide a model extension to include the use of phaseals in the models.

Table 8 - Characteristics production systems

	Characteristics			Objective	
Production system	Vial volume	How to cluster	Production system trade-off	Costs of spillage	Costs of disposal
One-stop-shop	X			X	
Clustering	X	X		X	X
Hybrid	X	X	X	X	X

5. Experiments

In this chapter, we perform experiments with the models that are described in Chapter 4. First, we explain how we retrieved the input data and how we handle the data during this research (Section 5.1). Hereafter, we validate the models we made (Section 5.2) and show the results (Section 5.3). Furthermore, we verify the working of the models by making sensitivity analyses on the input data (Section 5.4) and provide a conclusion (Section 5.5). We implemented the models in AIMMS version 4.77.4.5, with solver CPLEX 20.1.

5.1 Input data

To provide an answer to the question what the costs of the different production systems are, we need input for the models. These model inputs are described in Chapter 4 as sets and parameters. We distinguish two categories of input we need, namely input related to the production orders and input related to the vials.

5.1.1 Production orders

The first dataset contains information about the production orders. This dataset is created based on historical data of order that is representative for the current output of the process. The dataset contains all orders from 1-2-2020 till 31-1-2021. This data is retrieved from CATO. Within this program, all historical order data is saved.

Section 2.2 presented a case mix of these orders. Furthermore, Appendix D provides a more detailed overview of the orders per active substance.

The input data of the production orders is based on historical data of production orders of one year. After conversations with the employees involved in the process, we can say that these orders broadly correspond to the process and give a good overall picture of the orders that must be produced within a year.

The characteristics of the orders are active substance, the amount of active substance needed, the shelf life of the medication after production which is equal to the number of days the medication can be produced in advance, the cancellation probability, the administration day, and the location of the administration. These characteristics can also be found in Table 9.

Table 9 - Data characteristics production orders

Characteristics production orders
Active substance
Amount of active substance needed (in mg)
Shelf life of the active substance (in days)
Cancellation probability
Administration day
Location of administration

The cancellation probability can only be calculated for the last 24 hours before administration. Within CATO, the program that is used while producing medication, we can find whether orders are administered or cancelled. Based on this we can calculate the ratio of cancellation per active substance by dividing the number of cancelled medication by the total number of produced medications of this active substance.

The probability that an order is cancelled before this 24 hours is based on interviews with the employees that are involved in the process of making and cancelling orders. The probability that an order is cancelled is higher when it is produced further in advance since there are appointments with the patients where the continuation of the treatment is discussed. Most of these appointments are 48 or more hours before the administration appointment and some between 24 and 48 hours. Via the conversations with the involved employees we determined the cancellation probabilities as follows:

- 0-24 hours before the administration: Cancellation ratio of the active substance.
- 24-48 hours before the administration: Cancellation ratio of the active substance * 1.25.
- 48+ hours before the administration: Cancellation ratio of the active substance * 1.5.

5.1.2 Vials

The second dataset contains information about the vials. The dataset is created based on the available vials for ZGT Pharmacy. All vials they can purchase can be used in the models. Thus, this data set contains more vials than ZGT Pharmacy is currently using in order to determine which vials can be used to lower the costs. We retrieved this data from the database of the purchasers within ZGT Pharmacy and the database Farmacotherapeutisch Kompas (Farmacotherapeutisch Kompas, 2021).

The characteristics are the active substance that is in the vial, the volume of the vial, the price per mg of the vial, the shelf life of the active substance, whether a phaseal can be used on this vial, the shelf life with a phaseal, and the probability that volume is used within the shelf life with a phaseal. These characteristics are also shown in Table 10.

Table 10 - Data characteristics vials

Characteristics vials
Active substance in the vial
Volume of active substance in the vial (in mg)
Price per mg
Shelf life of the active substance
Phaseal possibility
Shelf life of the active substance with a phaseal
Probability that the volume is used within the shelf life with a phaseal

5.2 Validation of the models

The models aim to optimize the production of patient-specific medication. When using the input of a whole year, a broad and good overview of the situation can be provided. Thereby the conclusions that will be drawn based on the outcome of the models will provide good input for the decision which production system is best for ZGT Pharmacy. However, processing the production orders of a whole year at once is impossible with the current resources available during this research. The computational power within our devices is not suited for such big models. Therefore, we provide an approximation on the costs of spillage and disposal and thereby the total costs per model. In this section we will explain the decisions we made and why we have chosen this approach.

First of all, we calculate the outcome of the models to make sure the models work correctly. We checked for different small data sets whether the choices of the models are indeed optimal and the calculation of the costs are determined right. This is the case, so we conclude that the models work in the right way.

Secondly, we must find a way in which we can process the data of a year in a way that is still computable. For this, we can choose different approaches. We will first explain the different approaches and then choose the most appropriate ones.

1. *Limited running time*. When running time is limited, this means that the model will not always find an optimal solution but still has a little integrality gap. Within a relatively short running time, a small gap can be accomplished, however, it takes very long to determine the optimal solution and thus retrieve a gap of zero.
2. *Initial solution*. The models will be solved in AIMMS, which uses a branch and bound algorithm to solve MILP models. When an initial solution is provided, the models can get to a good solution faster. However, the since the models are so extensive, it is hard to provide a good initial solution and this will require relatively a lot of effort. Since we perform several experiments and have three models, this is not a preferred approach given the limited time for our research.
3. *Smaller run horizon*, like a month or week. When this approach is used, the problem size decreases because only a limited number of orders and days have to be processed which makes it easier to run the models.
4. *Fixing the vials*. In this way, the decision which vials will be used does no longer have to be made by the model and this will decrease the run time. However, this is not preferable since we want to determine the optimal vials. Besides this, when processing the sensitivity analyses, it is very important to have the ability to use different vials since this has an effect on the costs.

We choose for approach 3, to run the models per week instead of the whole year. We have chosen this because this provides a reduction of the problem and therefore it will become processable on the available devices. Besides this, there is no production during the weekends and producing far in advance will result in a high probability of cancellation and thereby high disposal costs. This will lead to a very small probability that an order will be produced over the weekend and therefore this relaxation will only have a small effect on the outcome of the models. Besides this, it is possible to make a estimation of the extra costs related to producing weekly instead of a whole year. This will be further analysed in Section 5.4.3.

Besides using this relaxation, we also accept a small integrality gap while running the models. Within a small amount of time, the models determine a sufficient solution. However, an optimal solution takes a lot of time. Therefore, we decided that an integrality gap between 0% and 5% is allowed. For every production system, we determine a suitable run time per week at which the integrality gap will conforms to the allowed gap. After this run time or when an optimum is achieved, we stop running the model and provide the integrality gap as output. In Section 5.3 we specify what the running time and integrality gap of the models is.

The combination of these two approaches makes it possible to run the models and besides this, reduce the running time considerably but still provide good insight in the different outcomes of the models.

Validation focuses on the question whether these models will provide good input to answer our research question. The models will not result in optimal outcomes. However, it will provide a good estimation and therefore provide a good overview of the order of magnitude the costs will be. Based on these outcomes it is possible to make a good decision which production system will be best for ZGT Pharmacy.

5.3 Results of the models

Now that the models are validated we can show the results of the models. The data of a whole year is processed, per week. The running times and integrality gap per week per production system are shown in Table 11. Besides this also the mean gap and the standard deviation is shown. Later in this section we analyse these integrality gaps.

Table 11 - Running time and integrality gap per week per production system

Production system	Runtime in minutes	Optimal runs (%)	Mean gap of not optimal runs	Standard deviation of not optimal runs
One-stop-shop	1	100%	NA	NA
Clustering	3	37%	0.08%	0.16%
Hybrid	10	0	2.04%	2.80%

The results of the models in terms of costs are shown in Figure 9. As shown, the costs of a one-stop-shop production system are the highest with spillage costs of nearly €XX per year. The costs of a clustering production system are more than €XX spillage costs and almost €XX disposal costs. The production system with the least costs is the hybrid one, with nearly € XX spillage costs and more than €XX disposal costs.

Figure 9 - Results of the models

As stated before, we gathered results for a whole year but ran the model per week. This allows us to analyse the performance of the production systems per week. The results per week are shown in Appendix F.

In Figure 9, the results per week per production system are shown in a boxplot. For all 52 weeks, the models resulted in the same production system ordering. The best production system is for every week the hybrid system, followed by the clustering production system, and the one-stop-shop production system. Figure 9 shows that the spread in one-stop-shop is the much bigger than the spread of clustering and hybrid. This is due to the fact that within the clustering and hybrid production system there is more flexibility to reduce costs. For example producing on another day or via another production system. Within the one-stop-shop production system every order is produced per piece and the only way to save costs is by selecting the best vials.

While one-stop-shop has no integrality gap and a bigger spread in outcome per week against an integrality gap at clustering and hybrid but less spread, we conclude that having these gaps do not

influence the outcome significantly and thereby deduce that the method used determining the costs of the production system is solid.

Besides costs as result of the models, the models provide more output of how the production systems perform best. First, the models determined which vials must be stored in the clean room. An overview can be found in Appendix E. These differ for the three production systems. In the one-stop-shop production system, smaller vials are chosen by the model since the production is executed per order and small vials results in less spillage. In the cluster production system, bigger vials are used. Orders are clustered and therefore more volume is used at once. Thereby, bigger vials are often less expensive per mg. The hybrid production system is in between smaller and bigger vials and, when possible depending on the available storage places, a combination of small and big vials is stored. In this way, both one-stop-shop and cluster orders can produce at lowest costs.

