Monitoring and controlling critical process parameters at the retort production line of Abbott Zwolle

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Preface

After a very interesting and learningfull period at Abbott I'm proud to complete my master Industrial Engineering and Management. With much joy I look back on the master program, during which I had a great time at the University of Twente and the city of Enschede. The period of writing my thesis has been very informative to me. During the completion of my thesis I've learned a whole lot and I'm thankfull for the opportunity of graduating at Abbott.

While writing my thesis I did not only learn a lot about process monitoring and control. Also, writing a structured report and evidently substantiating my choices are areas in which I greatly developed myself during the past 6 months. To this end I would very much like to thank Leo van der Wegen, who was my first supervisor on behalf of the University of Twente. During the period of writing my thesis Leo was always very helpful when assisting me. He helped a great deal in structuring my research approach and he was always able to steer me in the right direction when things got though. Also, I would like to thank Engin Topan, my second supervisor. I greatly appreciate his theoretical input and the ideas that he shared during our progress meetings.

I'm also very greatful to the people at Abbott who supported me during the execution of my graduation project. Especially I would like to express my gratitude to Jaap Verweij, my supervisor at Abbott. Jaap was always willing to make room in his busy schedule to support me. I'm thankful for his sharp remarks and the help that he gave me throughout the project. I want to thank Tom Torpstra for making this project possible at the very start of this year. Also the choaching and the trust that he gave me are greatly appreciated. Finally, I would also like to thank Boris and Vincent. Without them the first steps of an implementation would have never been possible.

Especially I want to thank my family and loved ones, since I know I can always count on their endless support.

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Summary

Abbott Laboratories Zwolle produces medical nutrition consisting of powder as well as liquid products. An important process step for the production of Abbott's liquid products is the sterilization process step. During our research we investigate the best way to monitor and control the critical process parameters of the sterilization process. We answer the following main research question:

What is the best way to monitor and control critical process parameters at the retort production line of Abbott Zwolle?

We answer the main research question by answering multiple sub questions. First, we analyze the current situation at the retort production line. Next, we conduct a literature review about process monitoring and control to find ways to improve the current situation. After conducting the literature review we determine the best way for Abbott to monitor and control their critical process parameters, including an out-of-control-action plan. From our research we draw the following conclusions:

1. Current situation

In the current situation we conclude that we do not exactly know which process parameters influence the sterility of the products. Also, we conclude that some of the process parameters are guarded with alarms, while others are not. The alarms that are present in the current situation are based on past validations and product specifications. There is no use of a tool which helps to timely detect deviations in the sterilization process based on statistics or process variability.

2. Selection of critical process parameters

We determine the process parameters that influence the sterility of the products with help of a failure mode and effects analysis. In consultation with process experts we determine the way in which we measure each critical process parameter. In the table below, we summarize our conclusions regarding the selection of critical process parameters and the way in which we measure them, for each sterilization process step.

Process step	Process parameter	Measurement
End of filling PV	Water level PV	Single measurement
	Temperature PV	Single measurement
Come-up	Step time	Single measurement
	Flow	Average
	Water level	Average
Sterilization	Temperature PV	Continuous
	Flow	Continuous
	Water level PV	Continuous
	Pressure PV	Continuous
Cooling	Step time	Single measurement

3. Selection of method for monitoring and controlling critical process parameters

The best way to monitor and control critical process parameters at the retort production line is to use a control chart for individuals with six sigma control limits for every critical process parameter. To ensure we timely detect process changes the process experts of the retort production line are responsible for analyzing the control charts daily. When a critical process parameter is out of control the process experts are responsible for taking the right preventive action. Determining the right preventive action should be done with help of the out-of-control-action plan, which states who needs to act in which way when a process parameter is out of control. In the following table we summarize the out-of-control-action plan.

Out of control action plan (OCAP)				
	Process parameter	Deviation	Preventive actions/controls	Responsible for execution
1	Temperature	Outside control limits	1) Can be caused by wrong water level or pressure. Therefore, check stability of these parameters. 2) Check temperature sensor and clean or replace if required.	Manufacturing Excellence Engineer, Process Engineer and Mechanical Specialist
2	Flow	Outside control limits	1) Inspection circulation valves 2) Remove and inspect circulation pipe 3) Root cause analysis	1) Mechanical Specialist 2) Mechanical Specialist 3) Manufacturing Excellence Engineer & Process Engineer
		Flow suddenly drops to 0 during cooling process step	Sudden drop can be caused by a fouling flow meter. Therefore, clean the flow meter with acid.	1) Mechanical Specialist
3	Water level	Outside control limits	1) Check pressure sensor and clean or replace if required 2) Check pressure control valves circuit (PCV 11, 14 & 45) 3) Root cause analysis	1) Mechanic 2) Mechanic 3) Manufacturing Excellence Engineer & Process Engineer
4	Pressure	Outside control limits	1) Check sensorand clean or replace if required 2) Check pressure control valves circuit (PCV 11, 14 & 45) 3) Root cause analysis	1) Mechanic 2) Mechanic 3) Manufacturing Excellence Engineer & Process Engineer
5	Come-up time	Outside control limits	1) Inspection circulation valves 2) Remove and inspect circulation pipe 3) Root cause analysis	1) Mechanical Specialist 2) Mechanical Specialist 3) Manufacturing Excellence Engineer & Process Engineer

4. Value of monitoring and control method

The value of process monitoring and control lays in a reduction of food safety hazards and continuous improvement of the production process. With our solution we detect significant process changes within a day, which is much shorter compared to the previous situation. We estimate process monitoring and control saves the Process Engineer up to 8 hours per week and increases the capacity of the retort production line with 4 hours per week. The costs mainly consist of evaluating control charts and the execution of preventive actions. Evaluating control charts takes roughly 1 hour per week. Recalculating control limits takes roughly 8 hours for all process parameters.

Based on the findings of our study we recommend:

1. Follow up recommendations for further imlpementation

During our study we implemented a large part of the process monitoring and control solution. To reach a sustainable implementation we recommend adding the remaining critical process parameters to the process monitoring and control dashboard as well as documenting the process monitoring and control actions in Abbott's quality management system.

2. Alternative monitoring and control options

We recommend using an ideal curve for process monitoring and control when this become a possibility in the future. A curve gives us all the information that we need to know and reduces the number of control charts that we need to evaluate. Furthermore we currently do not recommend using exponentially weighted or cumulative sum charts to monitor the process due to the increased number of alarms and unnecessary complexity of process monitoring.

3. Specification limits

We recommend further research to determine the exact relation between the critical process parameters and the sterility of the products. The specification limits can be used together with the control limits to determine how well the process is capable of producing products that are within specification limits.

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Glossary

Abbreviation	Description
AMS	Action Management System
ARL	Average Run Length
CCP	Critical Control Point
CLT	Central Limit Theorem
Cusum	Cumulative Sum
DOE	Design Of Experiments
EDF	Empirical Distribution Function
EWMA	Exponentially Weighted Moving Average
FMEA	Failure Mode and Effects Analysis
FMECA	Failure Mode Effects and Criticality Analysis
LCL	Lower Control Limit
LSL	Lower Specification Limit
OCAP	Out of Control Action Plan
OPEX	Operational Excellence
PMC	Process Monitoring Control
PV	Process Vessel
QMS	Quality Management System
RCA	Root Cause Analysis
RPM	Rotation Per Minute
RTH	Ready to Hang
SCADA	Supervisory Control and Data Aquisition
SPC	Statistical Process Control
SV	Storage Vessel
UCL	Upper Control Limit
USL	Upper Specification Limit

1. Introduction

In this chapter we give an introduction about the research assignment. We start with an introduction about the organization in Section 1.1, followed by a brief description of Abbott's production plant in Zwolle in Section 1.2. Then, in Section 1.3 we explain the reason for the study, followed by the research plan in Section 1.4. Finally, in Section 1.5, we give an outline of the report.

1.1 Abbott

Abbott Laboratories is founded in 1888 by dr. Wallace C. Abbott. Abbott currently is one of the world's biggest companies in health services. Abbott develops, manufactures and sells products that are used in health services all over the world. The products can be divided into the categories medical diagnosis equipment, medical devices, nutritionals and pharmaceuticals. Worldwide Abbott has about 75,000 employees and is present in more than 150 countries.

1.2 Zwolle production plant

Abbott Laboratories in Zwolle is one of the manufacturing facilities where medical nutrition is being produced. The nutrition consists of Similac-powder (an infant nutrition) and liquid products for patients in hospitals, residential care homes or patients that want extra nutrition at home (see Figure 1.1). In total there are about 450 employees working at the Zwolle plant. The products are sold in more than 70 countries, mostly in Europe, Asia and South-America. The production lines run day and night shifts, and some lines even run 24 hours a day, 7 days a week.

Figure 1.1 Abbott's products

The production process in Zwolle starts with incoming goods like ingredients and packaging material. The ingredients are checked on quality and labeled for traceability. From here the products go to the processing department (see Figure 1.2 and Figure 1.3), where different types of semi-finished products are put together from the ingredients. In this phase of the production all products are still liquid.

Figure 1.1 Control room

Figure 1.3 Production area

Part of the liquid semi-finished products that come from the processing department are sold as powder products. A dry tower dries the fluid product by blowing liquid in a spray drier with hot air. After the drying process, different ingredients like flavorings are added to the powder. Next, the

powder products are packaged. To protect the powder from oxygen the air inside the package is replaced with an inert gas mixture.

Besides products in powder form Abbott also sells liquid products. The liquid products can be packed in two different ways. One way is to fill a can or bottle with the liquid and close it hermetically. The cans and bottles are heated in a retort machine to kill bacteria and sterilize the product. This is done to ensure a longer durability limit. The other way of packaging liquids is to sterilize the packaging material and the liquid separately and fill the packaging material with the liquid in a sterile environment.

After production the liquid and powder products are both set on pallets and prepared for shipment. From the expedition area the products are shipped to a warehouse in Breda. The products stay there while samples of the products are checked on quality. Once the quality checks are completed the products are released and no longer under the responsibility of Abbott Zwolle.

The project takes place in the department Operational Excellence (OPEX). OPEX is responsible for optimizing the material value stream, learning and development and culture within the company. Many improvement projects are coordinated at this department. An important aspect that OPEX focusses on are food safety threats, which is the subject of the master thesis. Food safety threats are potential hazards of the health of Abbott's customers due to the ingestion of Abbott's products, and must be prevented as much as possible. The department has a total of about 15 employees.

1.3 Reason for the study

In Subsection 1.3.1 we explain the reason for the study and identify the problem. Next, in Subsection 1.3.2 we elaborate on an approach that is used to cope with a similar problem at another production plant of Abbott.

1.3.1 Retort event

The 250 mL can products are sterilized by using three retort machines. During the production process different process parameters are measured, among which the time it takes to heat up the retort. At the beginning of September 2017, an operator recognized that the come-up (heating up the retort) step of a sterilization load in one of the retorts exceeded the expected time limit. An inspection confirmed that the excursion of the come-up time was caused by three (partially) blocked inlet valves of the retort. The valves were blocked by deposits that stacked in the valves and pipes (see Figure 1.4). This impacted the flow pattern of the hot water circulating over the retort process vessel. The impacted flow pattern affected the energy transmission and therefore the lethality of the sterilization cycle. This resulted in products that do not comply with Abbott's (commercial) food safety standards, since some products weren't sterilized well. This is a major issue since products need to be able to withstand sun hours and high temperatures during transport, and may not deteriorate before the end of shelf life. After analyzing historical data it appeared that the change of flow patterns started out since May 2017. Multiple batches that were affected by the retort event had to be thrown away, causing a significant damage.

Figure 1.4 Deposits in piping of retort v14

1.3.2 Problem identification

To make sure events like the retort event won't happen in the future a team has been put together to study the root causes in the months after the event. Multiple causes have been identified during the

investigation. Also, solutions for most of these root causes are implemented to make sure the same event won't occur again in the future. The following root causes have been identified:

1) Wrong valve settings

In September 2016 there were problems with the lethality distribution of the retort process. Products inside the retort did not reach the required heat to sterilize all products to the required specifications. After an engineering study circulation piping valves were adjusted (choked) to optimize the lethality distribution. The adverse consequences of changing the valve settings weren't known, yet did cause more corrosion inside the retort piping. Finding a solution for this issue is already in progress by re-adjusting the valve settings and ensuring knowledge transfer through job rotation between operators and engineers.

2) Lack of preventive maintenance

During the study in the months after the retort event deposit was found inside the piping of the retort. Since there was no preventive maintenance on the piping deposit could pile up inside the pipes. To prevent the same issue from happening again engineers now periodically demount the pipes to apply preventive maintenance and check for any deposit.

3) Process parameters are not well monitored and controlled

From the historical data about the flow inside the retort process engineers found out there was a change of flow since May 2017. One reason that the flow process parameter was not well monitored and controlled is that it was not known that this parameter influenced the food safety. Also, it was not known when the parameter was out of control or who needed to act on this parameter. A tool to statistically show when the process parameters are out of control is missing in the current control process. Events like the retort event that cause unintentional changes in process parameters should be detected and prevented with help of this tool. Events that cause changes in process parameters can for example be deposits inside the piping of a machine, a leakage, mechanical breakdowns or using the wrong machine settings.

According to H. Heerkens (Heerkens, 2018) we can identify a problem (Phase 1 of the MPSM) by finding out the starting problem, the problem context, the problem cluster and the core problem. The starting problem here is the food safety threat explained in Section 1.3.1. The problem context is

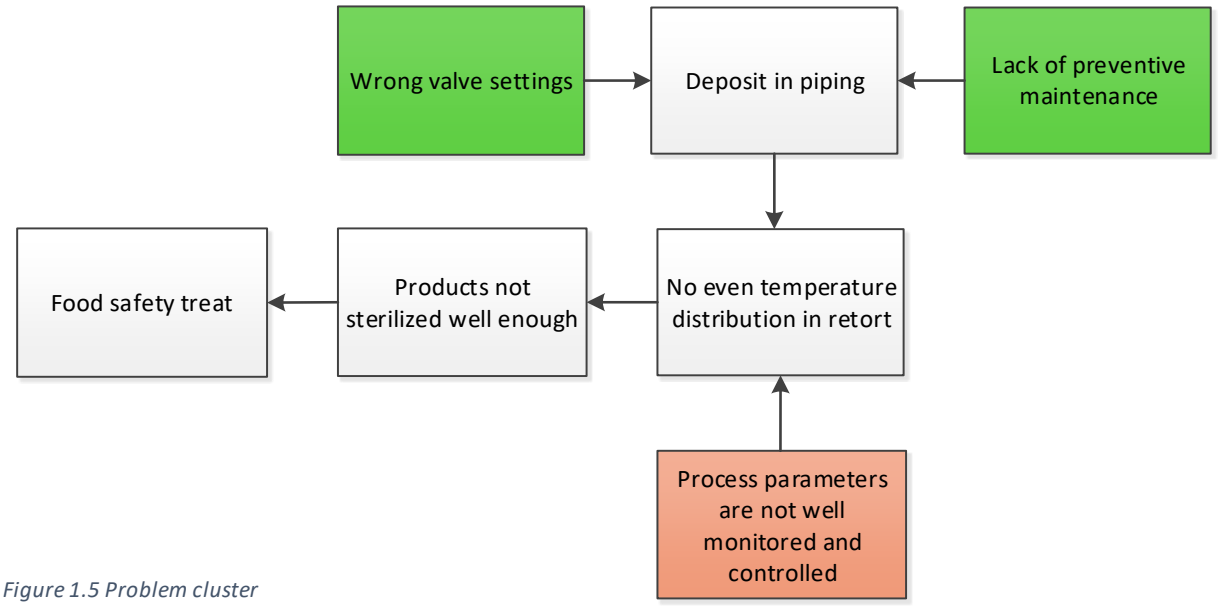


Figure 1.5 Problem cluster

described by the three root causes identified above. To find out what the core problem is we make use of Figure 1.5.

From the problem cluster we can see that food safety threats are the starting problem. If we go back into the causal chain we arrive at the causes of the starting problem. In the problem cluster we see two causes that are highlighted in green. Solutions for these causes are currently worked out and fall outside the scope of this project. The core problem of the process parameters that are not well monitored and controlled is highlighted in red. This is the core problem of this master thesis.

1.3.3 Cootehill approach

At another production plant of Abbott in Cootehill, Ireland, there was a similar project with the objective to timely respond to process changes. At the production plant in Cootehill project managers started a pilot project about process monitoring control on a single production line. The reason for the project was that the production line produced too much scrap products due to a poor-quality performance, and the process parameters were not measured or controlled. The project managers mapped the processes, data sources and quality checks of the production line and identified sources of variability and gaps with respect to data insight. After measuring the sources of variability they identified root causes for the sources of variation. The root causes were improved and controlled using statistical process control tools, which resulted in a scrap reduction of 21.6%.

1.4 Research plan

In this section we first define our main research question. To help answer our main research question we define sub questions in Subsection 1.4.1. Next, we define a research approach in Subsection 1.4.2.

The intention of the project in Cootehill was to improve the quality of the products whereas Zwolle wants to prevent future food safety threats. Therefore, the situation in Zwolle is somewhat different from the one in Cootehill, due to a different starting problem and different products and processes. However, Zwolle might still be able to learn from the approach used in Cootehill about controlling their process parameters. The problem for Zwolle, however, is that they do not exactly know how to do this in an optimal way. We formulate the following main research question that needs to be answered in order to solve the problem:

What is the best way to monitor and control critical process parameters at the retort production line of Abbott Zwolle?

1.4.1 Research questions

To answer the main research question we first need to find out what the current situation is at the retort production line. If process parameters need to be controlled differently in the future it is important to find out how this is currently done. Therefore, the first question we answer is:

1. How are the production processes of the retort production line currently monitored and controlled?

To answer this question we need to find out what the current process looks like, what is currently measured during the production process, and how the process parameters are currently monitored and controlled. Therefore, we answer the following sub questions:

1a. What does the current production process look like at the retort production line?
1b. What is currently measured related to the product and the retort production process?
1c. How are process parameters currently monitored and controlled?

Once we know what the current situation looks like we need to gather information about process monitoring and control. To come up with a solution that is suitable for Abbott we need to look for

ways to monitor and control process parameters. The question we answer here is:

2. What does the literature say about process monitoring and control?

From the literature review we generate multiple solutions to the problem. However, before choosing any solution we first need to know which process parameters we want to monitor and control. We do this by finding out which process parameters influence the sterility of the products. Also, we need to know how we want to measure these process parameters. We answer the following research question:

3. How do we measure the critical process parameters?

Critical process parameters are those process parameters that influence the sterility of the products. To answer Research Question 3 we need to know what the critical process parameters of the retort production line are. The next thing is finding out how to measure each individual critical process parameter. Since the way that measure the critical process parameters pushes us into the direction of a solution, it is important that we first evaluate the demands and wishes of Abbott related to monitoring and controlling their process parameters. Therefore, we answer the following sub questions:

3a. What are critical process parameters at the retort production line?
3b. What are the demands and wishes of Abbott related to monitoring and controlling their process parameters?
3c. How should we measure each critical process parameter?

At this stage of the research we know what the current situation at the retort production line is, we are familiar with different methods to monitor and control process parameters, and we know how to measure each critical process parameter at the retort production line. The next step is choosing a solution for the problem. We do this by answering the following question:

4. What is the best way for Abbott to monitor and control the critical process parameters of the retort production line?

The final thing that we need to know if we want to answer the main research question is who needs to act when, and in which way if the critical process parameters go out of control:

5. Who needs to act, in which way, if the critical process parameters go out of control?

1.4.2 Research approach

We plan the way to the solution of the research questions with help of the solution planning phase of the MPSM, described by H. Heerkens (Heerkens, 2018). For each sub question we enlist the things that need to be known about the questions or the choices that are made regarding the scope of the questions.

1a. What does the current production process look like at the retort production line?

- Available documents (primary sources of Abbott) that describe the production process are consulted.
- Operators are observed and interviewed to get a clear view on what they do and what the process looks like.

1b. What is currently measured related to the product and the retort production process?

- Consulting available documents (primary sources of Abbott) that describe the production process.
- Operators, process engineers, quality engineers and other stakeholders are interviewed to explain the measurements that are conducted.

1c. How are process parameters currently controlled?

- Operators and other stakeholders are interviewed to get a view on the current way of controlling the process parameters.

After answering the first sub questions the current situation of the production line is clear. The deliverables in this part of the study are a report on the current situation, including flow charts of the production process and related measurements, and a description of the current way of controlling process parameters.

2. What does the literature say about process monitoring and control?

- To answer this question we conduct a literature study on process monitoring and control. We use a structured approach to determine the source material for the study. Inclusion and exclusion criteria are used to set the boundaries for the study and leading journals and books are used to find relevant articles. From the relevant articles we go backward by reviewing citations to determine prior articles that we want to consider, and we go forward by using web of science.
- We also use primary sources of other Abbott sites to generate solutions. For example we consult available documents of the project about controlling process parameters at the production plant in Cootehill. Also, the project manager and other stakeholders of this project are available for questions about their approach.

After answering these sub questions we have an idea on different ways to control the process parameters (e.g. the type of control charts, different ways to determine control limits, and other possible options). The deliverable in this part of the study is a report about the relevant literature and methods that other production facilities use to control their process parameters.

3a. What are critical process parameters at the retort production line?

- We conduct a failure mode and effects analysis with process experts to determine the critical process parameters. People that we consult in this phase are a project manager of operational excellence, a process engineer, an automation engineer, a quality engineer and an operator.

3b. What are the demands and wishes of Abbott related to controlling their process parameters?

- We answer this question by using a semi-structured interview (Cooper & Schindler, 2008) to get to know the demands and wishes of the relevant stakeholders.

3c. How should we measure each critical process parameter?

- We answer this question by evaluating the critical process parameters determined in 3a with a process engineer and an automation engineer. The process and automation engineers are experts on the sterilization process and related measurements.

A deliverable in this part of the study is a list of critical process parameters including the type of measurement that we use. Together with the information that we generated by answering the previous research questions we can now make a decision on the monitoring and control method that we want to use.

4. Which method do we choose to monitor and control the critical process parameters?

- From the literature review (Research Question 2) we generate multiple methods to monitor and control the critical process parameters. By relating the pros and cons of each method to the demands and wishes of Abbott we decide what the best method is to monitor and control the critical process parameters.
- It is likely that the method we choose to monitor and control the process depends on the way we measure the process parameters. Hence, the information from Research Question 3 will affect the method that we choose to monitor and control the process parameters.

A deliverable in this part of the study is a definite decision for the approach that we use at Abbott. We write a report about how we would apply the chosen approach at the retort production line.

5. Who needs to act, in which way, if the critical process parameters go out of control?

- Interviews with operators, a manufacturing excellence engineer (responsible for optimizing production lines) and a front-line leader (a team manager of multiple production lines) are conducted to determine the best way to act on out of control process parameters. The answer to Research Question 1c is considered to check if the current way of working needs to be adjusted, and if so, in what way. After answering this question we write an implementation plan to ensure that the chosen method can be implemented at the production line.

A deliverable in the last part of the study is an implementation plan on the actions that need to be taken in case the critical process parameters go out of control.

1.5 Outline of the report

The remainder of this research is organized as follows. In Chapter 2 we answer Research Questions 1a, 1b and 1c by explaining the current situation at the retort production line. Next, in Chapter 3, we answer Research Question 2 by reviewing the literature regarding process monitoring and control. In Chapter 4 we answer Research Questions 3a, 3b and 3c by defining the critical process parameters, determining the demands and wishes of Abbott, and explaining how we measure each critical process parameter. In Chapter 5 we answer Research Question 4 by selecting the best method to monitor and control the critical process parameters. Then, in Chapter 6, we answer Research Question 5 by determining an action plan for out of control process parameters. Finally, in Chapter 7, we end the report with a summary of conclusions and recommendations. To give an overview of the further outline of the report we summarize the research questions that we answer per chapter in Table 1.1.

Chapter	Research Question(s)
2	1a, 1b, 1c
3	2
4	3a, 3b, 3c
5	4
6	5

Table 1.1 Research questions per chapter

2. Current situation

In this chapter we describe the current situation at the retort production line. In Section 2.1 we first discuss the production department, followed by the production process in Section 2.2. In Section 2.3 we proceed by describing the sterilization process, followed by the measurements during the process in Section 2.4. Then, in Section 2.5, we discuss the controls related to the process. We close the chapter with conclusions in Section 2.6.

2.1 Retort department

Part of the liquid products that Abbott produces is sterilized at the retort department. The retort department contains two production lines, one to sterilize 250 mL nutritional drinks (also called can products), and one to sterilize 500 mL bottles (See Figure 2.1). The can products are mainly used as a supplement on a diet or to fulfill an increased energy requirement of a client. The 500 mL bottles are used to feed a client by a stomach tube and are also called Ready To Hang (RTH) bottles. The product is filled in a can or bottle and then closed with a seal. After closing the package the can or bottle is sterilized by a thermal process at one of the retort production lines. Since the products that are sterilized at the retort department are used for medical purposes it is very important that the process is accurate and sanitary. Customers that use these products have a low resistance and are usually very sensitive to become ill.