Secondly, the day at which the orders are produced is determined for the cluster hybrid production system. At the clustering production system, 80.6% of the orders is produced 24 hours before administration. At the hybrid production system, 69.3% of the orders that is produced via clustering is produced 24 hours before administration. Important to note Is that all orders of Monday should be produced on Monday since production over the weekend is not possible.

A more extensive analysis of the production day of the orders can also be found in Appendix E. Here we provide more insight in the production days, the difference between expensive and less expensive active substances, the difference between active substances with a high and a low cancellation probability and an analysis of the production day per active substance.

Last, the production system is determined within the hybrid production system. 45.3% of the orders are produced via a one-stop-shop approach and the remaining 54.7% via the clustering approach. A more extensive analysis of this decision variable can be found in Appendix E.

5.4 Sensitivity analyses

The production of patient-specific medication can change over time. Therefore it is very important that we get insight in the results of the model when the input changes. Besides this, it is critical that the decision which production system is best for ZGT Pharmacy, shows stable results although the input may change and that we know when the decision must be reconsidered.

To test whether the outcomes are stable, we perform some sensitivity analyses. A sensitivity analysis is a study of how uncertainty in the output of a model can be apportioned to different sources of uncertainty in the model input factors (Saltelli & Sobol, 1995). We describe how we performed these sensitivity analyses, show the results, and draw conclusions based on these results.

It is very time-consuming to run every sensitivity analysis with the data of a whole year. However, we want the sensitivity analyses to give a good overview of the possible outcome, so the input data should represent the data of a year properly. Therefore, we searched for a dataset that shows comparable results as the data of a year in terms of costs of all three models and the number of orders within the time window. The analysis is shown in Appendix F. It resulted that month 7 (week 25 till 28) represents the whole data set best. The costs per production system and the number of orders are within an interval of ±6%. The sensitivity analyses will be performed with this data set.

5.4.1 Run horizon

As explained in Section 5.2, we ran the models per week so it is processable on the available devices. However, it is thereby interesting what the result of this is on the costs of the production systems. To

see what impact this will have on the outcomes of the models, we also ran experiments with a horizon of two weeks. The results are shown in Figure 10 . The costs of the one-stop-shop models are the same. This is logical since every order is produced separately and a longer time window has thereby no effect on the costs. For the clustering and hybrid method, there is a slight cost reduction between producing per week and producing per two weeks. This is respectively 0.1% and 2.1%. This is due to the fact that a small cost reduction can be achieved by producing orders over the weekend.

Figure 10 - Cost analysis run horizon

Although the results slightly improve when producing over the weekend is possible, it is important to note that processing these larger problems needed to be done on another device with more computational power. Besides more computational power, also the run time increased to obtain a similar integrality gap. The run time results are shown in Table 12.

Table 12 - Run time and integrality gap when running per two weeks

Production system	Running time per week	Running time per 2 weeks	Integrality gap
One-stop-shop	1 minute	2 minutes	0%
Clustering	3 minutes	30 minutes	3%
Hybrid	12 minutes	120 minutes	5%

5.4.2 Storage capacity

The second sensitivity analysis we perform is an analysis of the costs when the storage capacity differs. Currently, the capacity is 48 different vials. Besides this, at least a capacity of 38 places is needed since there are 38 different active substances and of each of these active substances at least one vial should be stored. Therefore, we analyse the costs of the production systems with a storage capacity of 38, 43, 48, 53, and 58.

The results are shown in Figure 11. For this and the remaining sensitivity analyses in this report, we provide a figure with the results of the sensitivity analysis. Within these figures, there is a graph that shows the results of each production system and besides this there is a graph that combines the results of all three models, so we can compare how the different production systems relate to each other.

As displayed in this figure and in Table 13, the costs of the production of medication only slightly changes when the storage capacity changes. Besides this, we see that for the one-stop-shop and hybrid production system no cost reduction is made when more than 48 storage places are available.

We conclude that the storage capacity has only a very small impact on the costs of the production systems and that regardless of the storage capacity the hybrid production system remains the system with the least costs and the one-shop-stop production system the system with the highest costs.

Table 13 - Cost savings increased storage capacity

Production system	Cost difference between 38 and 58 storage places
One-stop-shop	-0.25%
Clustering	-0.25%
Hybrid	-0.63%

Figure 11 - Sensitivity analysis on Storage Capacity

5.4.3 Order case mix

The current composition of orders of ZGT Pharmacy can be changed in the future. Therefore it is important to get insight into the effect of the changing orders on the costs of the production systems. The composition can change in several ways. We analyse four changes:

- *Fewer orders*: this analysis includes fewer orders per week. Randomly one-third of the orders will not be included in the analysis.
- *Less frequent orders per active substance*: this analysis includes less frequent orders of the same active substance. Of the active substances of which on average more than 8 orders per week occur, randomly one-third of the orders per active substance will not be included in the analysis.
- *More frequent orders per active substance*: this analysis includes more frequent orders of the same active substance. Of the active substances of which on average more than 8 orders per

week occur, randomly one-third of the orders per active substance will be added extra in the analysis. These orders will be comparable to the current orders for this active substance.

- *More orders*: this analysis includes more orders per week. These orders will be a comparable composition to the current orders. One-third extra orders will be added.

The results are shown in Figure 12. As expected, de total costs decrease when fewer orders have to be produced and the costs increase when more orders have to be produced. Furthermore, we see that the difference between the costs of one-stop-shop and clustering increases. So the more orders produced in the production system, the less interesting the one-stop-shop production system gets. This is due to the fact that when more orders have to be produced, clustering these orders is more preferable since economies of scale occurs. Via clustering spillage costs can be reduced, while via one-stop-shop the costs will only grow further. Besides this, we conclude that the hybrid production system will perform best in all cases.

Figure 12 - Sensitivity analysis on Order Composition

5.4.4 Order frequency

In Section 5.4.5 we have shown that order composition has a significant effect on the costs of the production systems and thereby on the decision of which production system performs best. Therefore it is interesting to analyse at which moment which production system is preferable.

When there is only one order per active substance, clustering is not preferred since no orders can be clustered and disposal costs appear within this production system. This results in more costs than producing via a one-stop-shop production system. To test the sensitivity on this aspect, we test at how many orders of the same active substance the turning point arises.

To test this, we created order sets of one to seven randomly generated orders per active substance out of the data set. The costs per production system are shown in Figure 13. As shown, the turning point between one-stop-shop and clustering is between three and four orders per active substance. When

less than four orders per active substance occur, the one-stop-shop production system performs best. When four or more orders per active substance occur, clustering becomes better than one-stop-shop. This can be explained by the fact that the spillage costs decrease as more orders can be clustered. Together with the disposal costs these spillage costs gains result in less costs than via the one-stop-shop approach.

Besides this, we see that the costs of one-stop-shop are approximately linear. However, the costs of clustering and hybrid are not. This is due to the fact that producing four orders per active substance can be clustered very well and therefore results in less spillage costs.

Furthermore, we conclude that the hybrid approach will always be the best performing production system, since it will always have equal of lower costs than both other production systems. This is due to the fact that the hybrid production system can choose to produce all orders via either of the two systems, or make a combination of production systems which even results in lower costs.

Figure 13 - Sensitivity analysis on Order frequency

5.4.5 Cancellation probability

The current cancellation probabilities are based on the data of ZGT Pharmacy. However, we want to test the production systems on their sensitivity when the cancellation probabilities changes. The cancellations probabilities is related to the disposal costs and will thereby will show a turning point between the one-stop-shop approach and the clustering approach since disposal costs do not occur in the one-stop-shop system.

To analyse which production system performs best at which cancellation probability and what the turning point is, we perform four experiments with cancellation probability of 2.5%, 5%, 7.5% and 10% for one day in advance. The cancellation probabilities further in advance will be calculated as stated in section 5.1.1.

The results are shown in Figure 14. Between a cancellation probability of 5% and 7.5%, one-stop-shop becomes more preferable than clustering. The disposal costs of clustering no longer outweigh the higher spillage costs of one-stop-shop. Hybrid still performs best since this production system determines the optimal trade-off between one-stop-shop and clustering for every order and thereby reduce costs.

Figure 14 - Sensitivity analysis on cancellation probability

5.5 Additional improvement opportunities

To further improve the situation of ZGT Pharmacy, there are some methods that can be used. As described in Section 3.3.4, dose banding and phaseal could help reducing costs. In this section, we analyse both methods and perform experience to determine the potential savings that implementing these methods could result in.

5.5.1 Dose banding

In Section 3.3.4 we introduced dose banding. Dose banding is a method that is used to reduce spillage. It can be implemented in different ways, such as rounding dosages or the use of standardised dosages. Standardised dosages have as additional benefit that this can reduce disposal costs since a cancelled end-product can be used for another patient. Since this approach of dose banding needs pharmaceutical evidence concerning that it can be used with the same working, we decided to not include this in our research but give insight in the possible savings that can be made when dose banding is used. This will only be an approximation since we do not know the exact standardising of the dosages.

It is important to state that a change in dosage should always be confirmed by a pharmacist and therefore should be known before production. Furthermore, the reimbursement from health insurance for an order depends on the dosage, so when the dosage is increased by 10%, the reimbursement will be 10% more as well.

The standard dosage must be within a range of ±10% of the prescribed dosage based on the patient characteristics. Therefore we implement a dose banding range in the models. We change the constraint

$$\sum_{k=1}^{p}\sum_{d=1}^{q}\sum_{s=1}^{t} \text{Produce}_{i,j,k,d,s} = \text{Required}_{i,j}$$

To

$$\text{Required}_{i,j} \times (1 - \text{DoseBanding}) < \sum_{k=1}^{p}\sum_{d=1}^{q}\sum_{s=1}^{t} \text{Produce}_{i,j,k,d,s} < \text{Required}_{i,j} \times (1 + \text{DoseBanding}),$$

where DoseBanding is a parameter that describes the percentage dose banding that is allowed. This forces the dosing of produced order i to be within +/- DoseBanding% of the required dosage. We perform two experiments with a dose banding of 5% and 10%.

Our second dose banding analysis aims to generate standardised dosages, by rounding the required dosages to tens, when this is possible between the range of ±10%. This is an method that is easy to implement, and forces dosages of various orders with the same active substance to be more easily clustered due to the similar sizes, and in case of cancellation be reused for another patient. The reuse of cancelled orders is not included in this analysis but is may also provide opportunity to save disposal costs and is therefore interesting for further research.

The results of the experiments are shown in Figure 15 and the potential improvement percentages are shown in Table 14 - Potential improvement Dose BandingTable 14. As shown, the costs of dose banding with 5% and 10% tolerance will result in a costs saving. This is caused by the fact that dosages can be adjusted to the vial volume. For example when there is an order of 35 mg and an order of 44 mg and the vial contains 80 mg. Dosages could be changed to 38 mg and 42 mg respectively, so only one vial needs to be opened and no spillage occurs.

Besides this, also rounding to tens will reduce the costs of all three production systems and could therefore be a potential cost saver for ZGT Pharmacy.

Table 14 - Potential improvement Dose Banding

	Dose banding method		
Production system	+-5%	+-10%	Round to tens
One-stop-shop	-20%	-34%	-17%
Clustering	-39%	-47%	-24%
Hybrid	-48%	-59%	-29%

We conclude that both dose banding with a tolerance as well as standardising by rounding to tens results in a costs saving. However, implementing a tolerance is a more extensive task and therefore rounding can be a good interim solution.

Figure 15 - Experiments on Dose Banding

5.5.2 Phaseals

In Section 2.1.5, we introduced phaseals. These are special caps that can be used on vials to reduce spillage. For cytostatic medications phaseals are not used yet since it is not scientifically proved that the active substances remain sustainable when these caps are used. Therefore we cannot take into account phaseals when determining the optimal production system for ZGT Pharmacy. However, we can show the impact of phaseals on the costs. Therefore we perform an experiment with phaseals.

In order to do this, we have made two assumptions. First we assume that the active substances remain preservable for seven days when a phaseal is used. Furthermore, we have to determine the probability that the remaining volume of the vial will be used when a phaseal is added. We did this by a simple analysis on order data of one year. The probability that the volume is used is calculated by the number of weeks in which the active substance is used for production divided by the total weeks per year. This is not an exact probability but a rough estimation. Since this sensitivity analysis is only performed to give insight in the possible cost savings when phaseals are used, we think this will provide a good overview.

As already mentioned in Section 5.2, the models are quite extensive and therefore hard to run. When the phaseal extension is added to the hybrid model, the model becomes intractable for the available devices. Therefore these results are not included. However, we can assume that the results for hybrid will be equal or lower than the best performing production system, since this production system is the best of the other two production systems.

The results of the experiment are shown in Figure 16 and the potential improvement percentages are shown in Table 15. As shown, the costs drastically decrease when phaseals are used and are therefore a promising method to reducing spillage costs. Besides this, we see that, when phaseals are used, the one-stop-shop production system is 50% lower in costs than a clustering production system. This is due to the fact that disposal costs will not be reduced significantly when phaseals are used and these costs

will be a large part of the total costs when phaseals are used. Since no disposal costs appear in the one-stop-shop models, this will result in very low costs of only almost €XX.

Table 15 - Potential improvement Phaseals

Production system	Potential improvement
One-stop-shop	-92%
Clustering	-75%

Figure 16 – Experiments on Phaseals

5.6 Conclusion

This chapter describes the performed experiments with our models. The models are run per week instead of per year, to make it possible to run the models and also reduce run time. Furthermore, we accept an integrality gap of a maximum of 5%. With these relaxations, we determine the order of magnitude of the costs of the production systems to be able to answer the question which production system performs best for ZGT pharmacy.

The results of the models for ZGT Pharmacy are shown in Table 16. As shown, for ZGT Pharmacy the hybrid production system is the least expensive system, against a cost of almost €XX, and the one-stop-shop the most expensive system, against 98% more costs.

Table 16 - Results of the production systems

To analyse the effects of changes on input settings and values, we performed several sensitivity analyses. This shows that a change in the order frequency or the cancellation probabilities, effect the decision which production system performance best since these show a turning point between the one-

stop-shop production system and the clustering production system. When more than four orders per active substance are produced per week, clustering becomes better than one-stop-shop. Furthermore when a cancellation probability becomes between 5% and 7.5% or more, one-stop-shop becomes preferable over clustering. Therefore it is important to keep this in mind when the situation within ZGT Pharmacy changes or for other hospital pharmacies when choosing the best production system.

Furthermore, our results show that several costs reductions are possible. The use of dose banding and phaseal show great potential to reduce the spillage and disposal costs. When dose banding is used a cost reducing between 17% and 59% can be achieved and when phaseals are used a cost reduction of 75% or 92% can be made.

6. Performance

In this chapter, the performance of the different production systems is given. First, we determine the costs of the different production systems for ZGT Pharmacy (Section 6.1). Subsequently, we describe the effect on the employee deployment (Section 6.2), patient experience (Section 6.3), and hospital changes (Section 6.4). When all results of the KPIs are known, we explain the working of the AHP (Section 6.5) and perform an AHP and decide what the best production system is for ZGT Pharmacy (Section 6.6). Finally, we describe the implementation plan for ZGT Pharmacy (Section 6.7)

6.1 Performance on waste of raw material and end-products

In this section, we analyse the performance of the production systems based on the situation of ZGT Pharmacy. The one-stop-shop production system is not possible for every order since these orders have to be transported to another location. Therefore we divide the following three production systems:

- The hybrid production system in which all external orders are clustered and the internal orders are produced via a one-stop-shop approach. This is the closest possible production system to a one-stop-shop given the location restriction.
- The Clustering production system.
- The hybrid production system in which all external orders are clustered and the internal orders may be produced in both ways. The model is allowed to determine the best way to produce the internal orders. This is the closest possible production system to a hybrid production approach.

The results of these production systems are displayed in Figure 17. Compared to the current situation, all three production system will reduce the costs. This is caused by the fact that the production systems aim for optimality. Thereby, the production days and vials in the clean rooms are determined and this already results in a costs reduction.

As shown, the one-stop-shop production system is the most expensive with almost € XX spillage costs and more than € XX disposal costs. Followed by the clustering production system with more than € XX spillage costs and € XX disposal costs. The least expensive production system is the hybrid system with more than € XX spillage costs and € XX disposal costs.

Figure 17 - Results of the models for ZGT Pharmacy

6.2 Performance on employee deployment

This KPI focuses on the required number of employees to let the production system run smoothly. We measure this KPI in terms of the number of needed employees to fulfil all necessary process steps.

6.2.1 One-stop-shop

When a one-stop-shop production system is used, this has a major effect on employee deployment. First of all, the checks whether an appointment will continue can be completely omitted. These were necessary to make sure that there is no medication produced which is not used. Besides this, also other checks could be skipped. Checking whether there is both an appointment and a recipe is not necessary anymore since production will only take place when a patient is already at the hospital and an order is placed.

An extra step that needs to be added to the process is delivery. Currently, the delivery is done in batches. However, when a one-stop-shop production system is implemented it is important to deliver the medication directly after production to avoid long waiting times. Therefore, more transportation employees will be needed.

Furthermore, when the production of medication is done per order and not in batches, the production may take a bit longer. Steps like cleaning in-between production and preparing supplies have to be executed more frequently and therefore increase the production time. Besides this, producing via the one-stop-shop production system can lead to more fluctuation in workload since orders arrive during the day and need to be produced as quickly as possible. More than one order may arrive at the same moment and that the work accumulates. When the fluctuation is very high, more production employees may be needed.

To summarise we can say one employee less is needed because the checks are not needed anymore. However, an extra employee is needed for the delivery of the medication and maybe even some extra manpower is needed at the production of medication. So, approximately eight and a half employees are needed per day for this production system.

6.2.2 Clustering

Currently, as described in Section 2.4, eight employees are needed to produce medication via the clustering production system.

6.2.3 Hybrid

When a hybrid production system is used, the checks can be omitted for the one-stop-shop part of the production. For the clustering part, the trade-off must be made to which extent the costs of the manpower of the checks outweigh the cost savings of disposal when the produced medication is not used. In the hybrid production system, medication with a high cancellation probability is produced often via the one-stop-shop system, so the probability that the disposal costs are high is negligible. Therefore the checks could be omitted.

Besides this, also at the hybrid production system, the transportation must be extended and the workload may fluctuate. However, the latter will be less than with the one-stop-shop so we assume that this can be handled at the production.

Thus, one employee less is needed because the checks are not needed anymore and one extra employee is needed for the transportation. So approximately eight employees are needed to fulfil all needed steps in this production process.

6.2.4 Conclusion

For the clustering and hybrid production system, the same number of employees are needed, namely eight. For the one-stop-shop production system, eight and a half employees are needed.

6.3 Performance on patient experience

Two aspects will differ with various production systems and influence the patient experience. These are waiting time, which will be measured in an estimation of the waiting time, and the number of appointments, which will be an estimation too. Since two sub-KPIs are included in this KPI, we score the production systems on patient experience as a whole on a scale from 1 to 10. The higher the number, the better the patient experience.