Figure 2.1 250 mL can and a 500 mL bottle

The nutritional drinks and the tube feeding products can be divided into three categories:

- Nutritional drinks and tube feeding for children
- Nutritional drinks for adults
- Medical drinks- and tube feeding for specific diseases

The target group for the first category of products are children from 1 to 6 years old. For this group Abbott's products are the only sources of nutrition they receive, or a supplement on a diet. The products are balanced, free of lactose and glutes and are used in hospitals and home care. The first category consists of four different products. The target group of the second category of products are adults. The products in this category are mainly used in case of malnutrition or after a surgery. Also, these products are balanced and free of lactose and glutes. This category consists of three different products. The target group for the last category of products are people suffering from different kind of diseases (e.g. lung diseases, cancer, diabetes, ALS, kidney diseases, etc.). A total of eight different products is produced for this category.

For the nutritional drinks it is possible to add different kinds of flavors like vanilla, strawberry, chocolate and different variants of mushrooms and chicken. All the different products and flavors have their own viscosity, foaming and color characteristics. The characteristics of the products influence the way the products are processed at the retort production line to reach an acceptable sterility. The products need to be processed in such a way that the quality characteristics of the products are not degraded too much during the thermal process.

The sterility of the product is a food safety aspect and needs to be conform to commercial standards. The standard is called commercial because the products are not totally sterile after the production process, but sterile enough to not cause any health damage to the customer. The product is not totally sterile because of the other characteristics of the product, namely the quality aspects viscosity, color, taste, pH and the amount of vitamin C. If a product is 100% sterilized the product won't be of any value to the customer since the quality aspects would be destroyed by the thermal process. During this research the goal is delivering products that comply with food safety standards. However, it is important to keep in mind that also the quality aspects play an important role during sterilization.

2.2 Production process

All liquid products that arrive at the retort department come from the processing department. The processing department is also called the kitchen of the production and is responsible for producing semi-finished products. The semi-finished products from the processing department are used in the powder department as well as the liquid department. Products that arrive at the retort department are ready to be packed and sterilized. This means that all flavors and other additions have already been added at the processing department. In Figure 2.2 we see the different production steps at the retort department.

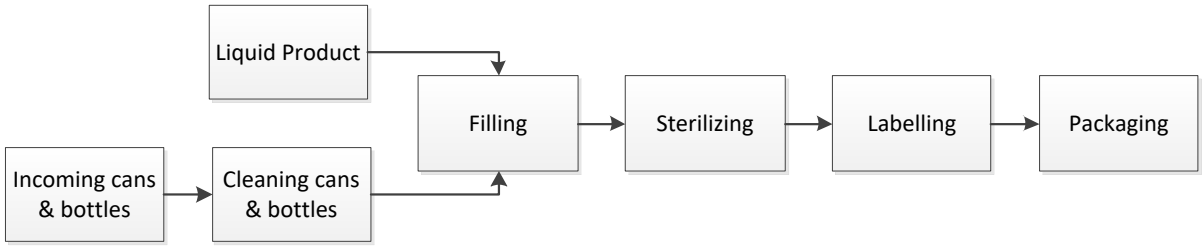


Figure 2.2 Flow chart retort department

Cans and bottles are produced in separate batches and on separate production lines, but always follow the production steps described in Figure 2.2. The focus of the research is on the can production line due to two main reasons, namely the retort event happened at the can production line and the production line for bottles is replaced in the near future. Since the focus of the project is on the can production line we describe the exact process flow of the can products in more detail.

To get an overview of the flow of the cans during the sterilization process we describe the process at hand of a more detailed process flow chart (see Figure 2.3). A palletizer puts the empty cans on a conveyor, which transports the cans to the filling machine. During transport the cans are rinsed with hot water to ensure there is no dirt on the empty cans. An ionizing air dries the packages and makes them anti-static. Once the products are clean and anti-static a filling machine fills the cans with product and then seals the cans. A fill height checker controls the volume of each can and then the cans are cleaned once more. Finally, a conveyor transports the cans to a so-called LAN-loader. The LAN-loader picks up the cans with a magnet and puts them in large metal baskets.

Now the cans are cleaned and packed in the metal baskets, they are ready for sterilization. When four metal baskets are filled with cans a shuttle automatically transports the four baskets to one of the three retort machines, and loads them in the machine (Figure 2.4). When the sterilization process is finished the shuttle unloads the baskets from the retort machine and transports them to a LAN-unloader, which unloads the baskets and puts the cans on a conveyor. The conveyor transports the cans to a can dryer which blows the cans dry with hot air. The dry cans are now ready for labelling and packaging. In this project we focus on process monitoring and control during the sterilization process, which takes place in the three retort machines (retort v14, retort v15 and retort v16) viewed in Figure 2.4.

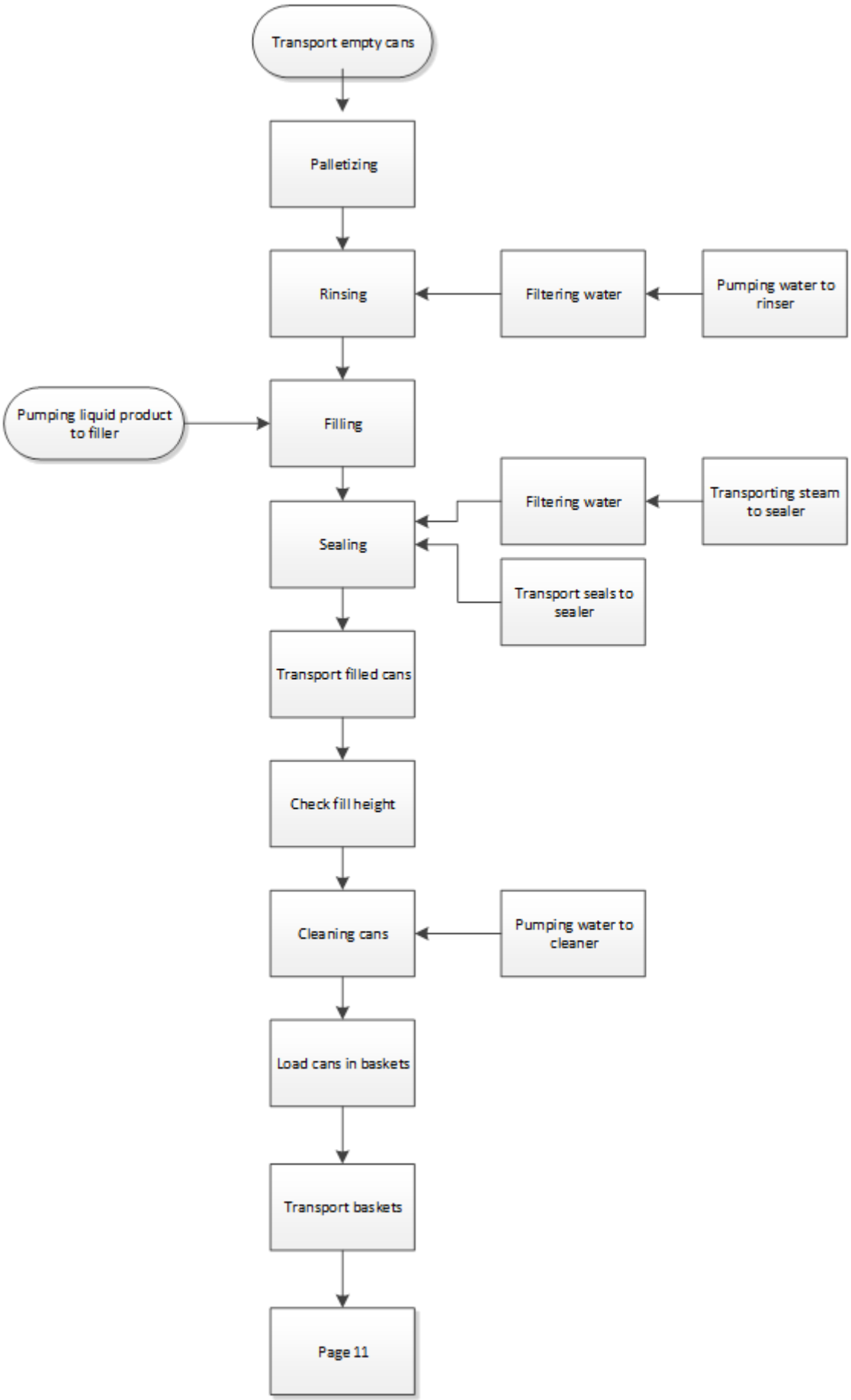


Figure 2.3 Flow chart preparing cans

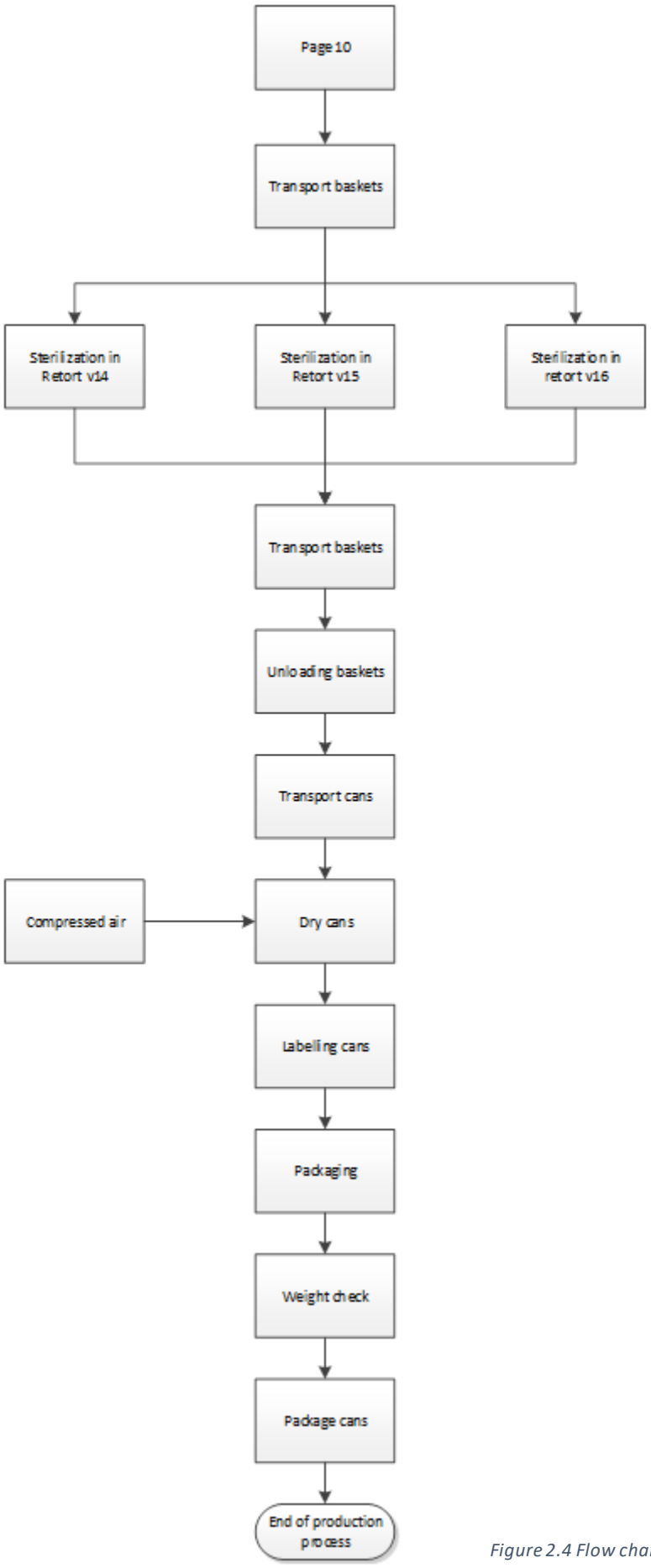


Figure 2.4 Flow chart sterilization process

2.3 Sterilization process

The sterilization process is one of the "critical control points" (CCP) within the production facility of Zwolle. A CCP is a process step that causes serious effects for the customer if the step is not performed accurately. The sterilization step is performed to kill micro-organisms through thermal processing. In case of an insufficient thermal process, micro-organisms are insufficiently killed and can grow inside the product. This can eventually lead to life threatening food poisoning or infection of the customer.

During the sterilization process the package and the product are sterilized with water of at least 125°C and a pressure of about 2.5 bar. The high pressure inside the retort machine is required to reach a temperature of 125°C. During sterilization the baskets with cans are rotated to cause an equal distribution of the heat. It is very important that the required time of the sterilization cycle, the temperature during the cycle and the rotation are reached during the sterilization process. If this is not the case there is a severe risk that (some of the) cans inside the baskets are not sterilized according to the commercial standards. A retort machine consists of two horizontally placed vessels, a storage and a process vessel. The vessels are placed underneath each other and are connected through metal pipes. The water in the storage vessel is heated so it can be used during the sterilization, which takes place in the process vessel (see Figure 2.5).

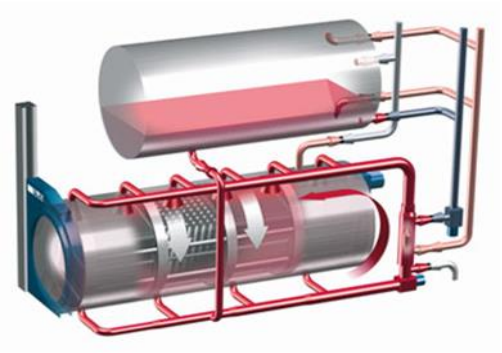


Figure 2.5 Retort machine

The process from loading the baskets in the retort, sterilizing the products, and unloading the baskets roughly takes half an hour. This process is called a sterilization run. The actual sterilization time of a product lays between 3 and 5 minutes, depending on the type of product that is being sterilized. A complete sterilization run consists of roughly five process steps (see also Figure 2.6):

1) Filling & heating storage vessel (SV)
2) Filling & heating process vessel (PV)
3) Heating process vessel
4) Sterilization
5) Cooling

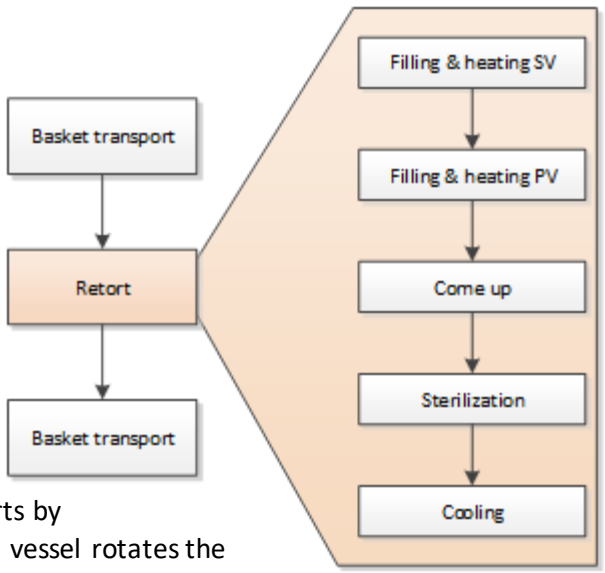


Figure 2.6 Sterilization process steps

In the first step the water in the storage vessel is heated to a temperature of 125°C. To reach this temperature it is required to raise the pressure in the vessel to about 2.5 bar. If the pressure would stay around 1 bar the water would cook at 100°C and the temperature would not raise any higher. When the water in the storage vessel reaches the right temperature the next step starts by opening valves to the process vessel. The process vessel rotates the baskets with cans and the metal pipes transport hot water from the storage vessel to the process vessel. The products have a temperature of about 5°C when they enter the retort, which means the temperature of the water in the process vessel drops beneath 125°C. The water temperature needs to rise again to 125°C. This is done during the come-up step. The pressure inside the process vessel is raised to 2.5 bar and the water is heated up to 125°C. Raising the temperature to 125°C is done with hot steam. Once the water reaches the required temperature of

125°C the sterilization step can start. During the sterilization step the water temperature may not drop below 125°C, which also means the pressure needs to stay at a minimum of 2.5 bar. Besides the temperature and pressure, an important parameter is the number of rotations per minute. Without the proper rotation some products inside the retort are too hot, while other products are too cold. When the sterilization is finished cold water flows inside the retort to cool down the products to a temperature of 35°C. The temperature at the end of the sterilization run may not be too high due to potential microbiological activity inside the product. After cooling the products the retort drains the water from the process vessel and the sterilization run is finished.

During the sterilization process some parameters are very important in a specific step to ensure the products are sterilized according to commercial standards. If for example, during the sterilization step, the temperature drops below 125°C or the retort has a wrong rotation, the products produced during the sterilization cycle may not be sold to the customer. To make sure Abbott only sells products that are sterilized according to commercial standards it is very important that the measurement and control system is functioning the way it should be.

2.4 Retort related measurements

In this section we distinguish three different kinds of measurements related to the sterilization process. First, in Subsection 2.4.1 we describe the process measurements during a production run, followed by the measurements that are done on the product after production in Subsection 2.4.2. Finally we describe the validation of the process om Subsection 2.4.3.

2.4.1 Process measurements

Abbott works with an operating system called SCADA (Supervisory Control and Data Acquisition). SCADA can be divided into two systems, namely supervisory control and data acquisition. The supervisory control is used to visualize and steer the process by comparing the measured value to the set value. Also, supervisory control can generate alarms if the system deviates from a desired value. The data acquisition system is used to pull data from the process. This data can for example be used to calculate the yield of the process, determine the bottleneck of a production line or read out the values of process parameters during a production run.

At a retort machine there are 129 different data tags that are collected during production. These data tags can generate information about failures during production, batch numbers, parameter alarms, set points of process parameters and actual values of process parameters during a production run. From the 129 data tags, a total of 9 data tags represent process parameters that are measured during the sterilization runs. The data can be retrieved via an “OSI-PI” software system. With OSI-PI we can plot the values of the data tags, for example of the process parameters during a sterilization cycle. Besides analyzing the data in OSI-PI the data can also be exported to other software (e.g. Excel or Minitab) for further analysis. The measurement data is currently mainly used by a process engineer that validates the process (see Subsection 2.4.3).

2.4.2 Product measurements

During the production of every batch an operator takes several samples from the sterilized product. Since a batch consists of many sterilization runs an operator only takes samples from the first and the last sterilization run (and one sample in the center of a batch, in case of a large batch). One part of the samples is sent to the microbiological laboratory to see if the thermal process was good enough to commercially sterilize the product. The result of the microbiological test is either a pass or a fail, indicating a sterile or unsterile sample. The other part of the samples is sent to the chemical laboratory for quality inspections. Only if the microbiological and chemical laboratory both give their approval, the produced batch may be released to the customer.

2.4.3 Process validation

Every two weeks the Process Engineer performs a validation of the retort machines. During the validation a Process Engineer and an Operator perform test runs with the retort machine to show that the process is stable and repeatable. Multiple different recipes are tested, all with different parameter settings. The baskets are filled with cans and loggers that can read out the temperature on the inside of the retort machines. This is in contrast with regular production runs, where we measure the temperature in the piping around the retort machines (there is no room for temperature loggers inside the retort machines during production). After the validation runs the Process Engineer reads out the data from the loggers and analyzes the inside temperature of the machine. If the retort is delivering a sufficiently consistent temperature distribution on the inside of the machine, and did not receive any alarms during the test runs, it is released for production.

The validation is a very important procedure for Abbott to show customers and regulatory authorities that the sterilization process complies with the required specifications. However, it is always possible that unforeseen changes take place in between two process validations. This could happen due to failure of system parts for example. To prevent the process from deviating from the validated process state it is very important to have the right monitoring and control procedures in place.

2.5 Management of controls

In the previous section we described the measurements related to the retort production process. The current measurements help us understand how the production process is currently controlled. We now proceed by explaining the monitoring of process parameters at the retort in Subsection 2.5.1, followed by the procedure that an operator follows if an alarm is generated during production in Subsection 2.5.2.

2.5.1 Process parameter checks

Alarms are set on some of the process parameters that influence the sterility to ensure these parameters do not deviate from the validated process. The SCADA system automatically monitors the parameters and generates an alarm if one or more of the parameters fall outside the specified limits. Since the limits are based on customer specifications an alarm in the current situation generally means that there is a negative impact on the risk of commercially unsterile products. The limits that are currently in place are called specification limits. The specification limits are determined from past knowledge and primarily based on the specifications of the customer, past validations and regulatory affairs. The use of specification limits is in contrast with statistical process control, where we use control limits. Unlike specification limits control limits are calculated based on the variation of the process parameter that we are measuring. Besides the way that the alarm limits are set we see that in total 9 process parameters are measured during every sterilization step. However, not all of these parameters are guarded with an alarm.

At the end of each sterilization run the operator checks a process report (see Appendix I) and a process graph (see Appendix II). The process report and graph contain information about four of the process parameters during a sterilization run. During the check the operator verifies that the parameters were within the specification limits during the sterilization run. For each sterilization step the operator checks the duration of the step, the temperature during the step, the pressure and the rotation. The operator also verifies if there were any alarms during the sterilization run and checks the graph to see if there were no irregularities regarding the process parameters. If the operator spots any irregularities in the graph or faces alarms during a production run, an action is required.

2.5.2 Actions in case of an alarm

There are two actions an operator can perform at the end of a sterilization run, namely approving the sterilization run or put the run on hold. If there were no alarms and the process report and graph show no irregularities the operator approves the production run and the products can proceed to packaging. In case there was an alarm during production it is possible that the operator decides to approve the production run. However, this may only be done after critically evaluating the process report and graph. If there is any doubt about the behavior of the parameters the operator needs to create an AMS-procedure (Action Management System). During an AMS procedure an operator consults the Quality Engineer and his supervisor and evaluates if the production run may be approved. This decision is mainly based on an analysis of process parameters during the sterilization run. In case of a disapproval the operator puts the production run on hold and takes samples of the product. The microbiological laboratory investigates the samples and decides if the products can be sold to the customer or not. All AMS procedures are registered to keep track of past irregularities. To give an overview of the type of AMS procedures at the retort production line we list the causes of all AMS procedures in 2017 in Table 2.1. We see that there was a total of 508 AMS procedures. The AMS procedures are sorted per category to give an overview of typical problems that lead to an AMS. For example, in Table 2.1 we see there were a lot of problems with heating up the retort machines in 2017. Also, the table shows us many AMS procedures are not categorized (row label: Other), which is due to a large variety of causes for an AMS. Understanding the current way of operating during an AMS procedure may help us define a procedure for acting on out of control process parameters in the future.

Retorted Can		
Row Labels	**Count of AMS ID#**	**% of total**
Heating Retort	208	40.94%
Other	112	22.05%
No check weigher	47	9.25%
Retort event release safeguard	41	8.07%
EMP	37	7.28%
Retort order	22	4.33%
Step time surpass	14	2.76%
Chlorine Retort	8	1.57%
Registration	7	1.38%
Fold thickness	3	0.59%
Early release	2	0.39%
Hourly average	2	0.39%
Leakage Aseptic	2	0.39%
F sample OAL	1	0.20%
CIP	1	0.20%
Coding	1	0.20%
Grand Total	**508**	**100%**

Table 2.1 AMS procedures 2017

2.6 Conclusions on current situation

In this chapter we described the current situation at the retort production line. We mapped the production process and identified the various steps in the sterilization process. During the sterilization process SCADA measures a total of 9 different process parameters. Some of the parameters are guarded with automated alarms, which are determined based on customer specifications. Operators check a process report and graph at the end of a sterilization run to see if there were no large highs and lows in process parameters. If an operator receives an alarm during production an AMS procedure is initialized if required. Together with a Process Engineer and a Quality Engineer the operator decides to either put the produced products on hold, or release the products to packaging. The controls in the current situation were not sufficient to prevent an event like the retort event (Section 1.3). Not all process parameters related to the sterilization process are guarded with alarms, even though it is not sure which parameters might affect the sterility of the products. The process parameters that are guarded with alarms are guarded with alarms based on customer specifications. This is in contrast with statistical process control tools in which warnings are generated as soon as process parameters show a trend in a certain direction, prior to reaching a specification limit. We can conclude there is no

preventive monitoring and controlling of process parameters. There is a reactive control system in place that responds to alarms based on customer specifications. The current control system does not periodically analyze process parameters and steer on deviations in process parameters.