6.3.1 One-stop-shop

In the one-stop-shop system patient only come to the hospital once. During this appointment, both the check-up and the administration of medication are done. Since the medication needs to be produced after the check-up, there is a waiting time for the patient. This waiting time is approximately 1.5 hours. However, this waiting time is known on forehand and the facilities can be set up to make this waiting time as bearable as possible. We score this as an 8.

6.3.2 Clustering

In this clustering production system, there is no waiting time since the medication is already produced. However, the patient needs to get to the hospital or another check-up location (for example to draw blood) before the administration to check their health. Per administration appointment, there are approximately 1.5 to 2 appointments for every patient. We score this as a 6.

6.3.3 Hybrid

As already mentioned, the hybrid production system is a combination of the two aforementioned. So, in a part of the cases, the patients will have only one appointment but during this appointment, there will be a waiting time. In the other part of the cases, there will not be a waiting time but there will be more appointments. For the patient experience, it can be quite confusing that different working methods are mixed up. We score this as a 4.

6.3.4 Conclusion

As described, every production system has its pros and cons in terms of the patient experience. Since on forehand known waiting time under good circumstances is acceptable, we score the one-stop-shop system as the best scoring on this KPI. The hybrid production system has, besides the pros and cons, an extra element namely that it can be confusing for the patients. Therefore we score this system as lowest. However, we must point out that the differences are not very substantial. With a good explanation of the approach and expectations that are met, patient satisfaction can be good in every production system.

6.4 Performance on hospital changes

This KPI described the size of the change that is necessary to make the production system work properly. We measure this on a scale from 1 to 10. 1 means that there are no changes and 10 means that there is a major change.

6.4.1 One-stop-shop

To implement a fully functioning one-stop-shop production system, some major changes are needed. First of all, the process of the production but also at other department needs to be revised. The change of the appointment in advance to appointments just before administration affects the working procedures of the oncology department. Besides this, there need to be waiting rooms for the patient while the medication is produced and the process at the day treatment needs to be adjusted.

Furthermore, transportation needs to be arranged for every produced medication instead of transportation in batches. Additionally, new production protocols must be written and the right vials must be stored to let the production be executed with the least costs.

We score this as 8 since there are multiple changes needed and mainly the change of the revision of the process will be a big one.

6.4.2 Clustering

The clustering production system is the currently used one. Therefore there will not be major changes when this production system is chosen. However, some improvements could be made. For example, a change in which vials are stored, based on the outcome of the models. Furthermore, some process improvements are suggested in Appendix C. Implementing these improvements requires small changes. We score this as 2.

6.4.3 Hybrid

The hybrid production system consists of both the one-stop-shop and the clustering production system. Therefore, it will take the same changes to obtain a hybrid production system as to obtain a one-stop-shop production system. However, when only a part of the medication is produced via the one-stop-shop approach, for example, due to a high cancellation probability, the change could be smaller. Little waiting area has to be arranged and also the transportation needs to undergo a smaller change. Therefore we score this change as 6.

6.4.4 Conclusion

For the one-stop-shop and hybrid production system, major changes are needed. Besides this, for the clustering approach, some improvements can be implemented, so this also results in a small change.

6.5 Explanation AHP

The decision which production system is best for ZGT Pharmacy is hard to make. This is mainly due to the fact that there are multiple stakeholders involved who have their own objectives. Besides this, there are also several alternatives to choose from and the KPIs are not always exact numbers resulting from measurements, but also scored on a scale. It is hard to compare both exact and approximated values. An Analytic Hierarchy Process (AHP) can handle these kinds of problems and will therefore be used during this research.

AHP is developed by Thomas Saaty between 1971 and 1975 while at the Wharton School (University of Pennsylvania). The AHP is a general theory of measurement. It is used to derive ratio scales from both discrete and continuous paired comparisons. These comparisons may be taken from actual measurements or from a fundamental scale that reflects the relative strength of preferences and feelings. The AHP has a special concern with departure from consistency, its measurement, and on dependence within and between the groups of elements of its structure (Saaty & Vargas, 2014 (2nd edition)).

The prime use of the AHP is the resolution of choice problems in a multicriteria environment. In that mode, its methodology includes comparisons of objectives and alternatives in a natural, pairwise manner. The AHP converts individual preferences into ratio-scale weights that are combined into linear additive weights for the associated alternatives. These resultant weights are used to rank the alternatives and thus assist the decision-maker in making a choice (Forman & Gass, 2001).

AHP is based on the principle that to make decisions, the experience and knowledge of people are at least as valuable as the data they use (Vargas, 1990).

The AHP is used in a wide range of applications. It is successful in diverse areas. Besides making decisions, for which we will use AHP, it is also used in prioritization and evaluation, resource allocation, benchmarking, quality management, health care, and strategic planning (Forman & Gass, 2001).

6.5.1 AHP method

We now provide insight into the working of the AHP. This information is retrieved from the book *Operation Research* by W. L. Winston (2003) and the article *The analytic hierarchy process—what it is and how it is used* by R. W. Saaty (1987).

The working of the AHP can be divided into four steps. Per step, we explain the procedure in steps. We have n objectives to measure the performance and m alternatives to choose from.

Step 1: Obtaining weights for each objective

First, we want to obtain the importance of each objective. This consists of 3 steps.

1. Make a n x n matrix A, known as the pairwise comparison matrix. Every entry in this matrix a_{ij} indicates how much more important objective i is than j. This is done on a 1-9 scale and the interpretation of the numbers can be found in Figure 18.
2. Normalize the matrix. This is done through dividing each column by the sum of the column, so the values in the column add up to 1.
3. Determine an approximation for the weights of the objectives, called w_i. This is done by the following formula: $w_i = \frac{\sum_{j=1}^{n} a_{norm\ ji}}{n}$. These values together result in a matrix **w** of n x 1.

Value of a_{ij}	Interpretation
1	Objective *i* and *j* are of equal importance.
3	Objective *i* is weakly more important than objective *j*.
5	Experience and judgment indicate that objective *i* is strongly more important than objective *j*.
7	Objective *i* is very strongly or demonstrably more important than objective *j*.
9	Objective *i* is absolutely more important than objective *j*.
2, 4, 6, 8	Intermediate values—for example, a value of 8 means that objective *i* is midway between strongly and absolutely more important than objective *j*.

Figure 18 - Interpretation of entries in a pairwise comparison matrix (Winston, 2003)

Step 2: Checking for consistency

To make sure that the comparison of the decision maker is consistent, we perform a check. This check consists of four steps

1. Compute $A\mathbf{w}^T$.
2. Compute $\frac{1}{n}\sum_{i=1}^{n} \frac{i^{th}\ entry\ in\ A\mathbf{w}^T}{i^{th}\ entry\ in\ \mathbf{w}^T}$.

3. Compute the consistency index
   CI = $\frac{(result\ of\ step\ 2)-n}{n-1}$.
4. Compare CI to random index (see Figure 19). If CI/RI < 0.10, the consistency in satisfactory so we accept the approximation.

n	RI
2	0
3	.58
4	.90
5	1.12
6	1.24
7	1.32
8	1.41
9	1.45
10	1.51

Figure 19 - Values of random index (Winston, 2003)

Step 3: Finding the scores of an alternative for an objective

Perform the following steps for each objective:

1. Make a pairwise comparison matrix of m x m of the alternatives.
2. Normalize the matrix
3. Find the approximation of s_{ij} for each alternative via $s_{ij} = \frac{\sum_{j=1}^{n} a_{norm\ ji}}{n}$.
4. Perform a consistency check as described in step 2.

Step4: Determining the overall score of each alternative

The previous steps have resulted in a weight for each objective and a score of each alternative on the objectives. The last step is to calculate an overall score for each alternative. This can be done via the following formula: $Overall\ score\ alternative\ j = \sum_{i=1}^{n} w_i * s_{ij}$

The best alternative according to AHP is the one with the highest overall score.

6.6 AHP results

In order to determine which production system is best for ZGT Pharmacy, we have to assign weights to the KPIs. We did this by interviewing the involved stakeholders and focused mostly on the management. Based on their option about what is most important for ZGT Pharmacy, we assigned the following weights to the KPIs which can be found in Table 17.

Table 17 - Weights of the KPIs

KPI	Weight
Waste of raw-material and end-products	0.31
Employee deployment	0.08
Patient experience	0.14
The magnitude of the change for the hospital	0.47

As shown, waste of raw material and end-products and the magnitude of the change for the hospital are most important for ZGT Pharmacy. Employee deployment and patient experience are less important. This is mainly due to the fact that the costs of the production of patient-specific medication is the main focus of this research. Besides this, a change for the hospital should only be made when

there is a significant improvement to achieve since this requires both manpower and other resources. Furthermore, the patient experience is only partly affected by the production system since it consists of various other too.

After determining the weights, we have to determine the scores for every production system on the KPIs. These can be found in Table 18. These are derived from the analyses as explained in Section 6.1 till 6.4.

Table 18 - Scores of the production systems on the KPIs

KPI	One-stop-shop	Clustering	Hybrid
Waste of raw-material and end-products	0.09	0.36	0.55
Employee deployment	0.20	0.40	0.40
Patient experience	0.57	0.29	0.14
The magnitude of the change for the hospital	0.11	0.58	0.31

Based on these weights and scores, the final scores are calculated. These can be found in Table 19. As shown, the clustering production system is best for ZGT Pharmacy, followed by Hybrid. The one-stop-shop production system is the worst.