3. Literature review

In this chapter we review the literature in relation to process monitoring and control. In Section 3.1, we start with a method for systematic risk assessment called failure mode and effects analysis (FMEA). Then, in Section 3.2 we give an introduction on process monitoring and control. In Section 3.3, we proceed with an explanation about probabilistic and assignable causes of variation, followed by the statistical basis of control charts in Section 3.4. In Section 3.5, we explain the assumption of normally distributed data, followed by sensitizing rules in Section 3.6. Section 3.7 describes the average run length of a control chart followed by the collection of sample data according to the rational subgroup concept in Section 3.8. Next, in Section 3.9 we describe the control chart application phases, followed by different types of control charts in Section 3.10. Section 3.11 shows which method we use if data does not follow a normal distribution. Finally we close the chapter with conclusions in Section 3.12.

3.1 Failure mode and effects analysis

To determine the critical process parameters that influence the sterility of the products we require a systematic approach. The FMEA procedure provides a systematic assessment of the risk of failure of a certain installation or machine. This procedure should be executed by experts who are in possession of good knowledge of the assessed installation. In his article, Braaksma (Braaksma, 2012) shows there are multiple ways of conducting an FMEA as he searches for different applications of FMEA regarding preventive maintenance strategies. However, since the FMEA is a systematic approach to identify risks, it may also be used as a systematic way to determine critical process parameters that can be a risk to the sterilization process. A big advantage of the FMEA is that it is widely used by Abbott employees and they are familiar with the procedure.

During the execution of an FMEA participants assess the way an installation or machine can fail to perform its intended function. The FMEA starts with identifying the scope of the installation or machine that is assessed. Once everyone agrees upon the scope we start the analysis with identifying different failure modes for a process step. A failure mode is anything that can fail or go wrong during a process, for example a conveying system that jams when a production line runs at full speed. During the identification of failure modes process experts brainstorm about anything that can fail within the identified scope. For every failure mode the experts identify the risk effect of the failure mode. The risk effect describes the impact on the product or process if the failure occurs. In the example of a jamming conveying system the risk effect may be a reduction in line efficiency. Then, for every failure mode, we identify potential causes of the failure. Any existing preventive controls that reduce the probability of the causes of the risks are listed. Finally, experts evaluate the impact on the end user for every failure mode by estimating the probability and severity of a failure mode. At the end of the FMEA we identify any process parameter that impacts the sterility of the product as a critical process parameter.

3.2 Process monitoring and control

There are various ways to apply process monitoring and control (PMC) to a production process. Similar to the current situation at Abbott it is possible to control the process with help of the specification limits. As stated earlier, specification limits are limits between which a process should operate to fulfill customer requirements. Another way to control production processes is to apply statistics to identify the variability of the processes. This method to control production processes is commonly called statistical process control (SPC). Montgomery (Montgomery, 2009) states that if a product is to meet or exceed customer expectations, generally it should be produced by a process that is stable or repeatable. The process must be capable of operating with little variability around the target or nominal dimensions of the product's quality characteristics. The most sophisticated tool that can

monitor the variability around a target is the control chart. Control charts are used to monitor the process variables. The charts are used to visualize process variables and can be useful in controlling process parameters and reducing the variance in production processes.

3.3 Probabilistic and assignable causes of variation

Montgomery states that the variation in the process can be divided into two categories, namely probabilistic and assignable causes of variation. Probabilistic causes of variation are inherent to the process. A process that only experiences probabilistic causes of variation is said to be in statistical control. Assignable causes of variation are usually caused by improper adjusted or controlled machines, operator errors or defective raw material. An example of an assignable cause of variation is the deposit in the piping of a retort machine which was found after the retort event. SPC focusses on eliminating assignable causes of variation as much as possible by using control charts to monitor the process and visualize assignable causes of variation.

3.4 Statistical basis of control charts

A control chart is a graphical display of a process or quality characteristic over time. A typical control chart is viewed in Figure 3.1. This type of chart is also called the Shewhart control chart. The chart contains information about a measured characteristic. The measured characteristic that we plot can be anything we want to monitor. For example, we can take a sample of 8 sterilization runs and plot the average temperature during those sterilization runs in one data point. Then, if another 8 sterilization runs are finished, we plot the next data point. Also, we could choose to plot the standard deviation of the temperature during the last 8 sterilization runs, or any other statistic that we want to monitor. An elaboration on the sampling of data can be found in Section 3.8. In the following example we choose each data point to be the average temperature during a single sterilization run.

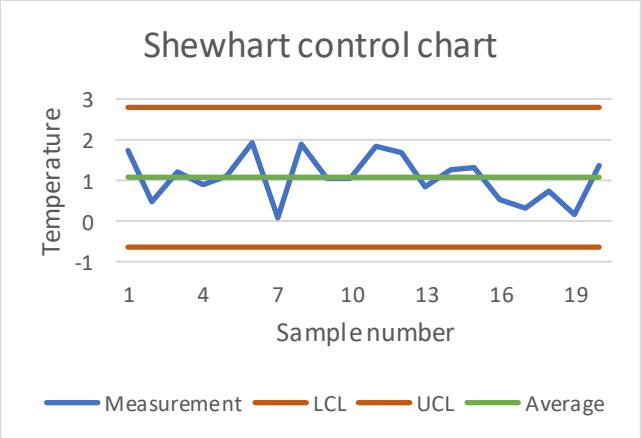


Figure 3.1 Control chart

The center line of Figure 3.1 shows the average of all data points, and the boundaries of a controlled process are depicted by the upper control limit (UCL) and lower control limit (LCL). If the measured values are within the two control limits the process is said to be in control, which means there are only probabilistic causes of variation present. The control chart can also help to detect if a process is about to go out of control. The measurements show non-random behavior if we can recognize a trend by for example multiple succeeding measurements above the average. We give an example of recognizing trends in Section 3.6. In case the graph shows an out of control process an action is required to bring the process in a controlled state again. The required actions should be taken according to an out-of-control-action plan (OCAP), which states the roles and responsibilities of involved employees. Without a clear OCAP the control charts are not likely to be a useful process improvement tool. Usually it is standard practice to express the control limits of a plotted measurement as the mean plus and minus three times the standard deviation. Expressing the control limits as a multiple of the standard deviation is justified due to the good results in practice, and lack of knowledge about the real distribution in practice (Montgomery, 2009). The three sigma control limits on each side of the mean are not to be confused with the Six Sigma philosophy, developed by

Motorola in the late 1980s. The Six Sigma philosophy of Motorola strives to set our specification limits a least ± 6 sigma away from the mean, meaning we only produce 3.4 defective parts per million.

If we take a sufficient number of measurements, in most cases we can use the central limit theorem (CLT) to assume the mean $\bar{x}$ is normally distributed. The number of measurements we take depends on how much the measurements deviate from the normal distribution. The CLT states that if we have *n* independent random variables with mean μ_i and standard deviation σ_i (*i* = 1,…,*n*), the sum of these random variables approaches a normal distribution. The approximation improves as *n* increases. According to the CLT we expect $100(1-\alpha)\%$ of the sample means $\bar{x}$ to fall between $\mu \pm Z_{\alpha/2} * \frac{\sigma}{\sqrt{n}}$, where μ and σ are the mean and standard deviation, respectively. The value of *n* represents the sample size and α represents the probability that the sample mean $\bar{x}$ lays outside the range $\mu \pm Z_{\alpha/2} * \frac{\sigma}{\sqrt{n}}$. The expression $Z_{\alpha/2}$ is the so-called z-score. We can look up the required z-score to reach a probability α with help of the standard normal table. As stated earlier, in statistical process control, it is customary to choose a z-score value of three. A z-score value of three represents a probability of 0.0027 that the sample mean $\bar{x}$ lays outside the range $\mu \pm 3 * \frac{\sigma}{\sqrt{n}}$. The validity of the assumption that the mean $\bar{x}$ is normally distributed can be verified with help of probability plotting.

3.5 Normality assumption

As stated in the previous section we can use the CLT to assume the data follows a normal distribution. However, if the measurement data is extremely non-normal we may draw false conclusions based on the control limit calculations. This may for example happen if the measurement data has a distribution which is heavily right or left skewed. To check if the measured data follows a normal distribution we can make use of probability plotting. Probability plotting is a graphical method that checks if the sample data conforms to a hypothesized distribution. We can make use of P-P probability plotting as well as Q-Q probability plotting. P-P plots compare the cumulative distribution functions of two distributions, while Q-Q plots compare the quantiles of two distributions. We prefer a Q-Q probability plot over a P-P probability plot since the Q-Q plot has a better performance in showing deviations in the tail of a distribution compared to a P-P plot. The procedure works as follows.

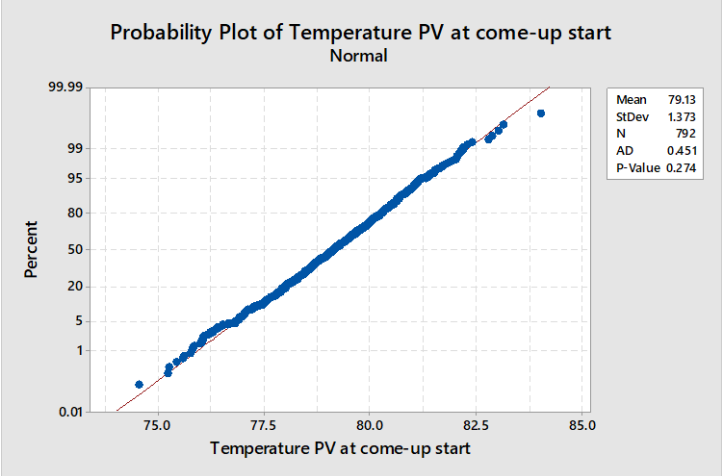


Figure 3.2 Probability plot

If we have a sample of size *n* we order all observations from small to large so that observation $x_j \leq x_{j+1}$ (*j*=1,…,*n*). The ordered observations are plotted against the cumulative frequency $(j-0.5)/n$. If the plotted values approximately follow a straight line the hypothesized distribution adequately describes the sample data. Probability plotting can be executed with help of Minitab software. In Figure 3.2 we see a probability plot made with help of Minitab. We can compare the p-value to a significance level (usually we use a significance of $\alpha = 0.05$) to test if the data approximately follows a normal distribution. If the p-value ≥ α, as in Figure 3.2, we fail to reject the null hypothesis H_0. Failing to reject H_0 means we cannot conclude the data does not follow a normal distribution. With a p-value ≤ α we reject the null hypothesis H_0, and accept the alternative hypothesis H_1. When we reject H_0 we conclude the data does not follow a normal distribution.

3.6 Average run length

The performance of a control chart can be expressed in the average run length (ARL) of the chart. The ARL shows how many points of an in-control process can be plotted on average before the control chart shows an out of control point. For an in control process the probability of a point falling outside the three sigma limits is equal to $p = 0.0027$ (see Section 3.4). Thus, for a control chart with three sigma control limits we calculate the ARL from $ARL = \frac{1}{p} = \frac{1}{0.0027} \approx 370\, points$. This means that for a control chart with three sigma control limits, on average, one out of 370 data points plots out of control, even when the process is in control. This is what we call a false alarm. For an in control process the probability of a point falling outside the two sigma limits is equal to $p = 0.0456$. Thus, for a control chart with two sigma control limits we calculate the ARL from $ARL = \frac{1}{p} = \frac{1}{0.0456} \approx 22\ points$. We see that a control chart with 3 sigma control limits has a better performance since this control chart will show less false alarms. However, a drawback of the 3-sigma control chart in this case is that it will take longer to detect an out of control situation. When setting up control limits it is important to evaluate the number of alarms we want to allow in production and the size of the shift that we want to detect. The ARL can be helpful to compare the performance of different types of charts.

3.7 Sensitizing rules

Besides using three sigma levels as control limits it is possible to use other out of control rules. Nelson (Nelson, 1984) discusses different rules for sensitizing control charts. Sensitizing rules like the two sigma warning levels help faster detection of an out of control process and can be very useful. However, there is a drawback for these rules since the probability of detecting an out of control situation while the process is in control increases when the control limits are narrowed. We generally call detecting an out of control situation while the process is in control a type I error. However, due to using sensitizing rules we decrease the probability of a type II error, which is the probability that we conclude that the process is in control, while the process is out of control. While setting control limits there is a trade-off between the allowable type I and type II error.

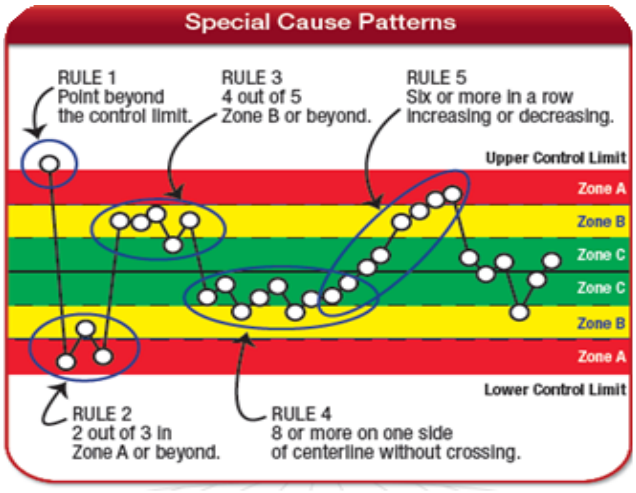


Figure 3.3 Sensitizing rules

As stated in Section 1.3.3 there was a project about controlling process parameters in Abbot's Cootehill plant. During this project engineers used the sensitizing rules from Figure 3.3 (picture from Abbott's PMC playbook). Montgomery refers to the first four sensitizing rules as 'Western Electric Rules', also described in the statistical quality control handbook of (Western Electric, 1956). When applying sensitizing rules, a control chart is divided into three zones, A, B and C. Zone C represents deviations until ± σ from the mean (the green zone in Figure 3.3), zone B from ± σ until ± 2σ (the yellow zone in Figure 3.3), and zone A from ± 2σ until ± 3σ (the red zone in Figure 3.3). When applying sensitizing rules, every time a sensitizing rule is violated, there is a special cause of variability and thus the process is out of control. Sensitizing rules help interpreting and detecting trends on control charts. We need to be very cautious when applying sensitizing rules since the rules cause an increased number of alarms. According to Champ and Woodall (Champ & Woodall, 1987), while using the Western Electric Rules, the ARL of a control chart is decreased to 91.25, compared to 370 when only using Rule 1.

3.8 Rational subgroups

According to Montgomery, sample data should be collected using the rational subgroup concept. The rational subgroup concept states that subgroups need to be selected in a way that the chance for differences *between* subgroups is maximized and that the chance for differences *within* a subgroup is minimized. In the following example, we picture a production facility that produces screws. The production facility operates in 2 production shifts of 8 hours. If we choose to monitor the thickness of the screws we can collect a screw every hour until we have a sample of $n = 16$ screws. We then plot the average thickness of the 16 screws as one data point in a control chart. In this example we plot one point in the control chart every working day. However, since 8 screws of the sample are collected during one shift and the other 8 screws are collected during the next shift, any differences between the two shifts might not be detected. Hence, the time order of production is usually a good basis for rational subgrouping. The time order can for example be the shift in which the products are produced. In the example of the screw factory this would mean using a sample size of $n = 8$ and plot a data point in the control chart every production shift. In total there are two approaches possible to apply rational subgrouping. In the first approach we take samples of products produced as close to each other as possible. This approach minimizes the probability of assignable causes of variation within a sample, and maximizes the detection of assignable causes between samples. We use the first approach if we want to detect any shifts in the process. In the second approach we take samples of products that give a representation of all products produced since the last sample was taken. Usually we use this approach when we want to decide on the acceptance of all products produced during the current sampling interval.

3.9 Control chart application phases

The type of chart we use is dependent on the process that we measure and the intention of the use of the chart. The use of a chart involves Phase I and Phase II applications, where each phase has its own objective. In Phase I it is assumed that the process is not yet in control. In Phase I we make control charts from historical data samples to see if there were any data points out of control. The causes of these data points being out of control are evaluated and improved so they can be discarded in the next control chart. We recalculate the mean and the control limits and plot a new control chart to see the state of the improved process. Any data points outside the control limits are evaluated and improved again. The procedure is repeated until a state of statistical control is reached. Phase II begins if we reach a state of statistical control. In this phase we add every new measurement to the control chart to see if there are any deviations in the process. The control limits should be reviewed periodically or if any process change has been made. There is a distinct difference in objective between Phase I and Phase II, since Phase I focusses on bringing the process in statistical control and Phase II focusses on monitoring the process. In Phase I, Shewhart control charts are most useful due to the easy use of the charts and their effectiveness, while in Phase II these charts are less likely to be effective because they are not sensitive to small and moderate process shifts (Montgomery, 2009). In Phase II other control charts than the Shewhart chart are more likely to be effective. However, this is dependent on the magnitude of the process shift that we want to discover.

3.10 Type of control charts

In this section we give an overview of different types of control charts and when to use them. We start with the traditional Shewhart type control charts proposed by Walter A. Shewhart, and described by Montogmery (Montgomery, 2009) in Subsection 3.10.1. We then proceed with application Phase II control charts, starting with the cumulative sum (Cusum) in Subsection 3.10.2, followed by exponentially weighted moving average (EWMA) control charts in Subsection 3.10.3.

3.10.1 Shewhart control charts

The Shewhart control charts are divided into two categories, namely control charts for variables and control charts for attributes. Since the control charts for variables are most applicable in this study, we only describe these control charts. Control charts that are used to monitor variables contain quality characteristic measurements on a numerical scale. To monitor the process we measure both the mean and the variability of the quality characteristic.

When we use a sample size of n > 1 we plot the variable measurements on a $\bar{x}$ and R chart or a $\bar{x}$ and s chart. With the $\bar{x}$ chart we measure the process average and with the R and the s charts we measure the variability of the process. In an R chart we monitor the variability with the range of the values and with an s chart we monitor the variability with the standard deviation. We calculate the range of a sample as $R = x_{max} - x_{min}$. An R chart is preferred over an s chart when the sample size is small and an s chart is used when the sample size is moderately large, say $n > 8$. To monitor variable measurements of sample size $n = 1$ we use a I-MR chart. The I chart, also called the "individuals control chart", monitors the individual values of the measurements. The MR chart monitors the variability with the moving range. We calculate the moving range of sample *i* as $MR_i = |x_i - x_{i-1}|$. In this equation x_i is the individual measurement value of sample *i.*

In every chart we have a center line which is represented by the mean value $\bar{x}$, $\bar{R}$, $\bar{s}$ or $\overline{MR}$. The control limits generally lay ± 3σ away from the mean value. Since we often do not know the real distribution of the data we need to estimate the population mean μ and variance σ^2 from past data. We may estimate the population standard deviation σ from the average standard deviation of the samples $\bar{s}$, the average ranges of the samples $\bar{R}$, or the average moving ranges of the samples $\overline{MR}$ (depending on the chart we use). According to Montgomery an unbiased estimator for the population variance σ^2 is the sample variance $s^2 = \frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{n-1}$. The sample standard deviation s however, is not an unbiased estimator of the population standard deviation σ. Since we did not yet decide which control charts we use in this study and the procedure for estimating the population standard deviation from either $\bar{s}$, $\bar{R}$ or $\overline{MR}$ is similar, we show how we estimate the population standard deviation σ from the sample standard deviation $\bar{s}$.

Suppose we take *m* samples of sample size *n,* and let s_i be the standard deviation of sample *i*. If the underlying distribution is normal, an unbiased estimator of σ is $\hat{\sigma} = \bar{s}/c_4$, where c_4 is a constant depending on the sample size *n* (see Appendix III for different values of c_4) and $\bar{s} = \frac{1}{m}\sum_{i=1}^{m} s_i$ is the average of *m* standard deviations. Furthermore, the standard deviation of s is equal to $\sigma\sqrt{1 - {c_4}^2}$ (Montgomery, 2009). Now we can estimate σ with $\bar{s}/c_4$ and calculate the control limits for the s chart as $\bar{s} \pm 3 * \frac{\bar{s}}{c_4}\sqrt{1 - {c_4}^2}$. To calculate the center line for the $\bar{x}$ chart we take the total average over all

Control limits $\bar{x}$ chart	*Control limits s chart*
$center\ line = \bar{\bar{x}} = \frac{\sum_{i=1}^{m}\bar{x}_i}{m}$	$center\ line = \bar{\bar{x}} = \frac{\sum_{i=1}^{m}\bar{x}_i}{m}$
$UCL = \bar{\bar{x}} + 3 * \frac{\bar{s}}{c_4\sqrt{n}}$	$UCL = \bar{s} + 3 * \frac{\bar{s}}{c_4}\sqrt{1 - {c_4}^2}$
$LCL = \bar{\bar{x}} - 3 * \frac{\bar{s}}{c_4\sqrt{n}}$	$LCL = \bar{s} - 3 * \frac{\bar{s}}{c_4}\sqrt{1 - {c_4}^2}$

Table 3.1 Calculations $\bar{x}$ and s charts

samples. Then, since we use $\hat{\sigma} = \bar{s}/c_4$ as an estimate of σ, we can calculate the control limits as $\bar{x} \pm 3 * \frac{\bar{s}}{c_4\sqrt{n}}$. In Table 3.1 we summarize the calculations for the $\bar{x}$ and s charts.

To clarify the formulas above, we show how to perform the calculations in an example. In Table 3.2 we see 8 samples (sample size 5) of data about the temperature during a sterilization process. First, for every sample we calculate the mean and standard deviation. Then, to calculate the center line for the $\bar{x}$ chart we calculate the average of all sample means. To calculate the center line of the s chart we calculate the average of all sample standard deviations. The control limits follow from looking up the constant $c_4 = 0.94$ in Appendix III and using the formulas in Table 3.1. In Table 3.3 and Figure 3.4 we show the control chart calculations and the $\bar{x}$ and s chart, respectively. One remark that we must make about Table 3.3 is that the calculation for the LCL results in a negative number. However, since the standard deviation cannot be a negative number, we set the LCL equal to zero.

Sample number	Observations					$\bar{x}_i$	s_i
1	126.676	126.216	126.435	125.407	126.651	126.277	0.521
2	124.533	126.605	124.786	125.324	123.612	124.972	1.103
3	125.426	125.759	124.765	126.622	123.979	125.310	1.001
4	125.181	125.003	127.965	126.039	124.321	125.702	1.406
5	126.588	122.721	125.010	126.281	124.748	125.070	1.533
6	126.963	124.522	124.057	125.599	125.046	125.237	1.124
7	124.340	125.025	125.106	124.071	126.517	125.012	0.950
8	124.985	125.594	122.937	125.067	126.249	124.966	1.242
$\bar{x} = 125.318$		$\bar{s} = 1.11$		$c_4 = 0.94$	$n = 5$	$m = 8$	

Table 3.2 Temperature data

Calculations $\bar{x}$ chart	Calculations s chart
$center\ line = \bar{x} = 125.318$	$center\ line = \bar{s} = 1.11$
$UCL = 125.318 + 3 * \frac{1.11}{0.94 * \sqrt{5}} = 126.902$	$UCL = 1.11 + 3 * \frac{1.11}{0.94}\sqrt{1 - 0.94^2} = 2.318$
$LCL = 125.318 - 3 * \frac{1.11}{0.94 * \sqrt{5}} = 123.734$	$LCL = \max[0; 1.11 - 3 * \frac{1.11}{0.94}\sqrt{1 - 0.94^2}] = 0$

Table 3.3 Example $\bar{x}$ and s calculations

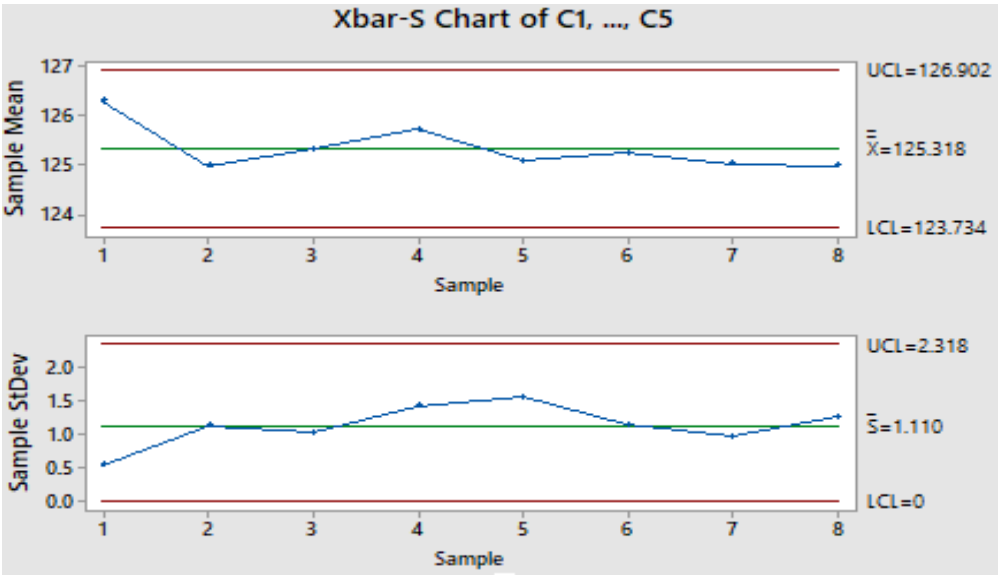


Figure 3.4 Example $\bar{x}$ and s chart

3.10.2 Cusum control charts

The cumulative sum (Cusum) control charts are a good alternative for the original Shewhart control charts. Cusum control charts are most effective for process monitoring in Phase II since the charts can detect smaller shifts for the process mean and variability. In a paper about the performance of the Cusum chart Koshti (Koshti, 2011) states that the chart is especially effective in detecting small process shifts of 1.5 sigma or less. In Figure 3.5 and Figure 3.6 we see a plot of 30 data points, from which the first 20 are drawn from a normal distribution with mean 10 and standard deviation 1. The last 10 data points are drawn from a normal distribution with mean 11 and the same standard deviation. The control limits in Figure 3.5 are calculated based on all 30 data points. We can see that the Cusum control chart shows a shift in process mean while the Shewhart control chart does not show any out of control points.