Table 19 - Final scores

One-stop-shop	Clustering	Hybrid
0.175	0.457	0.368

When a clustering production system is chosen and the by the clustering model determined production days and vials in the clean rooms are chosen, this will result in a cost reduction of €119,103.-.

6.6.1 Sensitivity on weights

The final score is a combination of both the weights of the KPIs and the scores of the production systems on these KPIs. It is interesting to analyse how the final scores of the production systems relate to each other when the weights are different. Therefore we perform a sensitivity analysis on the weights of the KPIs. We included six cases in the analysis and compare these to each other and to the current weights. These cases are equal weights, inverse weights of the current ones and four cases which mainly focusses on one of the KPIs.

The results are shown in Table 20. In most cases result in the same production system ordering. However, when the focus is mainly on waste or patients, the order changes, but clustering is still the second best option. This is due to the fact that clustering has lower scores on waste and patients than respectively hybrid and one-stop-shop. On the other hand, these weights deviate to a great extent to the current weights, so we can conclude that the decision clustering as best production system for ZGT Pharmacy is a robust one.

Table 20 - Results sensitivity analysis KPI Weights

	Current	Equal	Inverse	Mostly Waste	Mostly Employees	Mostly Patients	Mostly Changes
Waste score	0.31	0.25	0.14	0.70	0.10	0.10	0.10
Employees score	0.08	0.25	0.47	0.10	0.70	0.10	0.10
Patients score	0.14	0.25	0.31	0.10	0.10	0.70	0.10
Hospital score	0.47	0.25	0.08	0.10	0.10	0.10	0.70
Final score One-stop-shop	0.18	0.24	0.18	0.15	0.22	0.44	0.16
Final score Clustering	0.46	0.41	0.46	0.38	0.40	0.33	0.51
Final score Hybrid	0.37	0.35	0.37	0.47	0.38	0.23	0.33

6.7 Implementation plan

Now we know which production system is best for ZGT Pharmacy. We can describe how to obtain this production system. Since the chosen production system is the same as the current production system, not a lot needs to be changed. However, some improvements can be made. In this section, we describe which improvements could be made and how these improvements could be implemented.

As mentioned, there is a difference in costs between the current way of clustering and the optimal way of clustering. This is due to 2 aspects, the vials stored in the clean room and the production day of the orders. The models determine the optimal production day while taking into account all orders in a week. However, this is not possible in the real situation since not all orders of a week are known on forehand. Therefore it is not possible to achieve the optimal situation. However, we can take the production planning of the models into account while providing improvement opportunities.

6.7.1 Production day

As described in Section 5.3, in the optimal clustering production system 80.6% of all orders are produced within 24 hours before administration. The percentage orders of expensive active substances and active substances with a higher cancellation probability are even higher, with 87.1% and 93.5% respectively. As a rule of thumb, we advise keeping clustering the same way, within 24 hours before administration. However, we have some recommendations to reduce costs.

We analysed the disposal costs and more than 85% of the yearly disposal costs are caused by only 18% of the active substances. This corresponds to the Pareto principle (Dunford, 2014). Pareto states that roughly 80% of the consequences come from 20% of the causes. These active substances are shown in Table 21. By knowing this, there is a clear focus point in the goal of reducing disposal costs. By for example producing these active substances less far in advance or by trying to make it clearer whether these treatments will continue. Furthermore, more insight into why these administration appointments are cancelled could help to prevent this.

Besides preventing disposal, the high percentage of the total disposal costs per year is also due to the high costs of these active substances. The prices are not something that is in control of ZGT Pharmacy. However, they could investigate if there is a vial available with a more suitable volume for these active substances or with a lower price and the same volume. This would help reduce both disposal and spillage costs.

Table 21 - Active substances with a high percentage disposal costs

Active substance	Percentage of the total disposal costs per year
Trastuzumab Emtansine	25%
Pertuzumab	25%
Eribuline	16%
Panitumumab	8%
Irinotecan HCl	6%
Bevacizumab	6%
Bendamustine	3%

6.7.2 Vials

Since we advise to keep clustering one day in advance, the vials stored in the clean room should be adapted to this. In order to determine the optimal vials in the clean room, we ran the clustering model while it was only possible to produce an order within 24 hours before administration. The optimal vials for this situation are displayed in Table 22.

By replacing the current vials with the vials as stated in Table 22, a cost reduction of 16% can be achieved. Besides this, when the situation within ZGT Pharmacy changes, due to for example a growing or shrinking demand or a change in raw materials, the model can be run again to gain insight on which vials must be stored to achieve the most optimal situation.

Table 22 - Best vials to store for clustering

Active substance	Volume of vial 1 (in mg)	Volume of vial 2 (in mg)	Volume of vial 3 (in mg)
Abatacept	250		
Azacitidine	100		
Bendamustine	100		
Bevacizumab	100		
Bleomycine	15		
Bortezomib	3.5		
Botuline A toxine	100	300	
Cabazitaxel	60		
Carboplatine	50		
Cisplatine	10		
Cyclofosfamide	500		
Dacarbazine citraat	200		
Dexrazoxan	500		
Docetaxel	20		
Doxorubicine	10		
Doxorubicine liposomaal	20	50	
Epirubicine HCl	50		
Eribuline	0.44	0.88	
Etoposide	100		
Fludarabine	50		
Fluorouracil	250		
Ganciclovir	500		
Gemcitabine	200	1000	
Irinotecan HCl	30	50	
Methotrexaat	7.5		
Mitomycine-C	20		
Mitoxantron	20		
Oxaliplatin	50	200	
Paclitaxel	30	100	300
Paclitaxel (Albumine gebonden)	100		
Panitumumab	100		
Pemetrexed	100	500	
Pertuzumab	420		
Thiotepa	15		
Trastuzumab Emtansine	100	160	
Vinblastine sulfaat	10		
Vincristine sulfaat	1		
Vinorelbine	10		

6.7.3 Dose banding

As shown in Figure 15, dose banding provides a possibility to reduce the costs of the production of patient-specific medication. Two kinds of modifications can be made, standardise dosages by rounding to tens or allow a dose banding percentage. This can lead to a cost reduction of respectively 24% and 47% on top of the saving that can be made by replacing the vials. This lead to an extra cost reduction of €XX or even €XX.

Implementing rounding dosages to tens is easily implementable via CATO, the system that is used while producing. Therefore we advise implementing this directly and meanwhile search for a way in which

dose banding within a range of 10% can be achieved. However, before this can be implemented, there must be approval from the doctors and pharmacists.

6.7.4 Phaseals

As described in Section 5.5.2, using phaseals can lead to a cost reduction of 75% for clustering. Therefore it is a very promising method to reduce spillage costs. However, before this can be implemented it is important to have pharmaceutical evidence that keeping open vials with phaseals will not do any harm and is in line with the GMP-Z guidelines. Therefore we advise performing research on whether it is possible to use phaseals. Subsequently, the use of phaseals should be included in the production protocol.

We advise to keep in mind the rule of thumb as stated in Section 3.3.4. When the costs of a phaseal are lower than the expected gain when using a phaseal, it is worth using it. This results in the following calculation:

$$Remaining\ vial\ volume\ in\ mg\ \times price\ per\ mg \times probability\ that\ the\ remaining\ volume\ will\ be\ used\ within\ the\ shelf\ life$$

when the calculation is greater than the *price of a phaseal*, the phaseal must be used.

6.7.5 Process improvements

Last, to improve the production process and to reduce costs, the process improvements as described in Appendix C should be implemented. These will result in fewer employees needed and a smoother flow within the process.

7. Conclusion

In this chapter, we describe our conclusion in Section 7.1, followed by the recommendations for ZGT Pharmacy in Section 7.2. At last, we describe some interesting topics for further research that follow out of our research in Section 7.3.

7.1 Conclusion

We have conducted a research with the following objective:

> *The goal of this research is to find a production system that minimises spillage and disposal and thereby the necessity to perform checks, while maintaining the current production quantity.*

To find the most suitable production system for patient-specific medication at ZGT Pharmacy, we investigated which various production systems exist and how these production systems can be improved.

Within literature, not much is written on production systems of patient-specific medication. However, in practise some examples can be found. There are three production systems that are suitable for ZGT Pharmacy. These are a one-stop-shop production system, a clustering production system, and a hybrid production system. These production systems can be improved by selecting the most optimal vials, the best production day at the clustering productions, and the best hybrid trade-off.

In order to find the best production system for ZGT Pharmacy, we have built three MILP models which determine the most optimal way of production to reduce the costs of waste of raw material and end-products. Besides this KPI, also three other KPIs are part of this research. These KPIs are employee deployment, patient experience, and the magnitude of change for the hospital.

In order to find the best production system for ZGT Pharmacy, we performed an AHP. Based on the management of ZGT Pharmacy, the weights of the KPIs are determined. The scores of the production systems on the KPIs are determined based on the analyses of the performance of the production systems on these KPIs.

The AHP determines that clustering is the best production system for ZGT Pharmacy. Followed by, the hybrid production system and lastly, the one-stop-shop production system.

Although we advise the production system at ZGT Pharmacy to stay the same based on the AHP, improvements can be made to further improve the situation. By replacing the current vials in the clean room by the optimal determined ones, a cost reduction of €XX can be achieved. Furthermore, spillage and disposal costs can be reduced by focusing of the orders with a high price or cancellation probability.

Besides improve the current situation of ZGT Pharmacy, this research is also scientifically relevant. As mentioned before, there is little research performed on this topic already. The models of the production systems as built during this research and the performance of the production system within different situations provide not only insight for ZGT Pharmacy, but also for other hospitals and thereby is scientifically valuable.