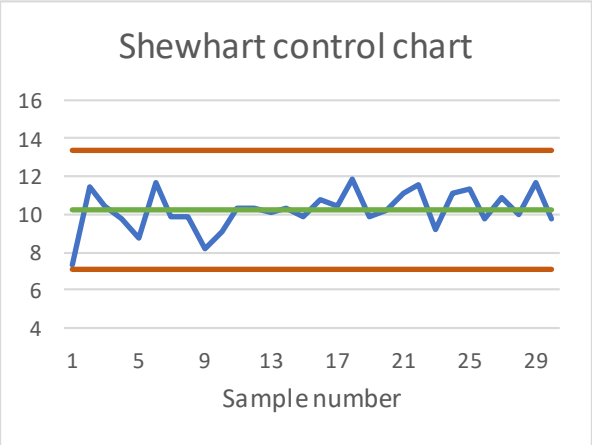


Figure 3.5 Shewhart control chart

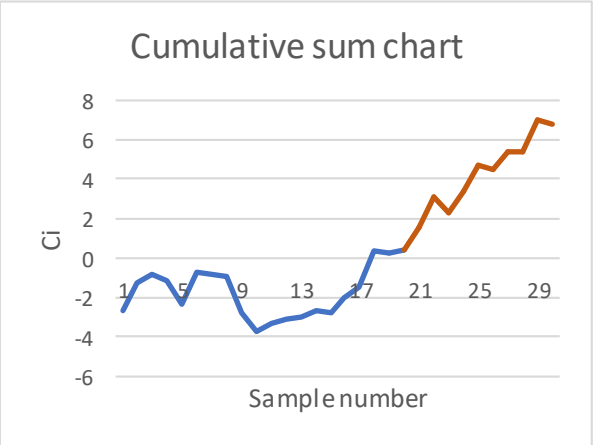


Figure 3.6 Cumulative sum control chart

To set up the Cusum chart we define a target mean for the process ($\mu_0 = 10$ in the previous example). The target mean is the value that we want our process characteristic to operate around. The idea is that, once the process characteristic drifts away from the target, the Cusum chart gives a signal. We explain the idea of a Cusum chart with help the previous example in which we used a sample with 30 measurements. Since we use a sample size of n = 1 (as is customary with application Phase II control charts) we plot every measurement in the control chart. We calculate the cumulative difference from the target mean as $C_i = \sum_{j=1}^{i}(\bar{x}_j - \mu_0)$. The value C_i is the value that we plot in the control chart. In the equation to calculate C_i, $\bar{x}_j$ is the mean of the j^{th} sample. In case we have a sample size of n = 1 (as in this example) $\bar{x}_j$ is equal to observation x_j. If the process is stable the value $x_j - \mu_0$ is close to 0 (see the example calculations in Table 3.4). If the mean makes a shift to either side of μ_0 the value of C_i increases and the CUSUM chart gives a signal by showing an up or downward shift. We cannot yet define Figure 3.6 as a control chart due to the lack of control limits.

To set up control limits for the Cusum chart we make use of a procedure that is known as the tabular (or algorithmic) Cusum. Before setting up control limits we assume that, when the process is in control, the measurements x_i follow a normal distribution with mean μ_0 and standard deviation σ. To set up the control limits we assume that σ is either known or that we have enough historical data to make a reliable estimate. Using the tabular Cusum we derive two statistics, C^+ and C^-, that indicate when observations are either above or

Sample (i)	Measurement (x_i)	$x_i - \mu_0$	c_i
1	9.34	-0.66	-0.66
2	10.50	0.50	-0.15
3	10.75	0.75	0.60
…	…	…	…
28	11.30	1.30	4.73
29	11.59	1.59	6.31
30	9.89	-0.11	6.21

Table 3.4 Cumulative sum calculations

Tabular Cusum calculations

$$C_i^+ = Max[0, x_i - (\mu_0 + K) + C_{i-1}^+]$$

$$C_i^- = Min[0, x_i - \mu_0 + K + C_{i-1}^-]$$

Table 3.5 Cumulative sum control limits

below the target, respectively. We calculate the statistics C^+ and C^- with help of the formulas in Table 3.5. The starting value for both C^+ and C^- is equal to zero and the value K is called the slack value. We choose the slack value K as half the size of the shift that we want to detect. In case we want to detect a shift of $n * \sigma$ we calculate the slack value as $K = \frac{n}{2} * \sigma$. Note that the statistics C^+ and C^- only detect deviations from the target value μ_0 that are larger than K. The process is out of control if either the statistic C^+ or C^- exceeds the interval H. Montgomery explains that a reasonable value for H is five times the standard deviation σ. We explain our findings with help of the previous example, in which we use a target value of $\mu_0 = 10$, a sample size of n = 1, a standard deviation of $\sigma = 1$, a slack value of $K = \frac{1}{2}$ and an interval of $H = 5 * \sigma$. In Table 3.6 we give an example of the Cusum calculations, and in Figure 3.7 we show the corresponding Cusum graph. We see the Cusum detects an out of control point at observation 29. If we compare the Cusum chart of Figure 3.7 with the Shewhart control chart from Figure 3.5 we can see that the Cusum can be a good method to faster detect of out of control points.

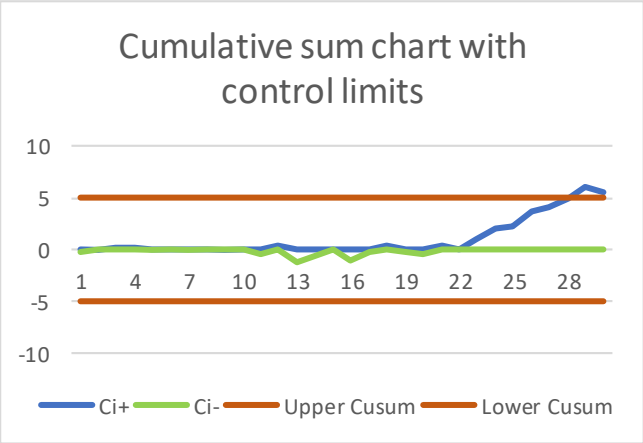


Figure 3.7 Example cumulative sum chart with control limits

Sample (i)	Measurement (x_i)	c_i^+	c_i^+
1	9.34	Max[0, 9.34 - (10 + 0.5) + 0] = 0	Min[0, 9.34 - 10 + 0.5 + 0] = -0.66
2	10.50	Max[0, 10.50 - (10 + 0.5) + 0] = 0	Min[0, 10.50 - 10 + 0.5 - 0.66] = 0
3	10.75	Max[0, 10.75 - (10 + 0.5) + 0] = 0.25	Min[0, 10.75 - 10 + 0.5 + 0] = 0
…	…	…	…
28	11.30	Max[0, 11.30 - (10 + 0.5) + 4.14] = 4.95	Min[0, 11.30 - 10 + 0.5 + 0] = 0
29	11.59	Max[0, 11.59 - (10 + 0.5) + 4.95] = 6.03	Min[0, 11.59 - 10 + 0.5 + 0] = 0
30	9.89	Max[0, 9.89 - (10 + 0.5) + 6.03] = 5.43	Min[0, 9.89 - 10 + 0.5 + 0] = 0

Table 3.6 Example tabular cumulative sum calculations

3.10.3 EWMA control charts

Another good alternative to the Shewhart control chart is the exponentially weighted moving average (EWMA) control chart. Roberts (Roberts, 1959) first introduced the EWMA control chart and used a simulation model to evaluate the properties of the chart. He showed that the EWMA control chart is excellent for detecting small shifts in the process mean. However, the chart can also be used for detecting larger shifts. The EWMA chart is similar to the CUSUM chart and in some ways more straightforward to operate. We define the exponentially weighted moving average as

$$z_i = \lambda x_i + (1-\lambda) z_{i-1}$$

In this equation the variable x_i is the measurement in sample *i* in case we use a sample size of *n* = 1. With a sample size of *n* > 1 the variable $x_i = \bar{x}_i$. The value $0 < \lambda < 1$ is a constant and the starting value $z_0 = \mu_0$, which is the process target mean. To show that z_i is a weighted average of all previous data points we rewrite the equation for z_i as

$$\begin{aligned} z_i &= \lambda x_i + (1-\lambda)[\lambda x_{i-1} + (1-\lambda) z_{i-2}] \\ &= \lambda x_i + \lambda(1-\lambda) x_{i-1} + (1-\lambda)^2 z_{i-2} \end{aligned}$$

If we proceed replacing z_{i-j}, *j* = 2, 3, … *t*, we can calculate the EWMA statistic as

$$z_i = \lambda \sum_{j}^{i-1} (1-\lambda)^j x_{i-j} + (1-\lambda)^i z_0$$

When we use $\lambda = 0.3$ we assign a weight of 0.3 to the current observation x_i. The previous observations are weighted according to the decreasing geometric distribution $\lambda(1-\lambda)^j$. We show an example of the assigned weights in Table 3.7, together with a graph of the same weights in Figure 3.8. A great advantage of the EWMA control chart is that the chart is very insensitive to the normality assumption. The chart is insensitive to non-normality since the EWMA is a weighted average over all previous observations. Also, the chart is more useful in detecting trends since we use the information from multiple samples instead of using the information of only a single sample when using Shewhart control charts.

Sample (i)	Weight
1	0.3
2	0.21
3	0.147
4	0.1029
5	0.072
6	0.0504
7	0.0353
8	0.0247

Table 3.7 Sample weights

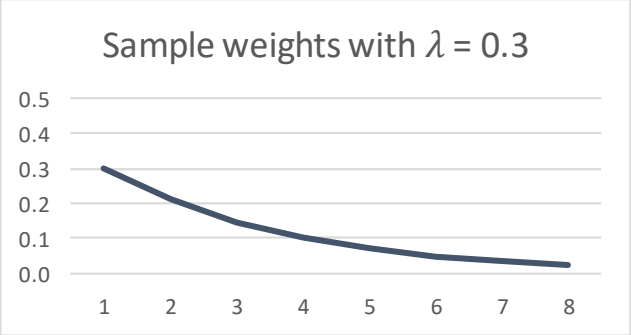


Figure 3.8 Graph of sample weights

When we plot the EWMA chart the center line is represented by μ_0. If we are not certain about the target mean we can use historical data to determine μ_0. The control limits are calculated according to the formulas in Table 3.8.

Control limits EWMA chart

$$UCL = \mu_0 + L\sigma \sqrt{\frac{\lambda}{(2-\lambda)}[1-(1-\lambda)^{2i}]}$$

$$LCL = \mu_0 - L\sigma \sqrt{\frac{\lambda}{(2-\lambda)}[1-(1-\lambda)^{2i}]}$$

Table 3.8 Calculations EWMA control charts

When calculating the control limits we need to decide on the width of the control limits, which is represented by the value L. A common value for L is somewhere between 2.5 and 3.5, depending on the shift that we want to detect. The control limits are variables depending on the sample number *i*. From the formulas in Table 3.8 we see that, when the sample number increases, the control limits approach the value $\mu_0 \pm L\sigma\sqrt{\frac{\lambda}{(2-\lambda)}}$. The tighter control limits for smaller values of i help faster detection of an out of control process at the start of setting up the EWMA control chart. In their paper, Lucas and Saccucci (Saccucci, 1990) provide a table with the average run length as a function of the parameters L and λ, and the anticipated shift in process mean that one wants to detect. The optimal design procedure consists of first specifying the desired ARL and the magnitude of the process shift that we want to detect, followed by selecting the combination of λ and L that provides the desired ARL performance (Montgomery, 2009).

To clarify the formulas for the statistic z_i and the control limits we explain them with help of an example. We use a process target mean of $\mu_0 = 10$, a standard deviation of $\sigma = 1$, a control limit width of $L = 2.5$ and for lambda a value of $\lambda = 0.1$. For a sample of 30 observations we show the EWMA calculations for the first and the last three observations in Table 3.9. In Table 3.10 we give examples of control limit calculations, and in Figure 3.9 we plot the EWMA control chart

Sample (i)	Measurement (x_i)	EWMA (z_i)
1	9.34	0.1 * 9.34 + (1 - 0.1) * 10 + 9.93
2	10.50	0.1 * 10.50 + (1 - 0.1) * 9.93 = 9.99
3	10.75	0.1 * 10.75 + (1 - 0.1) * 9.99 = 10.07
…	…	…
28	10.59	0.1 * 10.59 + (1 - 0.1) * 11.12 = 11.07
29	11.44	0.1 * 11.44 + (1 - 0.1) * 11.07 = 11.10
30	10.44	0.1 * 10.44 + (1 - 0.1) * 11.10 = 11.04

Table 3.9 Example EWMA calculations

Sample (i)	UCL	LCL
1	$10 + 2.5 * 1 * \sqrt{\frac{0.1}{(2-0.1)}[1-(1-0.1)^{2*1}]} = 10.25$	$10 - 2.5 * 1 * \sqrt{\frac{0.1}{(2-0.1)}[1-(1-0.1)^{2*1}]} = 9.75$
2	$10 + 2.5 * 1 * \sqrt{\frac{0.1}{(2-0.1)}[1-(1-0.1)^{2*2}]} = 10.34$	$10 - 2.5 * 1 * \sqrt{\frac{0.1}{(2-0.1)}[1-(1-0.1)^{2*2}]} = 9.66$

Table 3.10 Example control limit calculations EWMA control chart

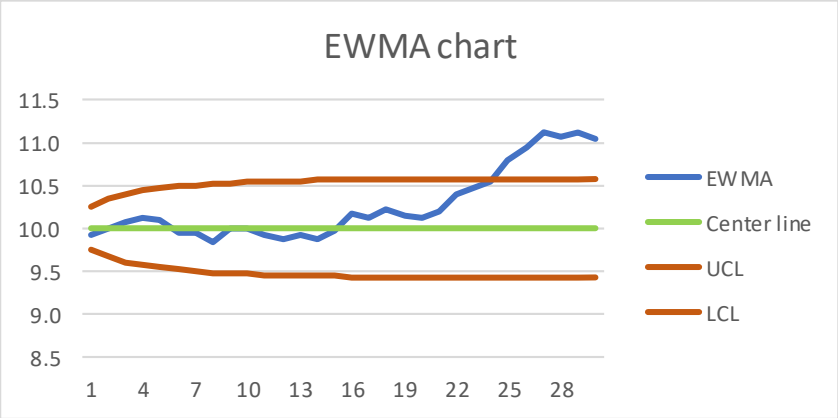


Figure 3.9 Example EWMA control chart

3.11 Designing control charts using an empirical reference distribution

In Section 3.5 we stated the importance of checking the assumption that the data is normally distributed. In case the data does not follow a normal distribution we need to be very cautious,

especially when using the Shewhart individuals control chart for process monitoring. In their paper, Borror, Montgomery and Runger (Borror, Montgomery, & Runger, 1999) investigated the influence of non-normality on the average run length of an individuals control chart. They conclude that the ARL of an individuals control chart with three-sigma limits is reduced from 370 to somewhere between 45 and 97 (depending on the skewness) if the data actually follow a gamma distribution. For the t-distribution the actual ARL ranges somewhere between 76 to 283 as the degrees of freedom increase from 4 to 50 (as t increases the t-distribution slowly transforms to a normal distribution). Due to these poor ARL results the Shewhart individuals controls chart is entirely inappropriate for process monitoring if the data follows a non-normal distribution. One approach for dealing with non-normal data is using a properly designed EWMA control chart, since the control chart is very insensitive to the normality assumption. Another approach for dealing with non-normal data is to use nonparametric procedures for setting up control charts. Nonparametric procedures do not have the assumption of normality. An example of a nonparametric procedure is designing the individuals control chart with help of empirical distribution function (EDF). When using this procedure, Montgomery states it is preferable to have historical data of about 200 observations.

In their paper, Willemain and Runger (Willemain & Runger, 1996) provide an approach to dealing with non-normal data. A prerequisite for using the approach is that we have sufficient historical data, which is a prerequisite that is satisfied in our study. If we have sufficient historical data, regardless of the underlying distribution of the data, we can set up control limits with help of the provided procedure. The procedure is as follows. We start with a sample statistic X, obtained from a process during normal operating conditions. We denote the probability density function and the cumulative distribution function of X as $f(x)$ and $F(x)$, respectively. The values $x_i, 1 \leq i \leq n$ are the observed values for X, and are the values that we plot on the control chart. The values x_i can be any statistic. It is important that the *n* observations are obtained during normal production conditions, since these are the values that we use to set up control limits.

We let $x_{(k)}$ be the k^{th} order statistic (the k^{th} largest value) in the sample, and $x_{(n)}$ being the largest. The possible values of X are divided into $n+1$ random length sections by the *n* order statistics. The random length sections are also known as "statistically equivalent blocks". The first block runs from $-\infty \; to \; x_{(1)}$, the second from $x_{(1)} \; to \; x_{(2)}$ and so forth. The last block runs from $x_{(n)} \; to \; \infty$. We can express P as the probability that X falls within a set of blocks, for example between the blocks $x_{(i)}$ and $x_{(i+j)}$. The probability of X falling within the two blocks is expressed as $P = \Pr\left[x_{(i)} \leq X \leq x_{(i+j)}\right] = F\left(x_{(i+j)}\right) - F\left(x_{(i)}\right)$. In this equation $0 \leq i \leq n$ and $1 \leq j \leq n+1-i$. We can now choose the control limits empirically, setting $LCL = \; x_{(i)}$ and $UCL = \; x_{(i+j)}$, with P being the probability that a future plotted point falls within the control limits. As stated earlier, we generally use ± 3 sigma limits, which means we use a probability of $P = 1 - 0.0027 = 0.9973$. In Figure 3.10 we illustrate the procedure with an example. The figure illustrates the approach with a set of *j* = 8 blocks, *n* = 11 order statistics and a total of *n* + 1 = 12 statistically equivalent blocks. In this example, the probability of a future point falling between the two control limits is equal to $P = \Pr\left[x_{(2)} \leq X \leq x_{(2+8)}\right] = F\left(x_{(10)}\right) - F\left(x_{(2)}\right)$. According to Mosteller and Rourke (Mosteller & Rourke, 1973), P follows a beta distribution, depending only on *n* and *j*. We can express the probability density function of P as $f(p) = Gp^{j-1}(1-p)^{n-j}, \; 0 \leq p \leq 1$ in which $G = \frac{n!}{(j-1)!(n-j)!}$. Note here that $f(p)$ does not depend on $f(x)$. Hence, the expected value of $P = E[P] = \frac{j}{(n+1)}$ only depends on the number of statistically equivalent blocks *n* + 1 and the number of blocks *j*. Therefore, in the example we can calculate the probability of a point falling inside the two control limits as $P = E[P] = \frac{8}{(11+1)} \approx 0.6667$.

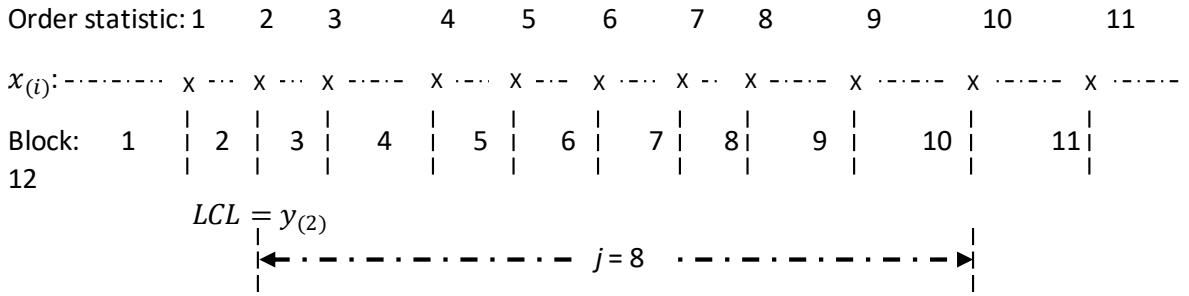


Figure 3.10 Statistically equivalent blocks

We slightly modify the procedure of Willemain and Runger to calculate the control limits in our study. We set the probability of X falling inside the control limits fixed to 0.9973. This results in an ARL of $ARL = \frac{1}{p} = \frac{1}{0.0027} \approx 370\ points$. This is the same ARL that we get if we use $\pm 3\sigma$ control limits for normally distributed data. In our study we use a fixed number of statistically equivalent blocks n. Then, we can calculate the number of blocks that we need to fall between our control limits as $j = P * (n+1)$. For a two sided control chart we have a total of $(n+1) - j$ blocks that fall outside our control limits. Hence, $\frac{1}{2}\big((n+1) - j\big)$ blocks lay above our UCL, and below our LCL. From the ordered data we can determine our control limits from the order statistics. We define our UCL as $x_{(n-\frac{1}{2}((n+1)-j))}$ and our LCL as $x_{(\frac{1}{2}((n+1)-j))}$. In Section 4.4.3 we give an example of the application of an EDF to calculate control limits.

3.12 Conclusions on literature review

There is very extensive literature available in relation to statistical process control. There are many different types of control charts available to monitor and control the process. The choice for using a particular control chart is not always obvious and depends on the objective that we want to achieve and the type of process or quality characteristic that we monitor. Also, the type of chart that we want to use depends on the application phase of the chart.

In this research we use the FMEA to determine the process parameters that influence the sterility of the products. Once we know the critical process parameters we need to find out how to measure the parameters and how to sample the data. Also, we need to check if the measurement data does not violate the normality assumption. After we checked the normality assumption we need to find out in which control chart application phase we are in. We do this by analyzing historical data of the critical process parameters. Next, we choose the best method to monitor and control the critical process parameters. While choosing the best method we need to specify which type of control chart(s) we want to use and which control limits and sensitizing rules we want to apply. This decision should be based on the demands and wishes of Abbott, and the distribution of the data. Finally, we define an out-of-control-action plan.

4. Selection of critical process parameters

In this chapter we determine the critical process parameters, the demands and wishes of Abbott, and the way that we measure the critical process parameters. First, in Section 4.1 we explain the scope of the FMEA, followed by the results of the FMEA in Section 4.2. Then, in Section 4.3, we determine the demands and wishes of Abbott. Next, in Section 4.4, we explain how we measure each critical process parameter. Finally, in Section 4.5, we close the chapter with conclusions.

4.1 Scope of the FMEA

To determine the critical process parameters we execute an FMEA as described in Section 3.1. An important aspect of the FMEA is that all participants agree on the scope prior to the start of the analysis. Within the scope of the FMEA are all process parameters that we measure during a sterilization run. As stated earlier in Section 2.4.1 we measure 9 process parameters during a sterilization run (see Table 4.1). Any process steps prior to loading, or after unloading the baskets in the retort machines are outside the scope of the FMEA. With the FMEA we want to find out which process parameters influence the sterility of the products during a certain process step. Process parameters can influence the sterility of the products when they relate to a failure mode that causes an insufficient thermal process. We use the term insufficient thermal process when the occurrence of a failure mode affects the sterility of the products. To explain how the FMEA helps us identify the process parameters that are critical we give some examples in Section 4.2.

All process parameters
Step time
Temperature SV
Temperature PV
Rotation
Flow
Water level SV
Water level PV
Pressure SV
Pressure PV

Table 4.1 Process parameters

We execute the FMEA with help of multiple process experts. The attendees of the FMEA are Abbott employees from the following departments: Retort Engineering, Sterility Technology, Quality Assurance, Process Engineering, Automation Engineering, Manufacturing Excellence and Operational Excellence. The role of Operational Excellence is making sure everyone stays within the agreed scope, keeping track on the timeline and registering the FMEA. Employees of the other departments are the process experts who deliver the required process knowledge to execute the FMEA.

4.2 Execution of the FMEA

While executing the FMEA we start with the process step filling and heating storage (upper) vessel, followed by the filling and heating of the process (lower) vessel. Then we analyze the come-up step (further heating up the process vessel to 125°C), followed by the sterilization step. Finally, we analyze the cooling down step. Since it is inconvenient to list all observations of the FMEA (listed in an Excel file of about 60 lines) we explain how we use the FMEA to determine the critical process parameters. We give the explanation with help of some examples and at the hand of Table 4.2. At the end of this section we summarize all critical process parameters per process step.