Furthermore, we have several recommendations and subjects for further research to improve the situation of ZGT Pharmacy even further. These will be mentioned in the upcoming sections.

7.2 Recommendations

In order to achieve a more optimal situation for ZGT Pharmacy, we have seven recommendations. These recommendations will help by improving the current situation through reducing costs of waste of raw material and end-products, let the process run more smoothly and gain a better view on the situation from where the process can even be improved further.

Our first recommendation is to keep the current production system, which is clustering. Based on the AHP results, this is the best production system. However, some improvements should be made to reduce the costs of waste of raw material and end-products.

One of the improvements is the vials in the clean room, we recommend changing these to the vials as stated in Table 22 since this leads to a reduction of the spillage and disposal costs. Furthermore, we recommend keeping in mind the active substances that cause high disposal costs. Adding extra attention to making sure that these treatments will continue when medication is produced is worth some extra effort.

Third, we recommend implementing the process improvements as described in Appendix C. These improvements lead to a reduction of employees needed and thereby let the process run more smoothly.

Besides this, also dose banding be can implemented to reduce costs. We recommend to start with rounding to tens since this is easy to implement. While this is used, we advise to research how dose banding within a range of 10% could be implemented.

Besides implementing the insights that are gained during this research, we also recommend collecting more data to make analyses more accurate. Especially on cancellation of appointments, there is not a lot of data available and this data is also not very reliable since cancellation can appear in several parts of the process and is not always documented. By gaining more information on when a cancellation of a treatment is applied, the analyses on disposal costs will be more valid. In this way, the models will result in a better optimization of the current situation.

Furthermore, we recommend running the models again when the situation within ZGT Pharmacy has changed (drastically). This has two reasons. First, the stored vials in the clean rooms can be redetermined and this can result in a reduction of the costs of spillage and disposal. Besides this, when the situation within ZGT Pharmacy changes drastically, the models can also be used to redefine the choice of which production system is best for ZGT Pharmacy.

At last, we recommend expending the research to the aseptic medication. Within this research we only took into account cytostatic medication, but also within the aseptic medication, improvements can be made. For this category of medication, we think it is useful to carry out the same research steps as performed for cytostatic medication. Especially the determination of the best models for ZGT Pharmacy and thereby the most optimal way of producing medication within these models provide promising cost savings.

7.3 Further research

Besides recommendations, we also acquired several aspects that require further research to improve the production process of patient-specific medication within ZGT Pharmacy.

When more data on cancellation is acquired, a good analysis of when medication is cancelled can be conducted. Thereby the production can respond to this by changing the production times. For example, when cancellations are mainly become known between 8 AM and 1 PM, the production of expensive medication can start after 1 PM. This would make the checks whether a treatment will continue less

important and reduce the costs of disposal. However, before this can be done, more accurate data on cancellations should be documented.

Furthermore, the experiments on phaseals showed that a large cost reduction can be made when phaseals are used. To be able to use phaseals on vials, more research on the shelf life of medication with a phaseal and the sustainability of the active substance should be executed. Since these cost savings could be so large, we think that this is a very important subject in order to further reduce spillage costs.

To further decrease the probability that a treatment will be cancelled, a more extensive analysis of the patient characteristics could be done. By analysing which factors affect the continuation of the treatment, disposal can be prevented and checks become less needed. To be able to perform such a analysis, data on these patient characteristics are needed.

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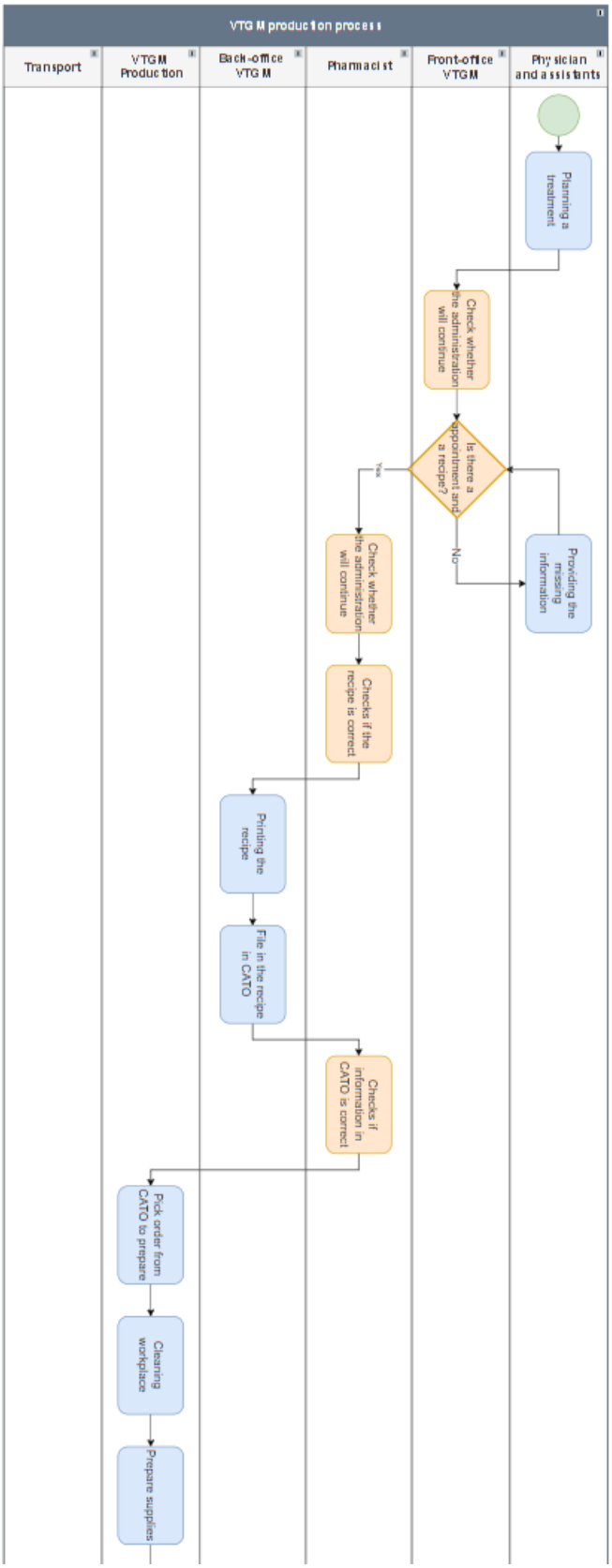
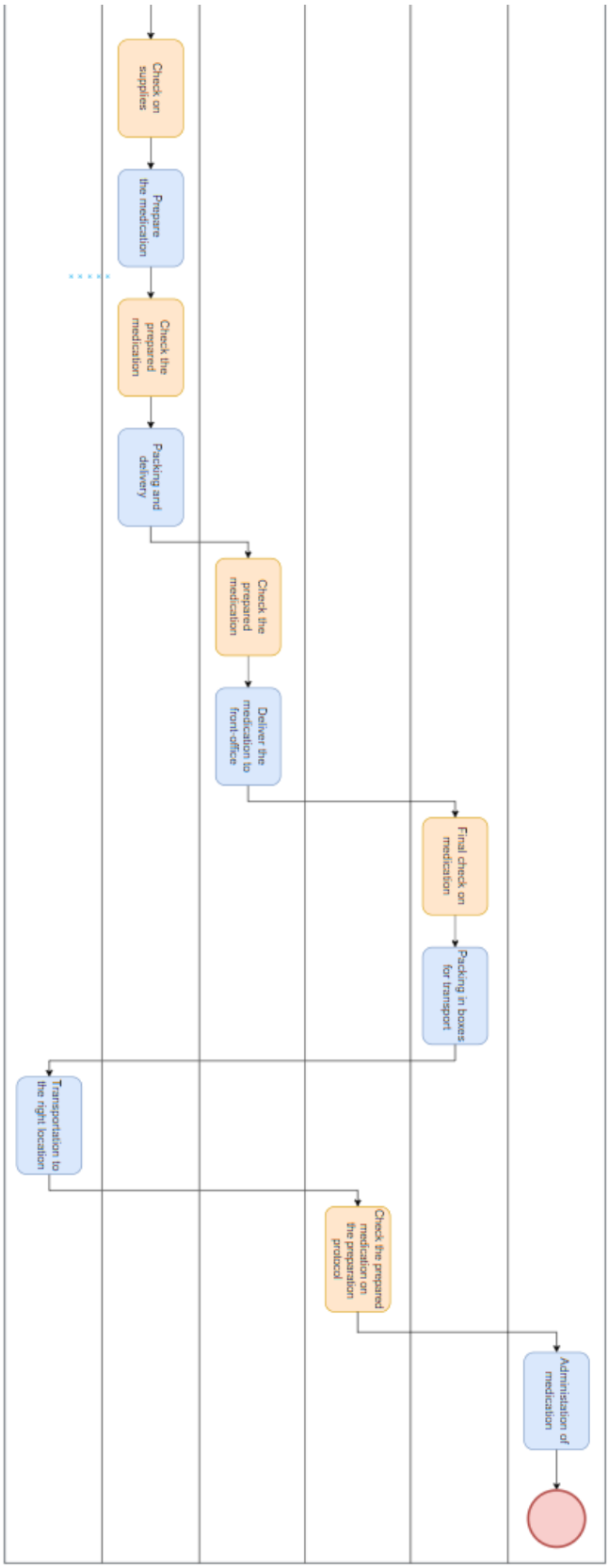
Appendix A

A.1 Process map




Check on supplies
Prepare the medication
Check the prepared medication
Packing and delivery
Check the prepared medication
Deliver the medication to front-office
Final check on medication
Packing in boxes for transport
Transportation to the right location
Check the prepared medication on the preparation protocol
Administration of medication

Appendix B

B.1 Case mix ZGT Pharmacy

Appendix C

C.1 Process improvements Clustering

With is knowledge, we can take a critical look at the cluster production process. Within this process, there are several steps that could be categorised as non-value added. In Figure 6 the production process of clustering is displayed with a visualisation of the value-added and non-value added activities.

First of all, the missing information from the doctor or the assistants, provide extra work and checks which could be covered as extra-processing. To remove this step, the appointment and recipe should be added to the system at once.

Furthermore, the check whether the appointment takes place is executed by both the front-desk VTGM and the pharmacist. There should be an alignment who is responsible for this instead of checking it twice. Checking whether the treatment will take place could be seen as waste on itself, however, since more waste, in terms of disposal of end-products, can be prevented, we assume that this step in the clustering process is unavoidable.

The last big change that could be made is making a better connection between HiX and CATO, the two software programs that are used to record patient information, recipes, and production protocols. Currently, the information of HiX should be transferred manually to CATO. Because errors can be made here, the recipe should also again be checked by a pharmacist. An electronic transfer could make these steps removable.

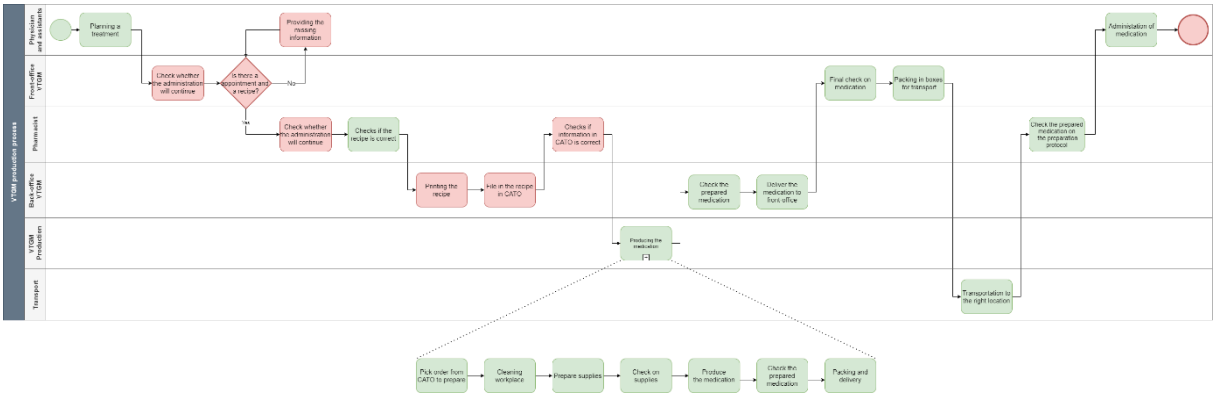


Figure 20 - Process map clustering with visualisation of action categories

Appendix D

D.1 Overview of the orders per active substance

Active substance	Times produced	Cancellation probability	Shelf life in days	Mean price per mg
Abatacept	82	0.00%	1	
Azacitidine	272	1.59%	1	
Bendamustine	52	14.29%	2	
Bevacizumab	504	2.03%	2	
Bleomycine	32	0.00%	4	
Bortezomib	566	0.61%	4	
Botuline A toxine	1456	0.58%	4	
Cabazitaxel	51	0.00%	1	
Carboplatine	982	1.72%	4	
Cisplatine	217	1.38%	4	
Cyclofosfamide	693	2.19%	4	
Dacarbazine citraat	38	2.63%	1	
Dexrazoxan	3	0.00%	0	
Docetaxel	502	3.08%	4	
Doxorubicine	603	2.42%	4	
Doxorubicine liposomaal	20	0.00%	5	
Epirubicine HCl	57	1.75%	4	
Eribuline	72	14.29%	4	
Etoposide	485	1.03%	4	
Fludarabine	6	0.00%	4	
Fluorouracil	852	5.42%	5	
Ganciclovir	29	0.00%	8	
Gemcitabine	589	6.02%	4	
Irinotecan HCl	365	6.38%	4	
Methotrexaat	183	0.00%	4	
Mitomycine-C	124	0.00%	4	
Mitoxantron	1	0.00%	4	
Oxaliplatin	745	4.57%	4	
Paclitaxel	2279	2.15%	4	
Paclitaxel (Albumine gebonden)	67	0.00%	0	
Panitumumab	65	4.55%	1	
Pemetrexed	202	0.00%	3	
Pertuzumab	708	1.07%	1	
Thiotepa	7	0.00%	1	
Trastuzumab	103	4.17%	1	
Vinblastine sulfaat	67	1.49%	4	
Vincristine sulfaat	264	3.17%	4	
Vinorelbine	86	5.26%	4	

Appendix E

E.1 Vials One-stop-shop

Active substance	Volume of vial 1 (in mg)	Volume of vial 2 (in mg)	Volume of vial 3 (in mg)
Abatacept	250		
Azacitidine	100		
Bendamustine	100		
Bevacizumab	100		
Bleomycine	15		
Bortezomib	3.5		
Botuline A toxine	100		
Cabazitaxel	60		
Carboplatine	50		
Cisplatine	10		
Cyclofosfamide	500		
Dacarbazine citraat	200		
Dexrazoxan	500		
Docetaxel	20		
Doxorubicine	10	50	
Doxorubicine liposomaal	20	50	
Epirubicine HCl	50		
Eribuline	0.44	0.88	
Etoposide	100		
Fludarabine	50		
Fluorouracil	250		
Ganciclovir	500		
Gemcitabine	200	1000	
Irinotecan HCl	4	50	
Methotrexaat	7.5		
Mitomycine-C	20		
Mitoxantron	20		
Oxaliplatin	50	200	
Paclitaxel	30	100	150
Paclitaxel (Albumine gebonden)	100		
Panitumumab	100		
Pemetrexed	100	500	
Pertuzumab	420		
Thiotepa	15		
Trastuzumab Emtansine	100	160	
Vinblastine sulfaat	10		
Vincristine sulfaat	2		
Vinorelbine	10		

E.2 Vials Clustering

Active substance	Volume of vial 1 (in mg)	Volume of vial 2 (in mg)
Abatacept	250	
Azacitidine	100	
Bendamustine	25	100
Bevacizumab	100	
Bleomycine	15	
Bortezomib	3.5	
Botuline A toxine	300	500
Cabazitaxel	60	
Carboplatine	450	600
Cisplatine	10	
Cyclofosfamide	500	
Dacarbazine citraat	200	
Dexrazoxan	500	
Docetaxel	160	
Doxorubicine	50	
Doxorubicine liposomaal	20	50
Epirubicine HCl	50	
Eribuline	0.44	0.88
Etoposide	100	
Fludarabine	50	
Fluorouracil	250	
Ganciclovir	500	
Gemcitabine	1000	
Irinotecan HCl	4	50
Methotrexaat	7.5	50
Mitomycine-C	20	
Mitoxantron	20	
Oxaliplatin	200	
Paclitaxel	300	
Paclitaxel (Albumine gebonden)	100	
Panitumumab	100	
Pemetrexed	100	500
Pertuzumab	420	
Thiotepa	15	
Trastuzumab Emtansine	100	160
Vinblastine sulfaat	10	
Vincristine sulfaat	1	2
Vinorelbine	10	

E.3 Vials Hybrid

Active substance	Volume of vial 1 (in mg)	Volume of vial 2 (in mg)
Abatacept	250	
Azacitidine	100	
Bendamustine	100	
Bevacizumab	100	
Bleomycine	15	
Bortezomib	3.5	
Botuline A toxine	300	
Cabazitaxel	60	
Carboplatine	50	450
Cisplatine	10	
Cyclofosfamide	500	
Dacarbazine citraat	200	
Dexrazoxan	500	
Docetaxel	20	
Doxorubicine	10	50
Doxorubicine liposomaal	20	50
Epirubicine HCl	50	
Eribuline	0.44	0.88
Etoposide	100	
Fludarabine	50	
Fluorouracil	250	
Ganciclovir	500	
Gemcitabine	100	
Irinotecan HCl	4	50
Methotrexaat	50	
Mitomycine-C	20	
Mitoxantron	20	
Oxaliplatin	50	200
Paclitaxel	30	100
Paclitaxel (Albumine gebonden)	100	
Panitumumab	100	
Pemetrexed	100	500
Pertuzumab	420	
Thiotepa	15	
Trastuzumab Emtansine	100	160
Vinblastine sulfaat	10	
Vincristine sulfaat	1	2
Vinorelbine	10	

E.4 Production day Clustering

All orders

Production day	Orders produced at this day (%)
1	80.6%
2	10.9%
3	4.8%
4	3.4%
5	0.2%