In Table 4.2 we give some examples of observations of the FMEA. In the left-hand side column we denote the process step that we currently analyze. Next to the process step we denote the function of the process step, followed by the failure mode that we identify. Next to the failure mode we denote the risk effect of the failure mode, followed by the potential cause of the failure mode and the preventive controls that are currently in place. Finally, we define an overall risk level based on the severity of the risk effect and the probability that the cause occurs. Judging the impact of a failure mode is an estimate based on the experience of all attendees together. We calculate the overall risk level with help of the probability*severity matrix (Appendix IV). Since estimating the impact is no decision on facts or historical data we solely use the impact of a failure mode to get a broad view on the overall risk level. The criticality plays a less important role in our analysis since the mitigation plan

is the same for all critical process parameters, namely applying process monitoring and control. Using process monitoring and control as mitigation plan for every failure mode related to the process parameters is also the reason why we do not execute a failure mode, effects and criticality analysis (FMECA), in which it is possible to quantify the criticality. The goal of the FMEA is merely to define those process parameters that can influence the product sterility so we can monitor and control those process parameters.

To explain how we use the FMEA to determine critical process parameters we use the failure mode "temperature being too low" during the sterilization process step as an example (line 10 in Table 4.2). The function of the sterilization process step is to sterilize all products with the right temperature, flow, rotation, water level and pressure during a certain time. In this example the temperature being too low is a failure mode since we lose the function of the sterilization process step if the failure mode occurs. The effect of a lower temperature is an insufficient thermal process since the products are exposed to a lower temperature during a certain time. Since the risk effect of the failure mode is an insufficient thermal process the failure mode influences the sterility of the products. Therefore, we conclude that the temperature during the sterilization process step is a critical process parameter that we want to monitor and control. During the FMEA we also evaluate potential causes of the failure mode and any controls in place that help prevent these causes. If, as in this example, a problem with the flow can cause a too low temperature, we see another process parameter from Table 4.1 that relates to a failure mode that causes an insufficient thermal process. Since we want to detect out of control parameters as soon as possible we want to monitor process parameters that directly or indirectly influence the sterility of the products. This means that we want to monitor parameters that are a failure mode as well as parameters that are a potential cause related to an insufficient thermal process. Therefore, in this example, we want to monitor and control the temperature as well as the flow during the sterilization process step. In Table 4.2 we highlight those process parameters from Table 4.1 that relate to an insufficient thermal process. In case the potential cause of the temperature being too low would have been a mallfunctioning pump we would conclude that a mallfunctioning pump falls outside the scope of the FMEA since it is not a process parameter that we measure during the sterilization process. Also, if the temperature being too low during the sterilization process step would not result in an insufficient thermal process, we would not select the temperature and flow as critical process parameters during the sterilization process step. Using this method we evaluate all process parameters listed in Table 4.1 for every process step. We define any process parameter(s) that relate(s) to a failure mode causing an insufficient thermal process as critical. One remark that we have to make is that if we mark a process parameter as being too high or too low, this remark is based on the expert knowledge. In these cases it is not always clear how much too high or too low is exactly. In Chapter 5 we determine how much too high or too low is with help of statistical process control tools.

To clarify the FMEA some more we take another example. In Table 4.2 we see a failure mode during the come-up step, namely the process step being too short (line 8). The function of the come-up step is heating the process vessel to 125℃ within a certain amount of time. In this example, the process step being too short is a failure mode since we lose the function of the come-up step if the failure mode occurs. The effect of a short come-up time is an insufficient thermal process since the products are exposed to a certain temperature for a shorter amount of time. A short come-up step can be caused by a too high temperature at the start of the process step. If the temperature at the start of the come-up step is too high it takes less time to reach the required temperature to proceed to the sterilization step, resulting in a too short come-up step. Also for this failure mode we assess the preventive controls and total impact. In this example we see that the time of the come-up step can influence the sterility of the products. Also, we see that the temperature at the start of the come-up

step can influence the sterility of the products. Hence, both parameters are critical process parameters that we want to monitor and control.

	PROCESS STEP	FUNCTION	FAILURE MODE	RISK EFFECT	POTENTIAL CAUSE	PREVENTIVE CONTROLS	INITIAL RISK		
	Describe the process step that is being assessed	Describe the function of the process step that we assess	Describe what can fail	Describe what the impact is if the failure occurs	Describe the cause of the of the failure	List any existing process considerations that would reduce the probability of the potential cause of the risk	SEVERITY (Based on Risk Effect)	PROBABILITY (The likelihood the cause occure and results in the Risk Effect)	OVERALL RISK LEVEL (Refer to Risk Threshold Matrix)
1	Filling & heating storage vessel	Filling and heating the storage vessel to a certain volume and temperature	Low tank level	Insufficient thermal process	Leaking valve	Periodic inspection on the valves	HIGH	REMOTE	MEDIUM
2			Low temperature	Insufficient thermal process	Lack of steam	Unable to start process	HIGH	REMOTE	MEDIUM
3			High temperature	Insufficient thermal process	Pressure problem	Unable to start process	HIGH	REMOTE	MEDIUM
4			Low tank level	Insufficient thermal process	Leaking valve	Periodic inspection on the valves	HIGH	REMOTE	MEDIUM
5			Too high temperature PV	Insufficient thermal process	Steam valve problems	No alarm present	HIGH	POSSIBLE	HIGH
6	Come up	Heating the process vessel from a certain temperature to 125℃ within a certain time frame	Too low temperature of process water at the beginning of the come up	Insufficient thermal process	Insufficient flow	Alarm is present for flow	HIGH	REMOTE	MEDIUM
7			Too high temperature of process water at the beginning of the come up	Insufficient thermal process	No rotation	Alarm is present for rotation	HIGH	REMOTE	MEDIUM
8			Process step is too short	Insufficient thermal process	Temperature too high at start of process step	Periodic lethality checks	HIGH	REMOTE	MEDIUM
9			Water level too low in PV after start of phase	Insufficient thermal process	Instrumentation	No preventive controls in place	HIGH	REMOTE	MEDIUM
10	Sterilization	Sterilize all products with the right temperature, flow, rotation, water level and pressure during a certain time	Temperature too low during process step	Insufficient thermal process	Reduced flow	Alarm is present for flow	HIGH	REMOTE	MEDIUM
11			Low flow	Insufficient thermal process	Too much rotation	Alarm is present for rotation	HIGH	REMOTE	MEDIUM
12			Water level too low	Insufficient thermal process	Pressure in process vessel too high	Alarm is present for pressure	HIGH	REMOTE	MEDIUM
13			Process step is too short	Insufficient thermal process	Instrumentation	No preventive controls in place	HIGH	REMOTE	MEDIUM
14	Cooling	Cool down the process vessel within a certain time range	Flow is too low	Economic spoilage due to thermophilic micro organism	Pump mall function	No preventive controls in place	MEDIUM	REMOTE	LOW
15			Water level too high in PV	Overcooking	Control system mall function	No preventive controls in place	LOW	REMOTE	LOW
16			Process step is too short	Insufficient thermal process	Water temperature is too low at end of sterilization step	No preventive controls in place	HIGH	REMOTE	MEDIUM

Table 4.2 Failure mode and effects analysis of the sterilization process

Since we do not measure all critical process parameters from Table 4.1 we also give an example of process parameters that are not selected for process monitoring and control. As an example we take the cooling process step (Line 14 in Table 4.2). In this example we see that the flow being too low is a failure mode that can be caused by a mall functioning pump. Even though the flow is a process parameter from Table 4.1, we do not want to monitor and control the flow during the cooling process step since the risk effect is no insufficient thermal process (highlighted in blue in Table 4.2). This means that, according to the process experts that execute the FMEA, the flow during the cooling process step does not influence the sterility of the products. Due to the same argument the water level being too high during the cooling step (Line 15 in Table 4.2) is no process parameter that we want to monitor and control. The examples of the flow and water level in the cooling step show how we exclude process parameters from monitoring and control when the process parameters do not influence the sterility of the products. As stated earlier, we use Table 4.2 to give examples of the procedure that we use to select process parameters. Not all failure modes and effects that exclude parameters for process monitoring and control are present in the table since it is too comprehensive to discuss the entire FMEA in this section. To show the parameters that we do select for process monitoring and control, we give a summary in Table 4.3. The process parameters that we select can be derived from the information in Table 4.2.

As a result of the FMEA we define a total of 17 critical process parameters divided over all process steps. In Table 4.3 we make a distinction between critical process parameters that we want to monitor and control by highlighting them in light blue, and others in green. The process parameters in green are process parameters that currently have preventive controls in place in such a way that they do not require additional monitoring and control. The process parameters in the filling & heating SV step for example, cannot influence the sterility of the products since the sterilization process cannot start when the water level of the storage tank is below the setpoint. The same counts for the temperature and pressure in the filling & heating SV step. Since the process cannot start if the parameters deviate from the required standard it is needless to apply statistical process control to these critical process parameters. After all, an action by an Operator or Process Engineer will always be required if the process does not start. Two other process parameter for which applying statistical process control doesn't make sense are the rotation of the process vessel and the duration of the sterilization process step. The rotation of the process vessel is always equal to the setpoint and has a deviation of zero. There is an alarm present that indicates if the rotation deviates from the setpoint. We do not apply statistical process control to the rotation since we won't be able to detect any trends or deviations over multiple sterilization runs. The rotation is simply good or not. Also, the duration of the sterilization process step is fixed. The sterilization process step always takes 3 minutes and 20 seconds, with a deviation of ± 2 seconds. When the deviation is more than 2 seconds the operator receives an alarm and initiates an AMS procedure.

Process step	Process parameter
Filling & heating SV	Temperature SV
	Water level SV
	Pressure SV
Filling & heating PV	Rotation
	Water level PV (at end of step)
	Temperature PV (at end of step)
Come-up	Step time
	Rotation
	Flow
	Water level PV
Sterilization	Step time
	Temperature PV
	Rotation
	Flow
	Water level PV
	Pressure PV
Cooling	Step time

Table 4.3 Critical process parameters

The process parameters highlighted in light blue are dynamic process parameters that can deviate over multiple sterilization runs. Hence, these are critical process parameters we want to monitor and

control. However, before we determine the monitoring and control procedure for the dynamical process parameters, we need to know what Abbott's demands and wishes are related to monitoring and control.

4.3 Demands and wishes of Abbott

Prior to making decisions related to process monitoring and control we determine the demands and wishes of Abbott. We determine the demands and wishes with help of a semi-structured interview. The interview is held with the production manager. The production manager is in charge of the entire liquid production department and is the one who decides on implementation and budget issues related to improvement projects. Therefore, the production manager is the one that we ask for demands and wishes related to process monitoring and control. Details about giving interpretation to the demands and wishes are discussed with operators, process engineers and manufacturing excellence engineers, who are the end users of the process monitoring tool. As a result of the interview we identify five demands that relate to process monitoring and control.

1) We want to be able to timely detect food safety hazards in the sterilization process. For us timely is ≤ 1 working day, which is 24 hours excluding weekends.
2) We do not want an excess of warnings in production. We want the number of alarms that we can expect to be verified with the end users before implementation.
3) We want a tool that is easy to understand and implement. Also operators should be able to understand the procedure.
4) The tool should be self-sustainable after implementation.
5) With help of the tool we want to gather more knowledge about the behavior of the critical process parameters during production. The implementation plan or recommendations of the research should reflect this.

We use the demands and wishes when we need to make decisions between different process monitoring and control methods. For example, we evaluate the demands and wishes when we determine the control limits, type of control chart and the out-of-control-action plan.

4.4 How do we measure each critical process parameter?

Since some of the process parameters in Table 4.3 are measured continuously we need to decide how to measure each parameter before we can compare them over multiple sterilization runs. In this section we evaluate different measurement methods and decide on the method that we use. We start with single measurements in Subsection 4.3.1, followed by continuous measurements during the sterilization step in Subsection 4.3.2. We explain continuous measurements during the come-up step in Subsection 4.3.3.

4.4.1 Single measurements

For the step time of the come-up and the cooling step we want to monitor and control the time it takes to complete each process step. There is only one option to measure the time that a step takes, namely timing each process step. The start and the end of each process step is timed and stored in Abbott's database. We can pull the start and end time from the database, and subtract them to calculate the time of a single process step.

Two other measurements that we see in the critical process parameters are the temperature and water level of the process vessel at the end of the filling & heating PV step. The end of the filling & heating PV step is equal to the start of the come-up step. Hence, for every sterilization run, there is only one point in time that we want to measure the temperature and water level in the process vessel for this process parameter. The single measurements are all measurements on a continuous scale,

however, based on a sample size of $n = 1$ per sterilization run. The remainder critical process parameters in Table 4.3 are measured continuously over a certain time interval. Measuring these process parameters requires another approach.

4.4.2 Continuous measurements during sterilization

The flow, water level, temperature and pressure in either the come-up or the sterilization step are measured continuously throughout each process step. Therefore, we have multiple options to apply statistical process control here. As an example we take the flow during the sterilization step of one sterilization run. In Figure 4.1 we see the continuous measurement of the flow (the dark blue line) during a sterilization run. The point at *t = 0* and the point at *t = 1* depict the start and the end of the sterilization step, respectively. Between *t = 0* and *t = 1*, we can measure the flow in different ways, for

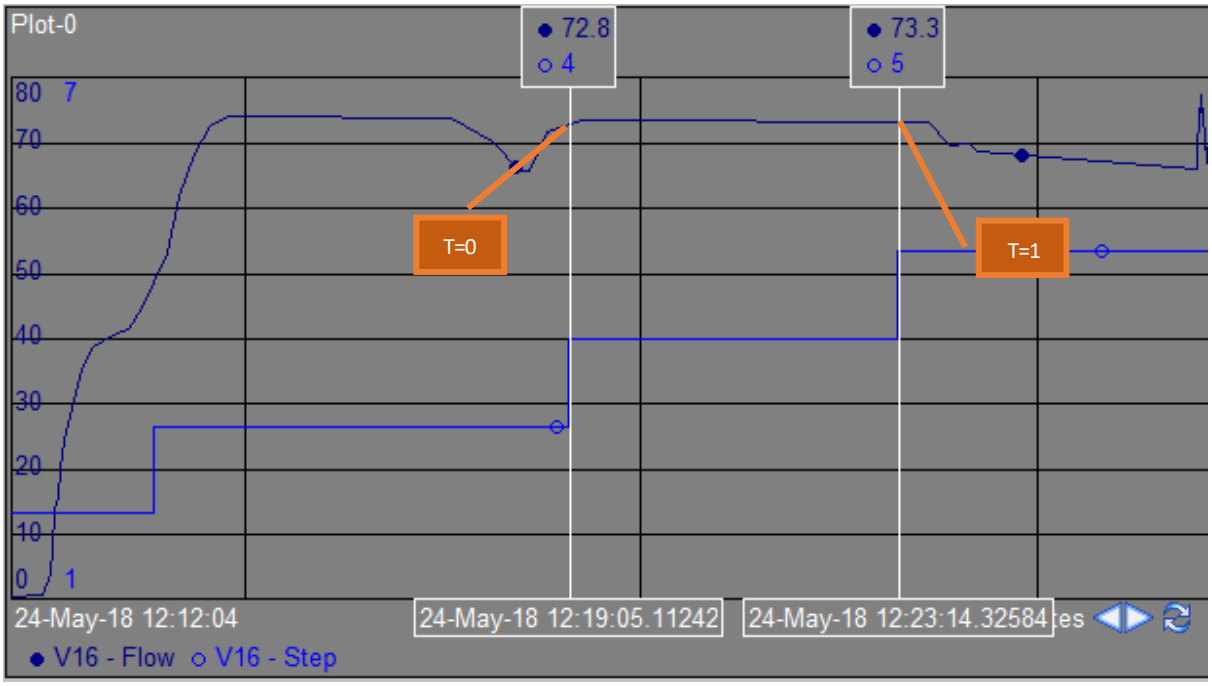


Figure 4.1 Flow during the sterilization process

example by taking the average, minimum, maximum or area under the flow curve. We can plot the measurements in control charts together with the corresponding measurements of other sterilization runs to see if the flow is in control or not. However, plotting all possible measurements of a parameter in different control charts results in a large number of control charts per parameter. Also, not every measurement gives us the information that we want to know about the process. Therefore, we need to select the measurement(s) that we want to use.

As stated previously one option is to calculate the average or the area under the curve and plot this value in a control chart. In case the flow starts to deviate over time we will see a change in average or area under the curve in the control chart and start looking for any special causes of variation. Choosing to monitor the average or the area under the curve is indifferent in detecting shifts since both statistics give a general information on the total flow during a period of time. Since the average flow of a sterilization run is a variable that results in a more tangible number for operators and process engineers we prefer working with averages. One disadvantage of only monitoring the average (or area under the curve) is that a high flow at the start of a process step can be compensated with a low flow at the end of the process step, and vice versa. Also, low peaks in the flow can be compensated with high peaks in the flow. Phenomena like this will not be detected on the control chart. This is a large drawback since a lower flow at any point in time during the sterilization step influences the sterility of

the products. A good alternative to only monitoring the average is to combine the average with a control chart for variability. The control chart for measuring variability can for example contain information about the range of the standard deviation of the values. Also, we can use an additional chart and monitor the minimum or maximum flow together with the average and/or variability. However, this option results in multiple control charts for the flow during the sterilization step. Since using multiple control charts per process parameter per process step results in an excess of control charts we investigate another option.

An alternative to measuring the average of the flow together with the variability is to monitor every individual measurement during a process step. Using this method we plot all flow data points of the last sterilization run between *t = 0* and *t = 1* together with all data points between *t = 0* and *t = 1* of prior sterilization steps in a control chart. We obtain a continuous graph representing the flow during the sterilization step of multiple sterilization cycles (see Figure 4.2). The advantage of this method is that we do not lose any information about the process parameter that we monitor. Another advantage for using this method is that we see the individual measurements as well as the variability of the measurements in one chart. Because of the advantages of monitoring all data points of a variable during a process step we decide, for the sterilization process step, to monitor all data points of the temperature, flow, water level and pressure in continuous control charts.

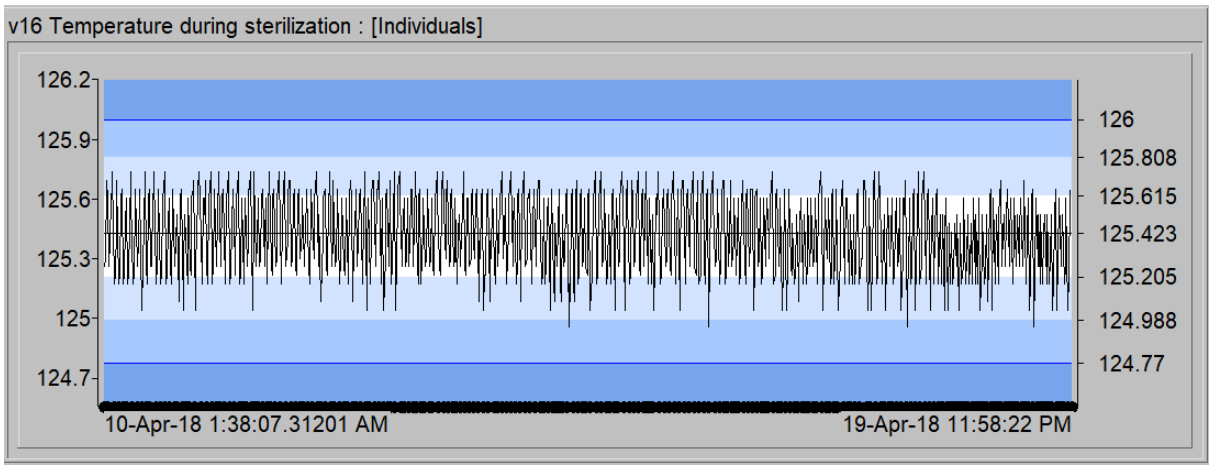


Figure 4.2 Continuous variable control chart

4.4.3 Continuous measurements during come-up

The critical process parameters that are continuously measured during the come-up step are the flow and the water level. The flow and water level are somewhat more difficult to monitor during the come-up step compared to the sterilization step. The reason for this is that the come-up of a retort machine is a dynamic process. The process parameters fluctuate more since we heat the temperature to 125°C during the come-up step. In contrast, during the sterilization step, we try to keep the temperature of 125°C constant. Heating the retort to 125°C requires building up the flow and the water level to a certain setpoint. When we use the same measurement method for the flow and water level in the come-up step as we use during the sterilization step we obtain unclear control charts like the one in Figure 4.3. The chart shows the come-up step of 5 different sterilization runs. At the start of each cycle the flow builds up to about 72 m^3/h, makes a drop to around 58 m^3/h, and then builds up again to around 65 m^3/h. This is the regular behavior of the flow during the come-up step. The control limits in the chart are ± 3σ away from the mean flow during the come-up step. Due to the large standard deviation the difference between the two control limits is more than 30 m^3/h. This range is much too broad to detect any irregularities in the flow.

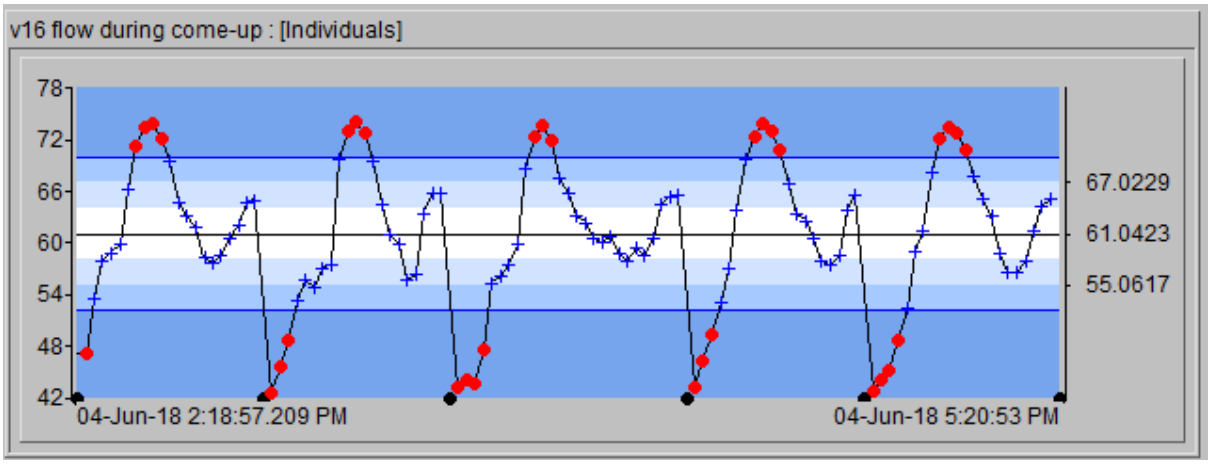


Figure 4.3 Flow during come-up process step

Measuring the variability of the flow or the water level during the come-up step results in a value that does not make sense for monitoring due to the large variability. Therefore, we search for an alternative solution. One option that we evaluate is to construct an ideal curve for the come-up process step. If we construct an ideal curve with an upper and lower boundary, we can compare the flow curve of future sterilization runs to see if the curve stays within the boundaries. We give an example of an ideal flow curve, including boundaries, in Figure 4.4. We construct the curve with help of historical data that we retrieve from Abbott's database. For the following example we use a sample of 255 sterilization runs (obtained from the process under normal operating conditions). We analyze the flow measurements for every 2 seconds during the come-up process step. This means we have 255 data points about the flow at times *t = 0:00:02, t = 0:00:04, …, t = n*, in which n represents the end time of the come-up process step. Since the data does not follow a normal distribution we use an EDF as described in Section 3.11 to construct the upper and lower control limit at every time *t* of the come-up step. We show the procedure with help of an example using *t = 0:00:02.*

Since we use a sample of 255 sterilization runs, we have 255 flow measurements at time *t = 0:00:02.* We order all data points from small to large and let f_k be the k^{th} order statistic in the sample, and $f_{n=255}$ be the largest (see Table 4.4). We divide the possible values of the sample into $n + 1$ = 255 + 1 = 256 statistically equivalent blocks. The first block runs from a flow value of $-\infty$ to f_1, the second from f_1 to f_2, and the last from f_n to ∞. As explained in Section 3.11, we can express the probability of the flow falling in a set of *j* blocks as $P = \frac{j}{n+1}$. If we want to use a probability of around 98% to conclude that the future flow values at time *t = 0:00:02* fall inside our boundaries we can use a value of $j = 252$ blocks to set our boundaries (control limits). This results in a probability of $P = \frac{252}{255+1} \approx 98.44\%$. To find our upper and lower control limits we 'cut off' the upper and lower two blocks, and read off the corresponding flow values from column "Flow (f_k)" in Table 4.4. According to our analysis we conclude that the ideal flow values at time time *t = 0:00:02* should lay between 39.18584 and 43.25637. We repeat the described procedure for the times between *t = 0:00:02* until the end time of the come-up step and plot an ideal graph of the flow during the come-up. We see an example of the ideal graph in Figure 4.4. We can use this method for

Order statistic (k)	Flow (f_k)	Block #
1	39.02973	1
2	39.18584	2
3	39.29269	3
4	39.29345	4
…	…	5
252	43.17856	…
253	43.19814	253
254	43.25637	254
255	49.25429	255
		256

Table 4.4 Flow order statistics

the flow as well as the water level during the come-up step. We discussed the method with Abbott's data specialist, and conclude that there is a drawback of the described method. The drawback is that the current software of Abbott does not facilitate plotting an ideal graph based on historical data to compare current sterilization runs with the ideal curve. According to the data specialist, there might be options for using an ideal curve in the future when other software packages are available at Abbott. However, for now we cannot apply this monitoring method in the OSI-PI software system, which can use to monitor live data and control charts. Since we want to keep the demands and wishes of Abbott in mind in which they state that they want a tool that is easy to understand and implement we decide that the use of an ideal curve is not an option that we prefer at this point in time. Since we do want to proceed with monitoring the flow and water level during the come-up process step we choose to monitor the average. If Abbott chooses to implement monitoring and control, monitoring the average in OSI-PI requires some adjustments to the software. However, as opposed to monitoring an ideal curve, it is possible with the available software. Also, according to the process engineer, in combination with the step time of the come-up, the average give us a broad idea about assignable causes when they are present. We prefer monitoring the average over the total flow or water level since the average is a more tangible value for operators and process engineers. In case the option of an ideal curve for process monitoring becomes reality in the future, we would recommend this over the use of averages since it gives us much more information.

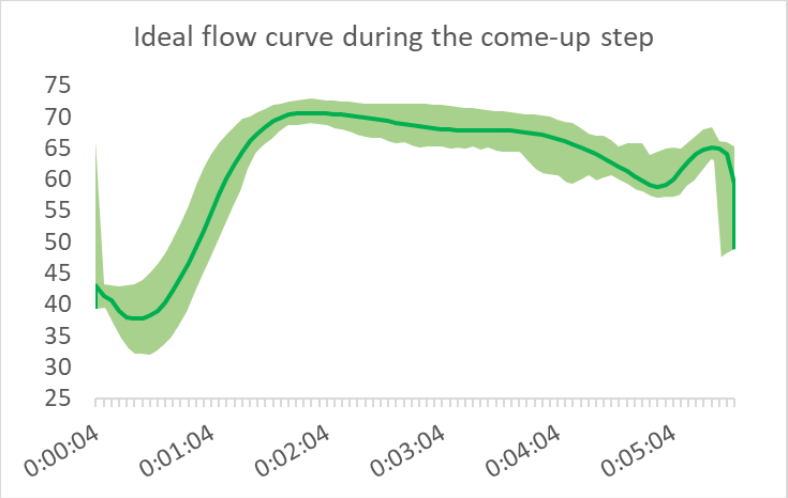


Figure 4.4 Ideal flow curve during come-up process step

4.5 Conclusions on critical process parameters

In this chapter we defined the process parameters that influence the sterility of the products with help of the FMEA. Also, we determined the demands and wishes of Abbott and defined how we are going to measure every individual critical process parameter. As a result of this chapter we summarize all critical process parameters and the way we measure them in Table 4.5.

Process step	Process parameter	Measurement
End of filling PV	Water level PV	Single measurement
	Temperature PV	Single measurement
Come-up	Step time	Single measurement
	Flow	Average
	Water level	Average
Sterilization	Temperature PV	Continuous
	Flow	Continuous
	Water level PV	Continuous
	Pressure PV	Continuous
Cooling	Step time	Single measurement

Table 4.5 Type of measurement per critical process parameter

5. Selection of the method for controlling critical process parameters

In this chapter we choose the best method to monitor and control the critical process parameters. First, in Section 5.1, we choose the type of control chart that we use to monitor the critical process parameters. Next, in Section 5.2, we determine what baseline data we use for our calculations. In Section 5.3 we check the normality assumption per critical process parameter and in Section 5.4 we calculate the control limits. In Section 5.5 we validate our method for controlling critical process parameters, and in Section 5.6 we estimate the value of the process monitoring and control method. Finally, we close the chapter with conclusions in Section 5.7.

5.1 Type of control chart

In this section we decide which type of control chart we use for monitoring. Since the type of control chart that we use depends on the type of measurement and the rational subgroups that we use for our sampling, we first explain these subjects in Subsection 5.1.1. Also, the type of control chart that we use depends on the control chart application phase that we are in, and the demands and wishes of Abbott. We discuss these subjects in Subsection 5.1.2.

5.1.1 Rational subgroups

When we determine the sampling of data we determine what we are going to plot on the control charts. In Section 3.8 we discussed the approach to take samples of produced products as close to each other as possible. This approach minimizes the probability of assignable causes of variation within a sample, and maximizes the detection of assignable causes between samples. We use this approach when we want to detect any shifts in the process. However, applying rational subgroups to the sterilization process would indicate that we take samples. Taking samples could for example mean that we calculate the average temperature during the sterilization step for $n = 10$ sterilization runs, take the average over all sterilization runs, and plot this average as one data point in a control chart. However, as explained in Chapter 4, we measure the critical control parameters during the sterilization process step continuously. Since we plot every measurement in a control chart we cannot define rational subgroups in our sampling for continuous process parameters. This is due to the sample size of $n = 1$. Due to the sample size of $n = 1$ we can only apply individuals control charts for the continuous process parameters. For the individual measurements and the average measurements (of Table 4.5) it is possible to use a sample size of $n > 1$. However, this does not make sense since we would then use different types of sample sizes for monitoring the same process. Hence, also for the individually measured critical process parameters, we choose to use control charts for individuals.

The sample size is not the only decision that we make during rational subgrouping. When applying rational subgroups we make a distinction between the machines (v14, v15 and v16) that are present at the retort production line. The machines operate independently and thus have their own variability in process parameters. For example, the flow during sterilization for the retort v15 is usually somewhat higher compared to the flow of retort v16. Since the machines operate independently we want to use different control charts per machine. If we would use a pooled data set of all machines to calculate our control limits, we have a larger variability, and thus wider control limits. This is a disadvantage when we apply statistical process control since assignable causes of variation might not be detected when the control limits are too wide. Therefore, we decide to make control charts per machine.

Another aspect that we need to keep in mind when defining the way of sampling are the different types of recipes that are produced. Different recipes are used to sterilize different types of product. The machine settings are slightly different per recipe that we produce. The setting that deviates for different recipes is the rotation per minute. Some products are produced at a rotation per minute

(RPM) of 18 while other products are produced at an RPM of 26. The rotation has a large influence on for example the water level and the flow during a sterilization run. In Figure 5.1 we show a scatterplot of the average water level over a period of roughly 4 months. Every data point in the scatterplot represents the average water level during the sterilization process step of a single sterilization run. The large difference in water level between the two rotation speeds shows that it is better to group the data per rotation speed. If we do not group the data per rotation speed we would see large deviations between sterilization runs that operate on a different rotation speed. The large deviations are probabilistic variability since the process naturally operates on two rotation speeds. The large variability that we experience when we do not group the data per rotation speed makes it harder to detect any special causes of variation due to unnecessary wide control limits. Therefore, as well as

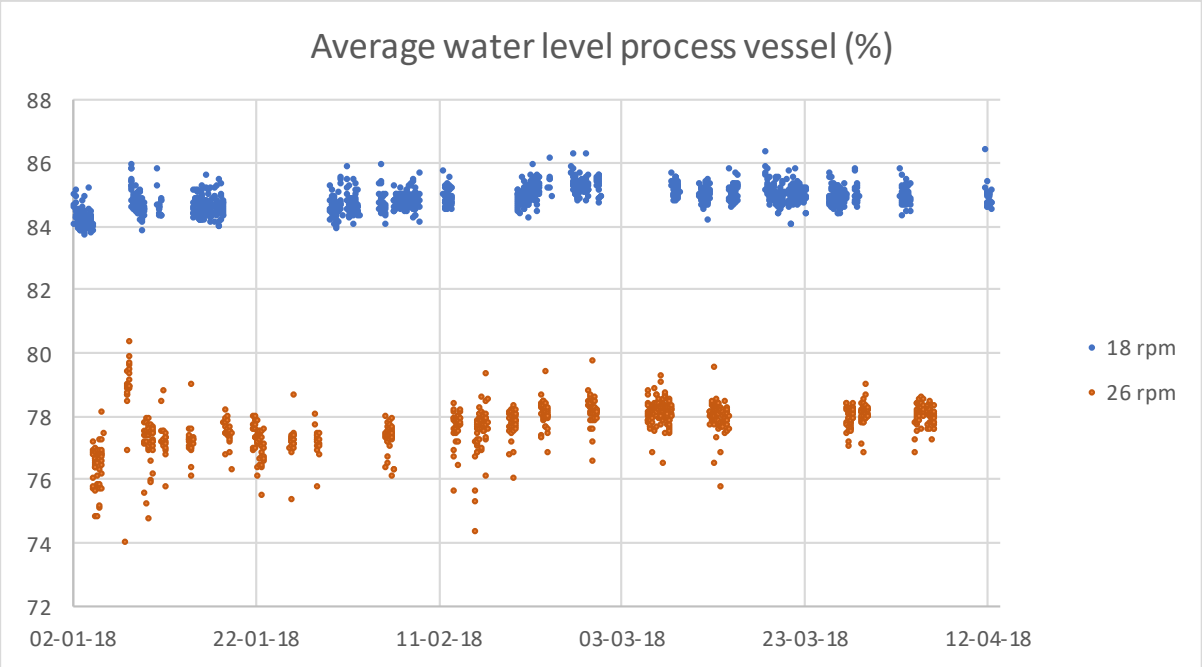


Figure 5.1 Example of rational subgroups

grouping the data per machine, we decide to also group the data per rotation speed.

5.1.2 Control chart application phase

Since we choose to use control charts for individuals we have multiple charts that we can use for monitoring. For example, we can use the I-MR chart, a Cusum chart or an EWMA control chart. The Cusum and EWMA chart are very good options if we want to detect small process shifts (e.g. 1.5 sigma). Also, the Cusum and EWMA charts are very insensitive to the normality assumption, while the I-MR chart shows a very bad performance when the data follows a non-normal distribution. However, in case our data does not follow a normal distribution we can use the approach explained in Section 3.11 to obtain a good ARL. Therefore, also the I-MR chart is a good option for process monitoring.

One subject that we discussed in Chapter 3 are the control chart application phases. In application Phase I we set up control charts from historical data to see if the process is in control. The control charts used in Phase I are most useful due to their ease of use and the effectiveness of the charts. Currently, Abbott is at the start of applying statistical process control to their process. Since the I-MR chart is the only individuals chart applied in Phase I we choose to use the I-MR chart for process monitoring. This is also in line with the demands and wishes of Abbott, in which they state that they want a tool that is easy to use and implement. Since the Cusum and EWMA control charts are somewhat more difficult to understand and explain to others (e.g. the end users of the charts), the I-

MR control chart would be the preferred option to start with. In a later statistical process control stage the Cusum and EWMA control charts might also be very good options. In Chapter 7 we elaborate on application Phase II control charts in the recommendations.

5.2 Baseline data

This section describes the collection of the data that we use. First, in Subsection 5.2.1 we describe the baseline of data that we use to check the normality assumption and calculate the control limits. Next, in Subsection 5.2.2 we explain the validation of our data.

5.2.1 Baseline for probability plot and control limits

To check if the critical process parameters follow a normal distribution we analyze historical data. As explained in Chapter 3, Montgomery states we need about 200 to 300 data points to set up initial control charts and make conclusions about the distribution. Therefore, we decide, in consultation with the Process Engineer, to use samples of 255 sterilization runs that have been produced during the period of 1-Apr-18 to 9-May-18. Due to the subgroups we make use of multiple samples, each consisting of 255 sterilization runs. We group the samples of sterilization runs per machine and rotation speed. The samples of sterilization runs exclude any test runs that were not used for production. We retrieve the data from Abbott's server with help of a so called 'PI-DataLink', which is an Excel add-in. To analyze critical process parameters per process step we use a filter in the data link. To explain the data collection procedure we give an example of the data collection for the temperature during sterilization in Table 5.1.

Data tags	104260_TT003_PV	104260_Speed_SP	104-260.CV_BatchNumberRaw	104260_Step
Tag description	v15 - Temperatuur onderketel	v15 - Toerental Setpoint	v15 - Batch Number	v15 - Step
Filter	instr('104-260.CV_BatchNumberRaw',"TEST")=0 AND '104260_Speed_SP'=26 AND '104260_Step'=4			
Start	01-Mar-18			
End	15-May-18			
Sample interval	2s			

Table 5.1 Data collection with OSI-PI datalink

The data tags represent the information from the database that we want to use. For example, the tag "104260_TT003_PV" represents the process vessel temperature of the retort v15 machine. The other data tags represent the setpoint of the rotation speed, the batch number and the process step of a sterilization run. In this example we apply the filter to exclude test runs, filter on the rotation speed, and to filter on the sterilization process step (which is Step 4). We use a start and end time to receive all measurements between the two dates. The sample interval determines how ofter we get a measurement. This can for example be every second, minute or day between the start and end day. We use a sample interval of two seconds to get a realistic view of the temperature during a sterilization run. Since the sterilization process step takes 3 minutes and 20 seconds (± 2 seconds) we receive approximately 100 temperature data points for a single sterilization run. Therefore, the total sample consists of approximately (255 sterilization runs) * (100 measurements per sterilization run) = 25,500 temperature measurements. We use a sampling interval of two seconds since we experience a bad performance of the PI-DataLink add-in if we use a larger dataset. Also, the 100 data points give a good representation of the temperature during a sterilization process step, so we do not require any more measurements.

The procedure above describes how we gather the baseline data for continuous measurements. We use similar procedures to gather the baseline data for the critical process parameters that we measure by single measurements and the critical process parameters for which we use average measurements. In Figure 5.2 we see the temperature curve of a sterilization run highlighted in blue and the process step highlighted in light blue. For the baseline of single measurements we use a 'timed data' function in the PI-Datalink which gives us the value of a process parameter at a certain point in time. For

example, if we want the temperature at the start of the come-up process step (Step 3, highlighted in green), we measure the temperature at time $t = 0$ in Figure 5.2. If we want to know the average of a parameter during the come-up process step, we calculate the average between points $t = 0$ and $t = 1$ with a additional function of the PI-Datalink.

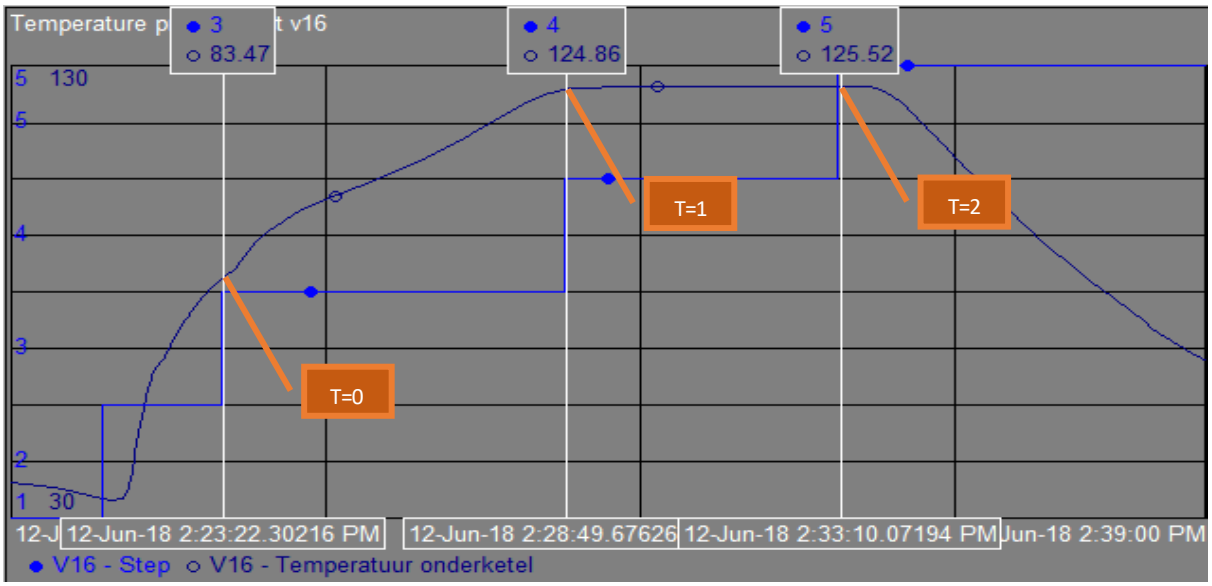


Figure 5.2 Sampling step times

5.2.2 Data validation

According to Cooper & Schindler (2008) the scientific requirements for a project call for the measurement process to be reliable and valid. The validity is the extent to which we measure what we want to measure. The reliability of a measurement tool describes the consistency of the measurement tool, i.e. the degree to which the measurement tool supplies consistent results. In our research, the measurement tools that generate our data consist of sensors inside the retort machines. Abbott has her own procedures to ensure reliable and valid sensor measurements. Since Abbott has years of experience in validating her measurement tools, and since we have no reason to doubt the effectiveness of Abbott's validation procedures, we leave the data validation outside the scope of our research. Therefore, in this research we use the data that is presented to us by Abbott's OSI-PI software system.

5.3 Normality assumption

Since we use an individuals control charts it is most important to check the normality assumption for our data. In case the data approximately follows a normal distribution, the most straightforward way to calculate the control limits is to set the upper and lower control limit as $\pm 3\sigma$ from the mean. However, as explained in Chapter 3, when the data does not follow a normal distribution we have a severe decrease of ARL and may draw false conclusions if we set the control limits $\pm 3\sigma$ from the mean. Therefore, we check the normality assumption with help of Q-Q probability plots. In Figure 5.3 we see a probability plot of the water level of the process vessel at the start of the come-up process step. Since we have a total of 255 sterilization runs we also have 255 data points for the water level of the process vessel at the start of the come-up process step. We plot the data points with help of the procedure as described in Section 3.5. The points plot along a straight line which indicates that the data is normally distributed. Also, the p-value of 0.151 tells us that we cannot conclude the data does not follow a normal distribution. In Figure 5.4 we show another probability plot. In this case we plot the data of the water level during sterilization. In the figure we clearly see that the measurements do

not plot along a straight line. Also, the p-value in Figure 5.4 shows that we reject H_0, which means we conclude that the data do not follow a normal distribution.

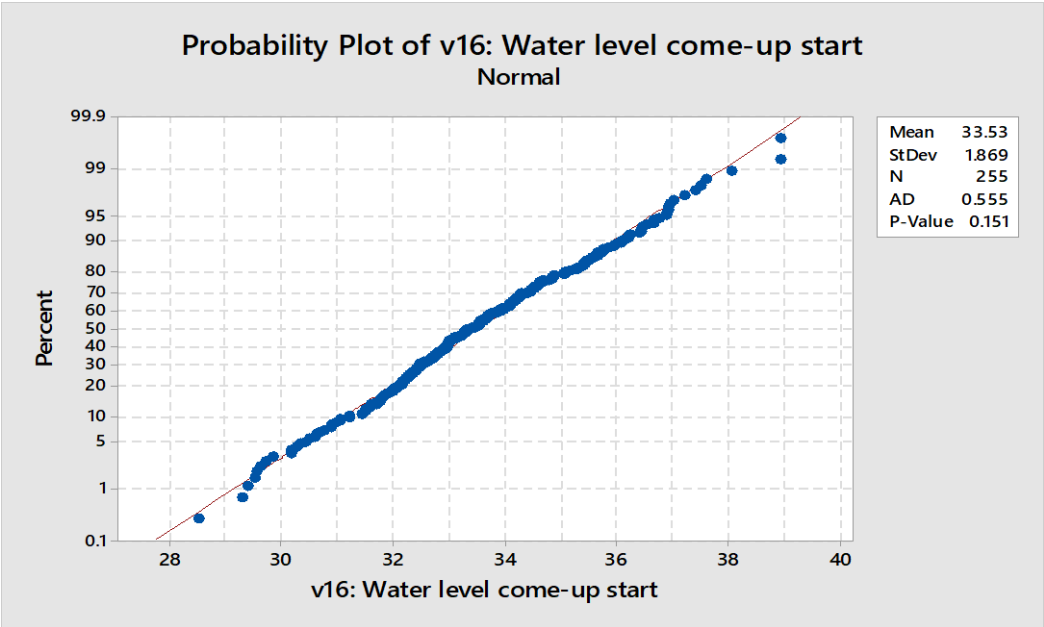


Figure 5.3 Probability plot of water level at the start of the come-up process step

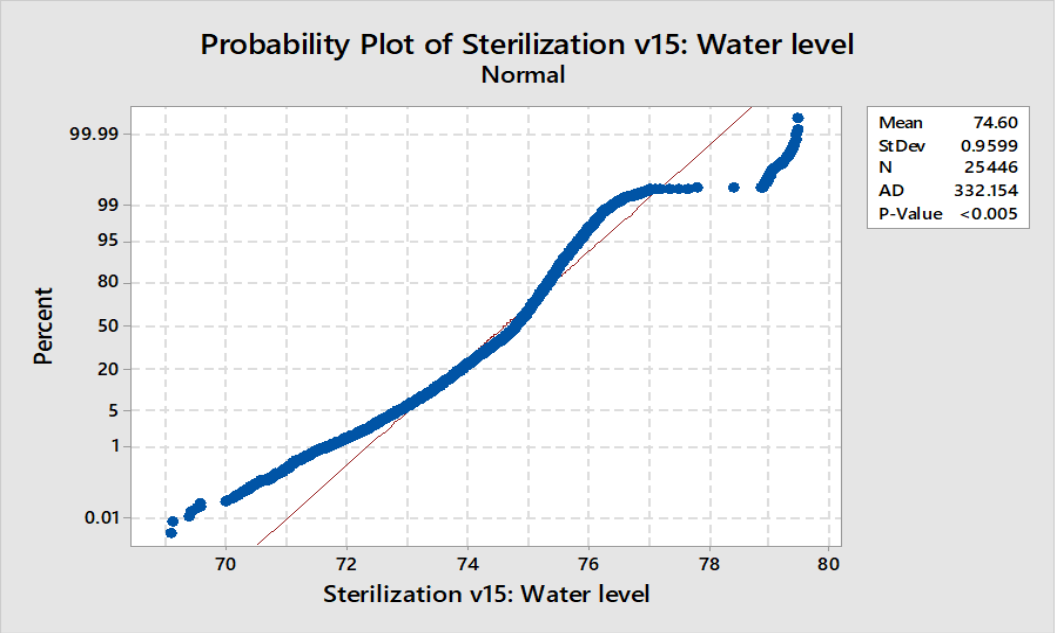


Figure 5.4 Probability plot of water level during sterilization

For the baseline data of every critical process parameter we check if the data follows a normal distribution. We use the probability plots to determine the calculation method for our control limits, which we explain in the next section. We summarize the results of probability plotting in Table 5.2. We see that for the retort v15 and v16 the critical process parameters which we time at the end of the filling PV process step approximately follow a normal distribution. Also, the average flow and water level during the come-up process step approximately follow a normal distribution. Every other critical process parameter does not follow a normal distribution.

Process step	Parameter	Normality test v14	Normality test v15	Normality test v16
End of filling PV	Water level PV	P-value < α = 0.05	P-value = 0.097	P-value = 0.151
	Temperature PV	P-value = 0.647	P-value = 0.741	P-value = 0.053
Come-up	Step time	P-value < α = 0.05	P-value < α = 0.05	P-value < α = 0.05
	Average flow	P-value = 0.071	P-value = 0.201	P-value = 0.112
	Average water level PV	P-value < α = 0.05	P-value = 0.131	P-value = 0.233
Sterilization	Temperature PV	P-value < α = 0.05	P-value < α = 0.05	P-value < α = 0.05
	Flow	P-value < α = 0.05	P-value < α = 0.05	P-value < α = 0.05
	Water level PV	P-value < α = 0.05	P-value < α = 0.05	P-value < α = 0.05
	Pressure PV	P-value < α = 0.05	P-value < α = 0.05	P-value < α = 0.05
Cooling	Step time	P-value < α = 0.05	P-value < α = 0.05	P-value < α = 0.05

Table 5.2 Summary of probability plots

For the retort v14 the only parameters that follow a normal distribution are the temperature at the end of the filling PV process step and the average flow during the come-up. One remark that we must make about Table 5.2 is that the retort v14 has been out of production due to the retort event. We cannot use the same baseline of data since the v14 has only been in production for a few weeks. Therefore, we perform the normality test and control limit calculations with the data that we have, namely from the end of May until the start of June. Another remark is that we do not see a distinction between the rational subgroups of 18 and 26 RPM. Most recently process engineers found out that the 26-RPM recipe has an advantage over the 18-RPM recipe regarding lethality of a sterilization cycle. Therefore, Abbott decided to change the sterilization process and produce every recipe at a rotation of 26 RPM. This decision affects our study since the 18-RPM recipe will not be used in the future. This is the reason that we only make probability plots and control limit calculations for the 26-RPM recipe.