Expensive active substances

Production day	Orders produced at this day (%)
1	87.1%
2+	12.9%

Active substances with a high cancellation probability

Production day	Orders produced at this day (%)
1	93.5%
2+	6.5%

Per active substance

Active substance	Orders produced at day 1	Orders produced further in advance
Abatacept	100%	0%
Azacitidine	100%	0%
Bendamustine	100%	0%
Bevacizumab	89%	11%
Bleomycine	0%	100%
Bortezomib	72%	28%
Botuline A toxine	82%	18%
Cabazitaxel	100%	0%
Carboplatine	77%	23%
Cisplatine	74%	26%
Cyclofosfamide	78%	22%
Dacarbazine citraat	100%	0%
Dexrazoxan	N.A.	N.A.
Docetaxel	91%	9%
Doxorubicine	84%	16%
Doxorubicine liposomaal	N.A.	N.A.
Epirubicine HCl	100%	0%
Eribuline	100%	0%
Etoposide	65%	35%
Fludarabine	0%	100%
Fluorouracil	83%	17%
Ganciclovir	N.A.	N.A.
Gemcitabine	91%	9%
Irinotecan HCl	93%	7%
Methotrexaat	0%	100%
Mitomycine-C	0%	100%
Mitoxantron	N.A.	N.A.
Oxaliplatin	72%	28%
Paclitaxel	92%	8%
Paclitaxel (Albumine gebonden)	100%	0%
Panitumumab	100%	0%
Pemetrexed	25%	75%
Pertuzumab	100%	0%
Thiotepa	N.A.	N.A.
Trastuzumab Emtansine	100%	0%
Vinblastine sulfaat	100%	0%
Vincristine sulfaat	33%	67%
Vinorelbine	0%	100%

E.4 Production day Hybrid

All orders

Production day	Orders produced at this day (%)
1	69.3%
2	17.8%
3	8.2%
4	4.3%
5	0.4%

Expensive active substances

Production day	Orders produced at this day (%)
1	77.8%
2+	22.2%

Active substances with a high cancellation probability

Production day	Orders produced at this day (%)
1	37.5%
2+	62.5%

Per active substance

Active substance	Orders produced at day 1	Orders produced further in advance
Abatacept	N.A.	N.A.
Azacitidine	100%	N.A.
Bendamustine	N.A.	N.A.
Bevacizumab	77%	23%
Bleomycine	N.A.	N.A.
Bortezomib	65%	35%
Botuline A toxine	82%	18%
Cabazitaxel	N.A.	N.A.
Carboplatine	66%	34%
Cisplatine	30%	70%
Cyclofosfamide	68%	32%
Dacarbazine citraat	N.A.	N.A.
Dexrazoxan	N.A.	N.A.
Docetaxel	64%	36%
Doxorubicine	61%	39%
Doxorubicine liposomaal	N.A.	N.A.
Epirubicine HCl	N.A.	N.A.
Eribuline	N.A.	N.A.
Etoposide	65%	35%
Fludarabine	N.A.	N.A.
Fluorouracil	61%	39%
Ganciclovir	N.A.	N.A.
Gemcitabine	56%	44%
Irinotecan HCl	N.A.	N.A.
Methotrexaat	71%	29%
Mitomycine-C	N.A.	N.A.
Mitoxantron	N.A.	N.A.
Oxaliplatin	74%	26%
Paclitaxel	78%	22%
Paclitaxel (Albumine gebonden)	N.A.	N.A.
Panitumumab	N.A.	N.A.
Pemetrexed	20%	80%
Pertuzumab	N.A.	N.A.
Thiotepa	N.A.	N.A.
Trastuzumab Emtansine	N.A.	N.A.
Vinblastine sulfaat	N.A.	N.A.
Vincristine sulfaat	N.A.	N.A.
Vinorelbine	N.A.	N.A.

E.5 Production system decision Hyrbid

All orders

One-stop-shop	Clustering
45.3%	54.7%

Expensive active substances

One-stop-shop	Clustering
84.8%	15.2%

Active substances with a high cancellation probability

One-stop-shop	Clustering
69.3%	30.7%

Per active substance

Active substance	One-stop-shop	Clustering
Abatacept	100%	0%
Azacitidine	79%	21%
Bendamustine	100%	0%
Bevacizumab	26%	74%
Bleomycine	100%	0%
Bortezomib	9%	91%
Botuline A toxine	4%	96%
Cabazitaxel	100%	0%
Carboplatine	37%	63%
Cisplatine	57%	43%
Cyclofosfamide	13%	87%
Dacarbazine citraat	100%	0%
Dexrazoxan	N.A.	N.A.
Docetaxel	26%	74%
Doxorubicine	49%	51%
Doxorubicine liposomaal	N.A.	N.A.
Epirubicine HCl	100%	0%
Eribuline	100%	0%
Etoposide	23%	78%
Fludarabine	100%	0%
Fluorouracil	55%	45%
Ganciclovir	N.A.	N.A.
Gemcitabine	81%	19%
Irinotecan HCl	100%	0%
Methotrexaat	22%	78%
Mitomycine-C	100%	0%
Mitoxantron	N.A.	N.A.
Oxaliplatin	48%	52%
Paclitaxel	34%	66%
Paclitaxel (Albumine gebonden)	100%	0%
Panitumumab	100%	0%
Pemetrexed	6%	94%
Pertuzumab	100%	0%
Thiotepa	N.A.	N.A.
Trastuzumab Emtansine	100%	0%
Vinblastine sulfaat	100%	0%
Vincristine sulfaat	100%	0%
Vinorelbine	100%	0%

Appendix F

F.1 Overview of the results per week

Total costs per production system per week

Week	One-stop-shop	Clustering	Hybrid	Nr orders
1	9131	5282	4557	254
2	8287	5978	5159	270
3	5593	3299	2373	281
4	9749	6802	5961	252
5	9608	6760	5778	251
6	5816	2801	1819	265
7	7086	5724	4899	254
8	5552	5024	4208	191
9	3636	2889	1825	214
10	5358	4494	3567	193
11	6637	3058	2365	190
12	3076	2165	1281	207
13	6769	6122	5130	187
14	9452	8400	7833	175
15	4766	3337	2326	234
16	8770	5672	4924	259
17	9276	6720	5600	255
18	7968	7097	5765	240
19	8111	4774	3724	286
20	8194	6499	5426	225
21	7701	7143	6175	251
22	7925	4140	2990	280
23	9125	6248	5185	299
24	10340	6522	5691	256
25	8019	5575	4349	280
26	10883	7070	5911	253
27	9613	6851	5951	238
28	6365	3975	3048	216
29	12551	7640	6145	303
30	16661	6260	5398	293
31	11570	5091	4025	286
32	10832	4007	3019	325
33	16666	7808	6845	271
34	14572	5590	4771	344
35	9121	5963	4650	244
36	9336	5496	4748	263
37	5362	4639	3932	241
38	9717	4586	3516	263
39	9744	6707	5768	262
40	7142	6015	5348	208
41	9363	5132	3939	293
42	12275	5952	5140	308
43	12898	8844	7564	253
44	12733	6521	5513	332
45	10635	5108	4291	291
46	8834	3952	3166	292
47	11020	5737	4954	258
48	8010	4633	3945	259
49	10178	5872	4767	323
50	9881	5254	4521	285
51	10122	6930	5207	284
52	7242	4482	3608	252
	469267	288641	238595	13429

Time horizon: per week

Week	One-stop-shop	Clustering	Hybrid	Nr orders
1	474790	274672	238964	13208
2	430938	310863	268268	14040
3	290831	171541	123396	14612
4	506937	353704	309995	13104
5	499633	351545	300482	13052
6	302424	145673	94566	13780
7	368455	297630	254726	13208
8	288727	261258	218829	9932
9	189079	150235	94877	11128
10	278601	233702	185502	10036
11	345131	159003	122975	9880
12	159946	112570	66600	10764
13	351972	318346	266752	9724
14	491485	436780	407312	9100
15	247809	173539	120970	12168
16	456028	294944	256045	13468
17	482330	349431	291189	13260
18	414358	369053	299780	12480
19	421761	248264	193633	14872
20	426066	337970	282169	11700
21	400472	371435	321077	13052
22	412123	215280	155488	14560
23	474502	324903	269644	12428
24	537665	339144	295921	13312
25	416985	289892	226137	14560
26	565904	367654	307371	13156
27	499880	356244	309471	12376
28	331002	206704	158521	11232
29	652659	397287	319549	15756
30	866372	325520	280711	15236
31	601622	264752	209281	14872
32	563252	208345	158965	16900
33	866645	406013	355939	14092
34	757735	290666	248099	17888
35	474278	310091	241796	12688
36	485471	285793	246906	13676
37	278807	241212	204459	12532
38	505280	238466	182855	13676
39	506668	348759	299931	13624
40	371385	312777	278115	10816
41	486853	266839	204807	15236
42	638291	309520	267284	16016
43	670677	459901	393335	13156
44	662112	339090	286663	17264
45	553015	265598	223111	15132
46	459358	205492	164654	15184
47	573045	298333	257583	13416
48	416525	240916	205122	13468
49	529251	305344	247872	16796
50	513812	273232	235100	14820
51	526352	360364	270760	14768
52	376592	233064	187359	13104

Time horizon: per 4 weeks (month)

Month	One-stop-shop	Clustering	Hybrid	Nr orders
1	425874	277695	234656	13741
2	364810	264027	217151	12493
3	243189	163877	117488	10452
4	386823	305902	262770	11115
5	436128	326179	266693	13078
6	456191	312690	260533	13338
7	453443	305124	250375	12831
8	670976	298976	241627	15691
9	646032	323141	273185	14586
10	415535	285304	241340	12662
11	614483	343838	288022	15418
12	500486	252585	212617	14300
13	486502	293001	235272	14872

Time horizon: per 12 weeks (quarter)

Quater	One-stop-shop	Clustering	Hybrid	Nr orders
1	345190	241596	195687	12036
2	442114	316791	263595	12932
3	568436	298450	247268	14196
4	521328	297729	247828	14552

Time horizon: per half-year

Half-year	One-stop-shop	Clustering	Hybrid	Nr orders
1	393652	279194	229641	12484
2	544882	298089	247548	14374