5.4 Control limits

This section describes the procedure of calculating the control limits. We describe the procedure of calculating control limits for critical process parameters that follow a normal distribution in Subsection 5.4.1, followed by the calculation procedure for critical process parameters that do not follow a normal distribution in Subsection 5.4.2. Per subsection we summarize the control limits and describe how we validate the number of out of control points that we can expect if we implement the control charts. Finally, in Subsection 5.4.3 we explain how we set up the control charts.

5.4.1 Normally distributed data

One option that we can use to calculate control limits for normally distributed data is to use an EDF as described in Section 3.11. We can use an EDF since the procedure works for every underlying distribution. However, a drawback of using an EDF to calculate control limits is that the procedure takes more time compared to calculating control limits with help of an estimate of the population variance. In Section 3.10.1 we explained that we can estimate the population variance with help of the moving ranges of a sample if the data approximately follows a normal distribution. This is also the procedure that software tools like Minitab use (Minitab, 2018). Minitab refers to the procedure described by Harter (Harter, 1960), who uses the same approach as described by Montgomery. Since it saves a lot of time when we use a software tool to calculate control limits we prefer to use Minitab over the use of an EDF. In Section 3.10.1 we gave an example of estimating the population variance from the sample standard deviation. The procedure of estimating the population variance with help of the moving range is similar to the procedure as described in Section 3.10.1. To explain the procedure of estimating the population variance with help of the moving range we show an example of estimating the population variance of the average water level during the come-up process step. To calculate the center line and control limits for the individuals control chart we use the formulas from Table 5.3.

Individuals control chart calculations

$$Center\ line = \bar{x}$$

$$UCL = \bar{x} + 3 * \frac{\overline{MR}}{d_2}$$

$$LCL = \bar{x} - 3 * \frac{\overline{MR}}{d_2}$$

Table 5.3 Calculations individuals control chart

We calculate the moving range of sample i as $MR_i = |x_i - x_{i-1}|$. Since we only have one average water level during the come-up process step per sterilization run, we have a sample size of size $n = 1$. We view the first and the last three water level observations including calculations in Table 5.4. To estimate the population standard deviation σ we look up the value d_2 in Appendix III. Since we have a moving range over $n = 2$ samples we find a value of $d_2 = 1.128$. With help of the sample mean $\bar{x}$ and the average moving range $\overline{MR}$ from Table 5.4 we calculate the upper and lower control limit as $UCL = \bar{x} + 3 * \frac{\overline{MR}}{d_2} = 78.67 + 3 * \frac{1.45}{1{,}128} = 82.52$ and $LCL = \bar{x} - 3 * \frac{1.45}{1.128} = 74.82$, respectively.

Sterilization run (i)	Average water level v15	Moving Range
1	79.45	
2	78.12	abs(78.12 - 79.45) = 1.33
3	80.18	abs(80.18 - 78.12) = 2.06
…	…	…
252	76.94	abs(76.94 - 76.17) = 0.77
253	75.81	abs(75.81 - 76.94) = 1.13
254	78.56	abs(78.56 - 75.81) = 2.75
	$\bar{x} = 78.67$	$\overline{MR} = 1.45$

Table 5.4 Example calculations average water level control chart

We use the calculation procedure as described above to determine the control limits for the critical process parameters that approximately follow a normal distribution. In Table 5.5 we summarize the control limits per retort machine and per process parameter. As described Section 3.9, in application Phase I we plot the baseline data in a control chart to verify the stability of every process parameter. Verifying the stability of the process parameters is important since Abbott does not want control charts to generate an excess of alarms/warnings in production. In Figure 5.5 we give an example of a control chart in which we plot the baseline data of the average water level during the come-up process step (for retort v15). In the control chart we notice that the process is within the control limits for most of the time. There are only three out of 255 data points that plot outside the control limits, which is equal to a probability that a data point falls between the six sigma control limits of $p = \frac{252}{255} \approx 99\%$. If we compare this probability with the generally accepted Phase II ARL probability of an in-control process (which we know from Section 3.7, is 99.73%), we see that there is only a minor difference of $99.73\% - 99\% = 0.73\%$. Since we are still in application Phase I of applying SPC, the minor difference is of less importance since in Phase I we focus on setting up control charts and bringing the process in a state of statistical control. Also, the minor difference in ARL probability won't cause an overflow of alarms when applying the charts in production in Phase I. We repeat the procedure of evaluating the stability for every process parameter that approximately follows a normal distribution.

We evaluate the charts with the Process Engineer and Manufacturing Excellence Engineer, who are responsible for responding to the charts (see Chapter 6). Together we conclude that the normally distributed process parameters were stable enough during the baseline period to apply the charts during production.

Retort	Process step	Process parameter	Upper control limit	Lower control limit
v14	End of filling PV	Water level PV (at end of process step)	38.40	29.16
		Temperature PV (at end of process step)	82.78	78.25
	Come-up	Average flow	75.94	65.36
		Average water level PV	76.88	61.90
v15	End of filling PV	Water level PV (at end of process step)	48.04	38.95
		Temperature PV (at end of process step)	87.04	82.36
	Come-up	Average flow	69.83	64.72
		Average water level PV	82.52	74.82
v16	End of filling PV	Water level PV (at end of process step)	39.00	28.18
		Temperature PV (at end of process step)	82.06	75.49
	Come-up	Average flow	64.33	59.03
		Average water level PV	74.40	66.28

Table 5.5 Control limits for normally distributed parameters

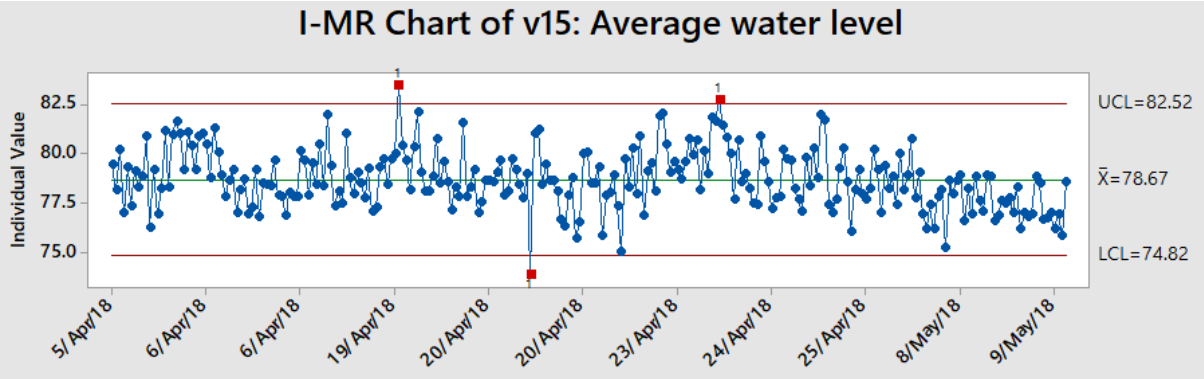


Figure 5.5 Individuals chart of average water level during the come-up process step

5.4.2 Non-normally distributed data

From Section 5.3 we know that the duration of the come-up and the cooling process steps as well as the continuously measured critical process parameters do not follow a normal distribution. Therefore, we calculate the control limits for these critical process parameters with help of an EDF. We briefly explained the procedure of using an EDF to determine an ideal curve in Section 4.4.3. To calculate the control limits for the non-normally distributed process parameters we use the same approach as we did to determine an ideal curve. The only difference between the ideal flow curve calculations and the control limit calculations for the non-normally distributed critical process parameters is the way we sample the data. Since we already explained the data sampling methods in Section 5.2.1 we do not elaborate on this subject any further. To clarify the procedure of calculating control limits for non-normally distributed data we give an example at the hand of the pressure during the sterilization process step.

Earlier we estimated the baseline for continuously measured parameters to consist of 25,500 observations. However, due to the deviation of ± 2 sec. in the sterilization process step time we observe a minor deviation. Hence, for the pressure (and any other continuously measured parameter) we have a baseline of 25,446 observations. To calculate the control limits we first start with denoting the observed pressure values as $p_i, 1 \leq i \leq n = 25{,}446$. Then, we order the observations from small to large, letting $p_{(k)}$ be the k^{th} order statistic in the sample, and $p_{(n)}$ be the largest observation. The

ordered values of the pressure divide the possible pressure values in $n+1 = 25{,}447$ statistically equivalent blocks. Each statistically equivalent block has its own random length. The first block runs from $-\infty$ to $p_{(1)}$, the second from $p_{(1)}$ to $p_{(2)}$, and so forth. The last block runs from $p_{(n)}$ to ∞. In the first column of Table 5.6 we see the observation numbers *i,* followed by the pressure observations p_i in the second column. In column three we see the statistically equivalent blocks. As described before, we order the pressure observations p_i from small to large. From Section 3.11 we know that we can determine the number of blocks that we want our future data to fall between as $j = p * (n+1)$. We use the same probability as for setting up three sigma control limits per side of the mean, namely $p = 0.9973$. Then, we calculate the required number of blocks as $j = 0.9973 * (25{,}446+1) \approx 25{,}378.3$. From Section 3.11 we know that we can calculate the UCL as $p_{(n-\frac{1}{2}((n+1)-j))} = p_{\left(25{,}447-\frac{1}{2}((25{,}447+1)-25{,}378.3)\right)} = p_{(25{,}412.15)}$ and our LCL as $p_{(\frac{1}{2}((n+1)-j))} = p_{(34.85)}$. Therefore, our control limits are $UCL = p_{(25{,}412.15)} = 2.57027$ and $LCL = p_{(34.85)} = 2.43050$, respectively.

Observation (i)	Pressure (pi)	Block #
1	2.41186	1
2	2.41332	2
3	2.41719	3
…	…	4
35	2.43050	…
36	2.43056	36
…	…	37
25411	2.57009	…
25412	2.57027	25412
…	…	…
25444	2.57943	25444
25445	2.57959	25445
25446	2.58293	25446
		25447

Table 5.6 Pressure control limit calculations

We use the same calculation procedure as described above to determine the control limits for the other critical process parameters that do not follow a normal distribution. In Table 5.7 we summarize the control limits for non-normally distributed process parameters. When we use an EDF for calculating the control limits we 'cut off' all points that lay on the outside of 99.73% of the distribution. For this reason, it makes no sense to perform a check by plotting the baseline of the process parameters against these limits. A check by plotting the baseline makes no sense since we would see

Retort	Process step	Process parameter	Upper control limit	Lower control limit
v14	Come-up	Step time	0:05:32	0:05:14
	Sterilization	Temperature PV	125.90	124.72
		Flow	77.02	68.55
		Water level PV	78.20	69.62
		Pressure PV	2.61	2.42
	Cooling	Step time	0:31:08	0:11:28
v15	Come-up	Step time	0:05:38	0:05:06
	Sterilization	Temperature PV	125.58	124.75
		Flow	71.01	68.10
		Water level PV	79.01	70.67
		Pressure PV	2.57	2.43
	Cooling	Step time	0:23:22	0:11:49
v16	Come-up	Step time	0:05:33	0:05:20
	Sterilization	Temperature PV	125.73	124.77
		Flow	69.12	64.36
		Water level PV	80.28	72.44
		Pressure PV	2.60	2.43
	Cooling	Step time	0:24:17	0:11:01

Table 5.7 Control limits for non-normally distributed parameters

that 0.27% of the observations plot outside the control limits. In Section 5.5 we show how we perform a check when we plot control limits calculated from a baseline against a new dataset.

When we plot the continuously measured process parameters in control charts we generally receive a large number of data points in a relatively short amount of time. Due to the large number of observations we obtain unclear process charts when we plot multiple days of production in one control chart. Since we want the control charts to be clear on first sight we reduce the number of observations by making use of an exception test. An exception test is a test that we can use to reduce the number of data points that we gather over a certain time period. We can automatically perform exception tests with help of OSI-PI. We explain how an exception test works with help of Figure 5.6.

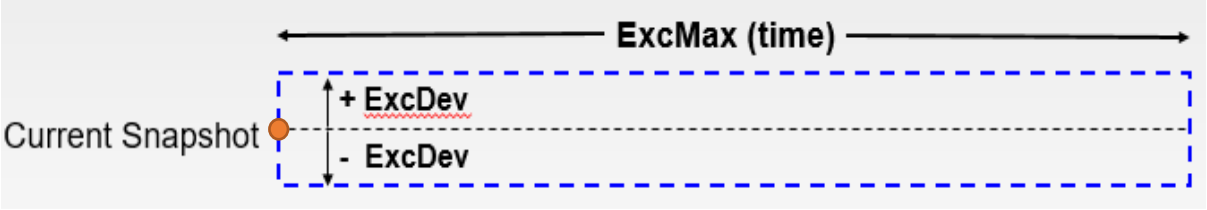


Figure 5.6 Exception test

The current snapshot (the orange dot) represents the value of a process parameter at a certain point in time. If we choose to only use the values after we executed the exception test, we only use the values that plot outside the blue dotted box. For example, if the current snapshot of the water level is 70%, and the water level stays within 70% ± ExcDev, we do not register any new values until we exceed the maximum time ExcMax. The exception test is very useful when we plot continuous measurements in control charts since we only want to see the changes of a process parameter. If a process parameter does not deviate between a certain time interval (ExcMax in this case), we are not interested in all the values between the current snapshot and ExcMax. When the value of a process parameter changes to a point outside the blue box we are interested in the new value and we do want to plot the new value in a control chart. When a point plots outside the blue box, this point becomes the new current snapshot. We summarize the exception test deviations for our continuously measured parameters in Table 5.8. In Figure 5.7 we give an example of a continuously measured parameter by plotting the baseline data of the temperature during sterilization in a control chart. We see that the process mean as well as the variability is very stable over time.

Description	Excdev	Excmax (sec)
Flow	0.25 m3/h	600
Water level	0.005	600
Pressure	0.005 bar	600
Temperature	0.075 °C	600

Table 5.8 Exception test values

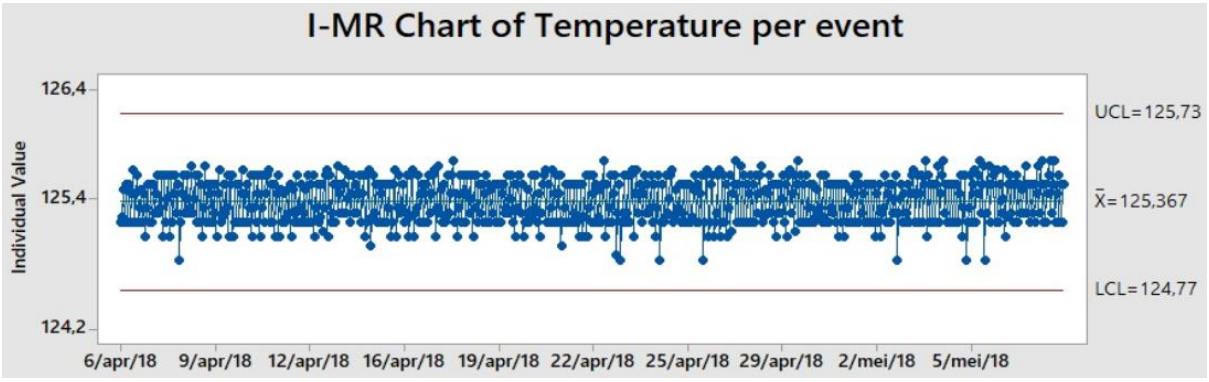


Figure 5.7 Retort v16 individuals chart temperature during sterilization

5.4.3 What do we plot in the control charts

In a meeting with the Process Engineer and the Manufacturing Engineer we discussed the information that we want to see in the control charts. One request that was posed during the meeting is that it's preferred to see the behavior of the critical process parameters over a period of two working weeks

(10 days). Plotting the measurements of two weeks allows the Engineers to look back a few days and compare the current observations of the process parameters with the observations of a few days ago. Plotting more than two weeks of production in control charts results in control charts that contain too much information. Therefore, we do not want to plot more than two weeks of production in a control chart. When plotting the control charts we plot the control limits that we calculated from the baseline data, obtained from good sterilization runs. Also, we plot the average of the baseline data as a fixed line. We plot new measurements in the control charts to see if there is any deviation over time.

5.5 Validation of monitoring and control method

To validate our choices regarding the type of control chart and the approach to calculate the control limits we test our decisions based on two case studies. We first evaluate the case study of the retort event in Subsection 5.5.1. Then, in Subsection 5.5.2 we validate our choices with another case study, namely a change in lethality during the month May 2018.

5.5.1 Validation with retort event

As explained in Subsection 1.3.1 the retort event was caused by deposits that were found in the piping of the retort v14. The deposits were found in the retort machine during the month September 2017. Due to the deposits in the piping of the machine it was not sure if the produced products complied with the commercial sterility standards. To make sure Abbott would not deliver commercially unsterile products to the market Abbott decided to discard a significant number of products that were still on stock. With help of the process monitoring solution explained in this chapter we want to evaluate if we would detect an event like the retort event in case we implement our solution. We do this by establishing a baseline of data prior to the retort event, and see if we would have detected changes in the critical process parameters that we selected with help of the FMEA.

The control limits that we calculated with the baseline data of Section 5.2.1 may not apply to the sterilization process from the year 2017. This is due to process changes like adaptions in machine settings and maintenance actions that were performed on the machines over the last year. Therefore, we use a new baseline of data. To determine the time period that we want to use for the baseline calculations we make a broad scatterplot of the flow prior to the detection of the deposits in the machine (thus, prior to September 2017). We show the scatterplot in Figure 5.8, in which each blue dot represents the average flow during the come-up process step of a sterilization run.

In Figure 5.8 we see two green circles. The green circle at the right-hand side of Figure 5.8 represents the flow after the piping of the retort v14 was cleaned from the deposits. Since the deposits blocked the piping and the valves of the retort machine the deposits were the root cause of the decreased flow. In the left-hand side circle in Figure 5.8 we see that the flow is roughly the same as the flow after the cleaning of the piping. Since the flow during the period between the two green circles shows a much larger spread compared to the flow inside the two green circles we use the flow data from the left-hand side circle for our baseline calculations. Therefore, our baseline data consists of measurements from 01-Mar-17 to 30-Apr-2017. We use the critical process parameter measurements of the retort v14 and filter for the 26-RPM recipe. First, we check the normality assumption for each parameter with probability plotting. Next, we calculate the control limits as described in Subsection 5.4.1 and 5.4.2. We summarize the results of the normality tests and control limit calculations in Table 5.9.

When validating our solution choice we plot the first two weeks of May 2017 for every critical process parameter in a control chart. Since Minitab automatically calculates control limits based on an estimate of the standard deviation we use Excel while plotting the charts. We use Excel since we

require an EDF to calculate most of the control limits, instead of an estimate of the population standard deviation.

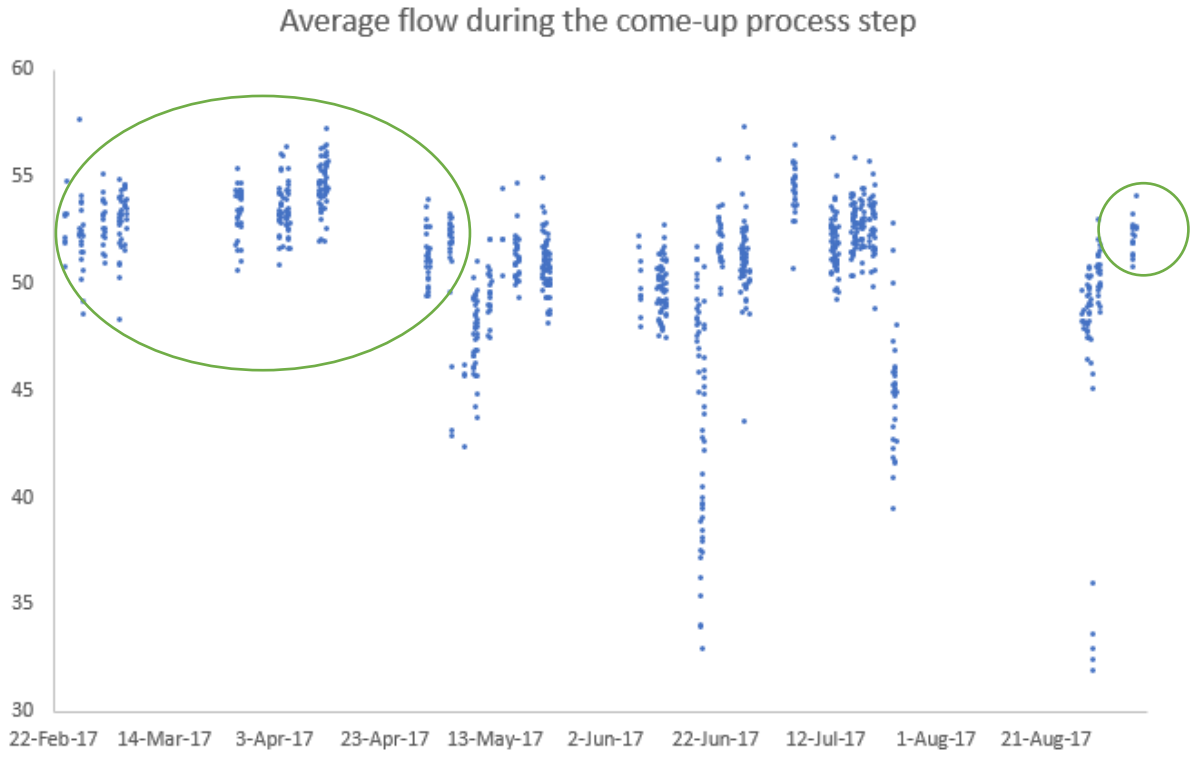


Figure 5.8 Average flow per sterilization run during come-up process step

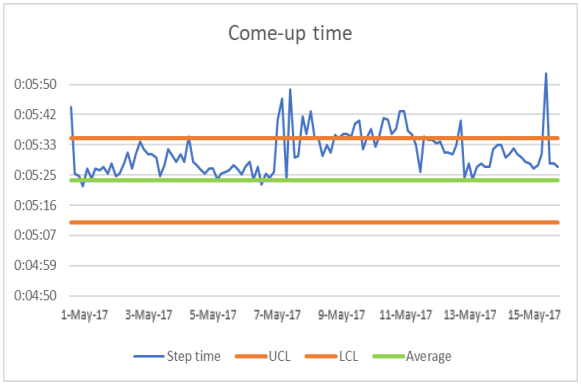
Retort	Process step	Process parameter	Upper control limit	Lower control limit
v14	End of filling PV	Water level PV (at end of process step)	42.11	33.95
		Temperature PV (at end of process step)	82.22	78.56
	Come-up	Step time	0:05:35	0:05:11
		Average flow	62.27	57.82
		Average water level PV	78.08	68.32
	Sterilization	Temperature PV	125.61	124.83
		Flow	66.72	60.53
		Water level PV	74.68	66.46
		Pressure PV	2.59	2.41
	Cooling	Step time	0:29:15	0:11:09

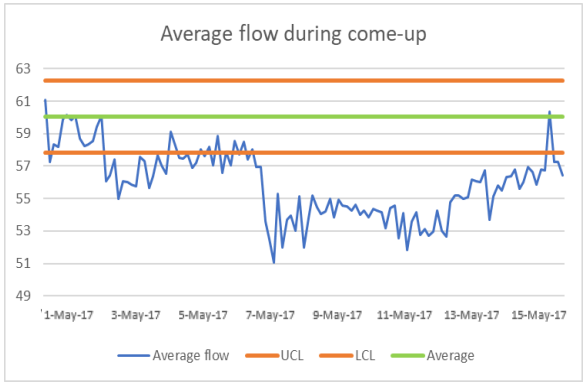
Table 5.9 Control limit calculations retort event baseline

In Figure 5.9 we plot the process parameters that show a deviation during the first two weeks of May 2017. We see a severe increase of come-up time as well as a severe decrease in average flow during the come-up process step. Also during the sterilization process step we see deviations in the flow. In the control chart of the come-up time we see that the measurements always plot above the average (green line) of the baseline data. Also, the flow during the come-up process step not only plots below the average of the baseline, but also plots well below the lower control limit. Finally, the flow during the sterilization process step almost always plots below the average, and sometimes also plots below the lower control limit. For the other process parameters of Table 5.9 we did not see significant changes.

We can clearly see that the control charts show changes in three of the critical process parameters during the first two weeks of May 2017. This is in great contrast compared to the retort event in which an operator detected a change in one of the process parameter at the beginning of September 2017. This is a difference of more than 3 months, in which production continued. When we would implement

the periodic review of control charts we would detect an event similar to the retort event in a significant shorter amount of time.





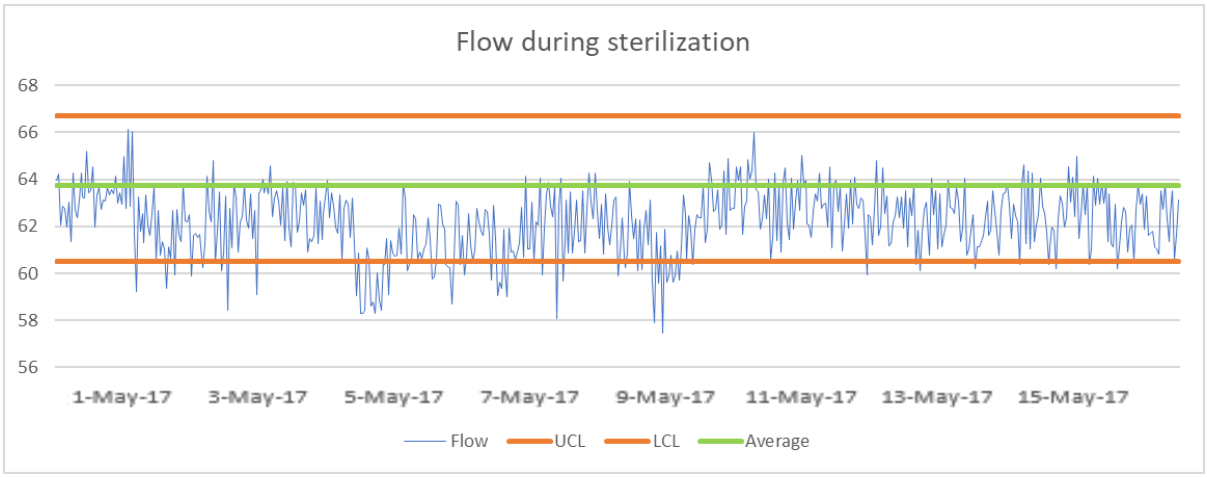


Figure 5.9 Change in process parameters during retort event

5.5.2 Validation with change in lethality

As described in Subsection 2.4.3 Abbott's Process Engineer validates the retort machines every two weeks. During a process validation the Process Engineer measures the temperature at the inside of every retort machine during several sterilization runs. Measuring the temperature inside the retort machines is in contrast with production, during which we measure the temperature in the piping of the machines. During the validation of Week 22 (28-May-18) the Process Engineer found out that there was a decrease of temperature inside the retort v15. After executing a root cause analysis Engineers found out that one of the valves of the retort v15 was clogged.

Performing validation runs is a mandatory preventive control which is in place due to the retort event of last year. The bi-weekly validation runs are very time consuming, and generally cost more than a day. A monitoring and control solution might be able to reduce the number of validation runs that we must execute every year since the tool helps to timely detect assignable causes of variation. Therefore, we evaluate if we would have detected the clogged valve of the retort v15 with the solution as described in Chapter 5. Since we used baseline data from 1-Apr-18 to 9-May-18 for our calculation in Chapter 5, we can use the control limits from Table 5.5 and Table 5.7 to validate our solution.

Since there was no decrease in lethality during (or prior to) Week 20 we evaluate the critical process parameters between Week 20 and Week 22 with help of control charts. While evaluating the parameters we determine if we can detect any changes of the critical process parameters in the control charts. In Figure 5.10 we show the control charts of the critical process parameters that show a significant change. We can see that the flow during the come-up process step increased around the

14th of May, as well as the flow during the sterilization. The increase in the flow shows a clear assignable cause of variation, since in both control charts the flow plot well above the upper control limits.

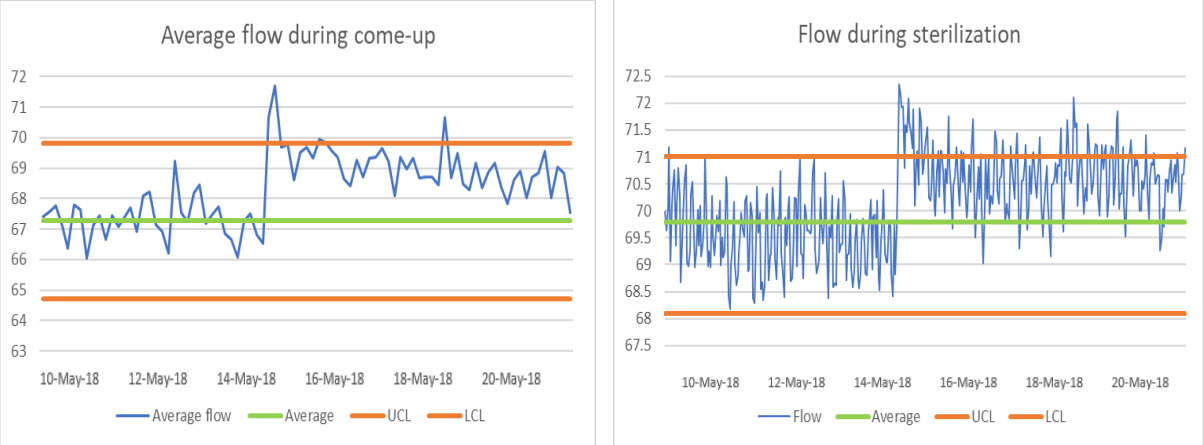


Figure 5.10 Change in process parameters due to clogged valve

5.6 Value of process monitoring and control

Together with the engineers that are involved in the SPC project we estimate the savings that SPC can yield. The savings are mainly expressed in the amount of time that we can save. The time savings related to SPC consist of batch reviews and lethality tests that become obsolete if we implement SPC. Currently, the Process Engineer must review and approve the behavior of the process parameters of every produced batch. This is a mandatory procedure which was initiated because of the retort event. Reviewing the process parameters of every batch roughly takes up to 4 hours a week. Besides the batch reviews the Process Engineer must periodically execute lethality tests, during which the Process Engineer measures the temperature at the inside of the retort machines. The Process Engineer executes the lethality tests to ensure that there were no changes in the temperature at the inside of the retort machines. The lethality tests require roughly 4 hours per week time of the Process Engineer. Due to the execution of the lethality tests the retort production line cannot be used for production during roughly 4 hours per week. If we implement SPC the batch reviews as well as the lethality tests become obsolete since we analyze the critical process parameters with help of the control charts. If there is a change in the process parameters that causes a decrease in lethality (as described in Subsection 5.5.2) we can detect the change with help of the control charts. Therefore, we do not require to execute the lethality tests periodically if we implement SPC. We summarize the time savings in Table 5.10.

Savings of process monitoring and control		
Object/Function	Time savings	Reason
Process Engineer	8 h/week	Obsolete batch reviews & lethality tests
Retort 250 mL production line	4 h/week	Obsolete lethality tests

Table 5.10 Potential savings related to process monitoring and control

Abbott's management calculates with an hourly cost rate of €2200/hour for the retort production line. Since we increase the capacity of the retort production line with 4 hours per week when we implement SPC, the value of the increase in capacity is equal to €8800/week. Abbott produces about 48 weeks a year. Therefore, the value of the capacity increase is estimated to be $48 * €8800 = €422{,}400$/year. One remark that we must make about these calculations is that the calculations merely represent the value of extra capacity that we have when implementing SPC. This means that

we cannot produce the same number of products with less time if we implement SPC. However, the extra capacity can be very helpful if Abbott wants to increase production of 250 mL products in the future.

The value of SPC not only lays in the time savings that we can establish. Also, we incur savings that are more difficult to express in numbers. For example, the implementation of SPC helps to prevent similar events like the retort event in the future. The retort event caused a significant amount of damage due to a large number of products that had to be thrown away. Also, managing the event after the deposits in the piping of Retort v14 were detected resulted in a cost of about 4 full time employees for roughly 4 months. Since the financial damage of the retort event is classified and since it is hard to determine a probability of the occurrence of an event like the retort event, we cannot express these savings in time or money per period of time. However, due to the validation of our solution in Section 5.5, we can conclude that implementing SPC prevents similar events from happening in the future. The validation shows that we would have detected the event in less than a week, compared to the old situation in which it took 4 months to detect the event.

When we estimate the value of SPC it is important to keep in mind that the implementation of SPC also results in costs. Since we can use the OSI-PI software system to visualize the control charts, the costs of an implementation mainly consist of time investments. Time investments are required by the employees who update and analyze the control charts as well as the employees who execute preventive actions. We estimate that analyzing the control charts requires a time investment of roughly 10 minutes per day if we summarize the control charts in a single dashboard. Recalculating the control limits according to the described procedure and updating the control charts takes roughly 8 hours for all process parameters. We recalculate the control limits every six months or after a process change. The Process Engineer is able to perform the calculations and is the one responsible for updating the control charts. Currently, we do not exactly know how often a process change occurs. Therefore, it is hard to estimate the required time investment for preventive actions as well as the follow up on these actions. Since we plotted the baseline data in control charts in Section 5.4, and saw that the process parameters were stable during the baseline period, we do not expect a very large time requirement for preventive actions. Also, the time investment that we require to deal with false alarms is relatively low, since we use a false alarm probability of 0.27%. In case the process experts experience this false alarm probability as too large, they are able to widen the control limits with help of the previously described procedure. For further elaboration on the control chart evaluation procedure and the required time investment, we refer to Chapter 6.

5.7 Conclusions on process monitoring method

In this chapter we chose the best method for Abbott to monitor and control their critical process parameters. We chose to monitor the process parameters with a control chart for individuals. Also, we used two different methods for calculating the control limits of the critical process parameters, based on their underlying distribution. We validated our decisions with two case studies. In both case studies we saw significant changes in multiple process parameters. We conclude that the monitoring and control solution is a very valuable tool when Abbott wants to timely respond to changes in their processes.

6. Implementation of process monitoring and control at Abbott

In this chapter we determine who needs to act in which way if the process parameters go out of control. We start with an out-of-control-action plan in Section 6.1, followed by the implementation in Section 6.2. In Section 6.3 we give recommendations for further implementation. Finally, in Section 6.4 we close the chapter with conclusions.

6.1 Out-of-control-action plan

In the out-of-control-action (OCAP) plan we describe who needs to act in which way if one of the process parameters is out of control. One important aspect of the OCAP is that we need to know when exactly we need to act on process parameters that are out of control. As discussed in Section 3.6 we can use sensitizing rules to help detect an out of control process. Sensitizing rules can help interpreting and detecting trends on control charts. For example, one rule states that the process is out of control when one observation plots outside either one of the two control limits. The other rules focus on detecting trends by for example stating that the process is out of control when we see multiple successive points above or below the mean. Even though the sensitizing rules may help detect assignable causes of variation faster, there are also drawbacks when we apply sensitizing rules. One drawback is that sensitizing rules increase the number of false alarms (see Section 3.6). Another drawback is that we plot continuous measurements during the sterilization process step. Since we plot continuous measurements in control charts we obtain many data points per control chart, even after applying an exception test. Due to the large number of data points it is somewhat difficult to apply strict rules for detecting an out of control process. For example, in the control chart of Figure 6.1, it is difficult to apply strict rules for detecting trends.

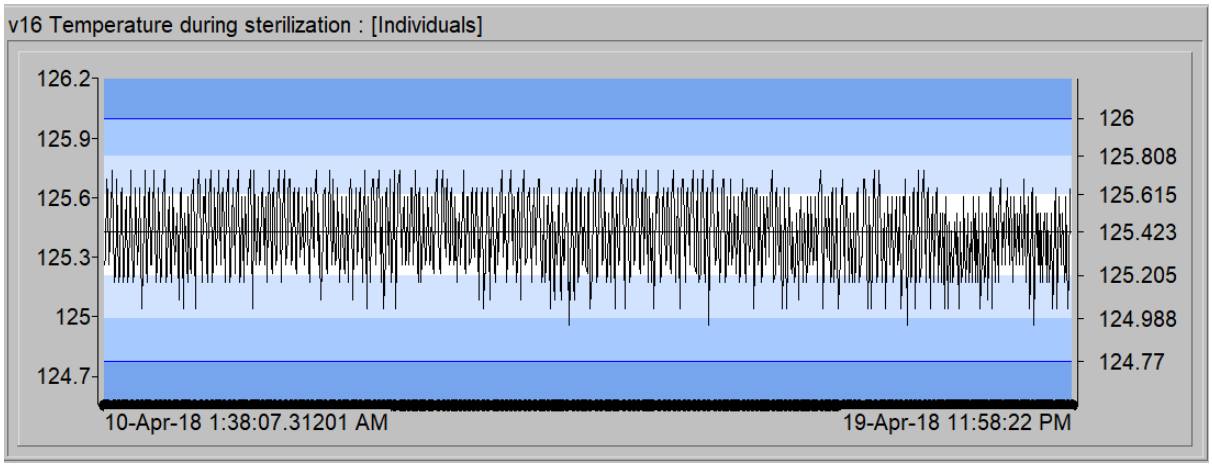


Figure 6.1 Temperature during sterilization

Due to the large number of data points it is difficult to apply strict sensitizing rules for the continuously measured parameters. One option to deal with this problem is to replace the continuous measurements with plotting the average measurement during a process step. Plotting the average per process step results in one data point per process step, instead of multiple data points per process step. We think this would be a good option to deal with the problem of too many data points. However, as explained in Subsection 4.4.2, a drawback of plotting averages is that we cannot see any high or low peaks in the process parameters if we plot the average during the sterilization process step. Also, (as explained in Subsection 4.4.3) currently OSI-PI does not allow us to plot averages in a control chart. Plotting averages is possible but requires an investment of several days of Abbott's Data Specialist. Since plotting averages is not something that we can currently implement we elaborate further on this subject in Chapter 7. For now, we continue plotting continuous measurements in the

control charts for the sterilization process step. One strict rule that we apply for detecting an out of control process is that we consider the process being out of control if a single data point plots outside either one of the control limits.

Now we know when to consider the process being out of control we need to decide who is responsible for analyzing the control charts. One option that we evaluate is to use a procedure similar to the current situation, in which an operator acts if there is an alarm on a specification limit. We described this procedure in Subsection 2.5.2, which states that an operator must create an AMS procedure when there is an alarm. When an operator creates an AMS procedure the operator puts the production batch on hold until the microbiological laboratory approves the batch. The disadvantage of using the same procedure for control limits is that the control charts serve as a warning that the process is out of control. Surpassing a control limit does not require that an entire batch is put on hold since the process parameter may not yet have passed the specification limit. For this reason, we do not want to create an AMS procedure when a process parameter passes one of the control limits. An additional argument is that an operator does not have the ability to steer the process. Steering the sterilization process is something that a Process Engineer does, usually in consultation with a Manufacturing Excellence Engineer. Since the Process Engineer and the Manufacturing Excellence Engineer can steer the process when the process requires a preventive action we prefer to put them in charge of analyzing the control charts.

In Figure 6.2 we show the process of the evaluation of the control charts. To ensure that we respond to changes in process parameters within one day we analyze the control charts at the retort 250 mL production line every day at 8:30 a.m. During the meeting the process experts of the retort production line are present. When none of the critical process parameters show an out of control process we do not require to take any action. However, in case one of the process parameters does show an out of control process the team must discuss which appropriate preventive actions should be taken. As stated earlier, we consider the process being out of control when a data point plots outside the control limits. Detecting trends is a subjective measure which relies on the discussion which the process experts perform during the analysis of the control charts. The OCAP is a document which lists the possible actions that the team can take if a certain process parameter is out of control. When the Engineers decide to execute a required preventive action, they follow up on the action during the next morning meeting at 10:00 a.m. The meeting at 10:00 a.m. is a root cause analysis (RCA) meeting. During the RCA meeting employees follow up on projects and problems that are present at a specific production line (retort production line in our case). The process repeats every day to ensure that any changes in the process parameters are detected in less than one day after a process change. Since a process change can cause a change in process parameters it is important to re-evaluate the control limits with help of the

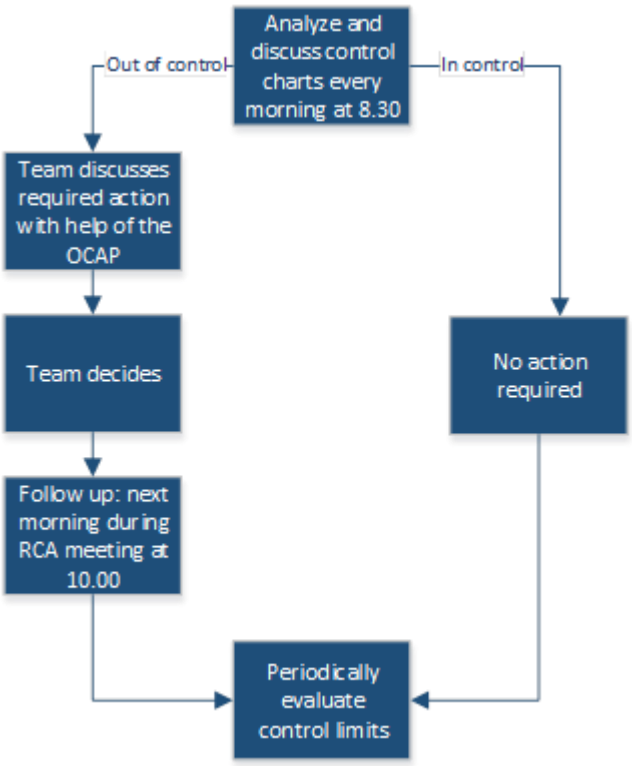


Figure 6.2 Flow chart for control chart evaluation

procedure as described in Chapter 5. A process change can for example occur due to cleaning or replacing parts of the retort machines. If there hasn't been a process change for a period of 6 months we advise to periodically review the control limits to ensure they are up to date.

In Figure 6.3 we see the first version of the OCAP. We constructed the OCAP together with the process experts. The OCAP is a document that stores knowledge about the process. Also, the OCAP helps decision making if the control charts show an out of control process. For every process parameter we see possible preventive actions that can be executed to determine the cause of the problem. Also, the OCAP states the person who is responsible for the execution of the preventive actions. The OCAP from Figure 6.3 is a first version since the document should be updated every time the Engineers find out new solutions to process problems. For example, the retort event taught us that a problem with the flow can be caused by deposits in the piping of the machine. Therefore, we include the inspection of circulation valves in the possible preventive actions if there is an issue with the flow. If there are any new issues in the future we include them in the OCAP. This allows us for continuous improvement and building process knowledge. The ultimate goal of the OCAP is that we have a preventive solution for every possible issue with a process parameter. In case we see deviations in process parameters that cannot be fixed with the preventive actions that are currently listed in the OCAP we decide to perform an RCA. Abbott's employees are trained in performing RCA's, during which they search for the root cause of a problem. When we find a solution to the root cause of a problem, we add the solution to the OCAP.

Out of control action plan (OCAP)				
	Process parameter	Deviation	Preventive actions/controls	Responsible for execution
1	Temperature	Outside control limits	1) Can be caused by wrong water level or pressure. Therefore, check stability of these parameters. 2) Check temperature sensor and clean or replace if required.	Manufacturing Excellence Engineer, Process Engineer and Mechanical Specialist
2	Flow	Outside control limits	1) Inspection circulation valves 2) Remove and inspect circulation pipe 3) Root cause analysis	1) Mechanical Specialist 2) Mechanical Specialist 3) Manufacturing Excellence Engineer & Process Engineer
		Flow suddenly drops to 0 during cooling process step	Sudden drop can be caused by a fouling flow meter. Therefore, clean the flow meter with acid.	1) Mechanical Specialist
3	Water level	Outside control limits	1) Check pressure sensor and clean or replace if required 2) Check pressure control valves circuit (PCV 11, 14 & 45) 3) Root cause analysis	1) Mechanic 2) Mechanic 3) Manufacturing Excellence Engineer & Process Engineer
4	Pressure	Outside control limits	1) Check sensorand clean or replace if required 2) Check pressure control valves circuit (PCV 11, 14 & 45) 3) Root cause analysis	1) Mechanic 2) Mechanic 3) Manufacturing Excellence Engineer & Process Engineer
5	Come-up time	Outside control limits	1) Inspection circulation valves 2) Remove and inspect circulation pipe 3) Root cause analysis	1) Mechanical Specialist 2) Mechanical Specialist 3) Manufacturing Excellence Engineer & Process Engineer

Figure 6.3 Out of control action plan

6.2 Process monitoring and control dashboard

To visualize the control charts in a single document we create a process monitoring and control (PMC) dashboard in OSI-PI. In Figure 6.4 we see the current version of the PMC dashboard on a smart screen in the production plant of Abbott Zwolle. The PMC dashboard contains live control charts of every critical process parameter of the sterilization process step, as well as the step times of the come-up and cooling process steps. The control charts show the measurements of the critical process parameters over the last two working weeks. Every morning at 8:30 a.m. the process experts of the retort production line get together to analyze the control charts and see if there are process parameters that plot outside the control limits. The process experts that are present during the

morning meeting are a Manufacturing Excellence Engineer, Process Engineer, Mechanical Specialist and a Quality Officer. Together the process experts analyze the control charts and discuss the required preventive actions when they see an out of control process. When determining the preventive actions the Engineers consult the OCAP of Section 6.1. In case a preventive action is required there is a follow up of the action during the next morning RCA meeting. During the RCA meeting the Engineers discuss the progress of the preventive actions.

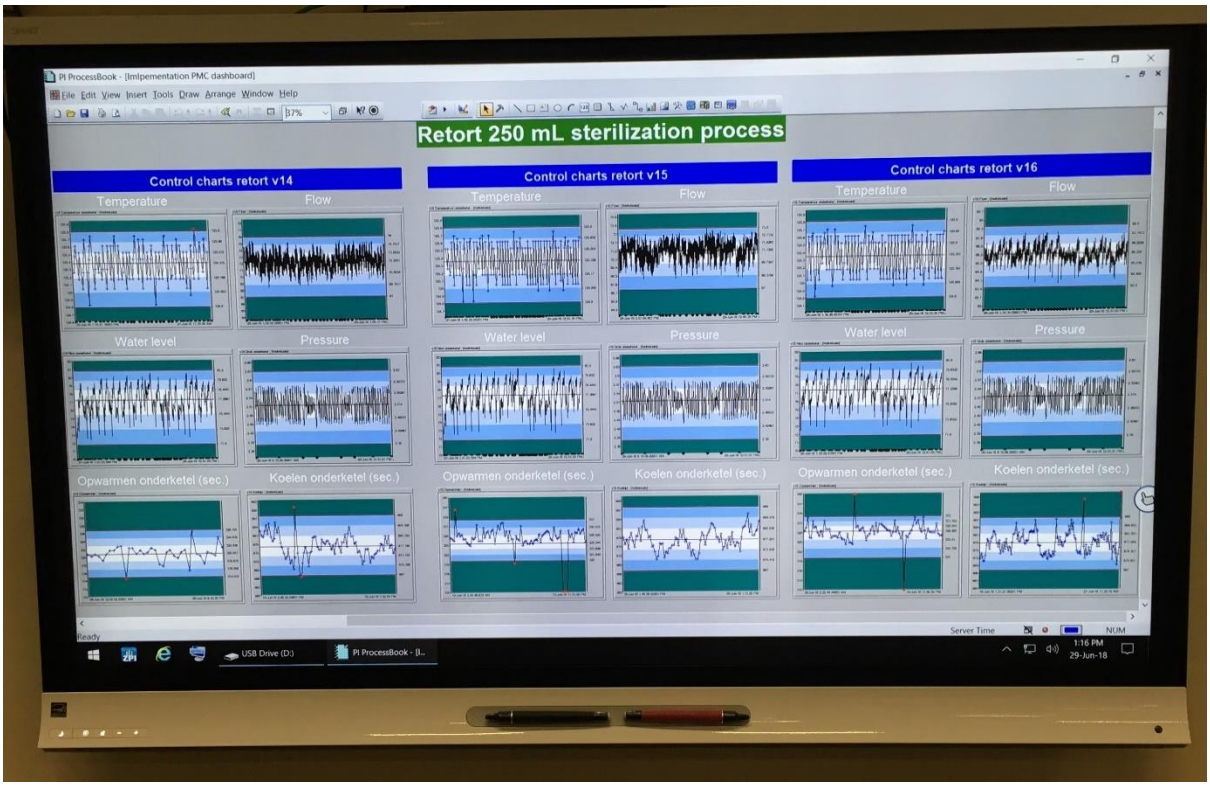


Figure 6.4 Process monitoring and control dashboard

After a few weeks of discussing the control charts every morning during the PMC meeting of 8:30 a.m. we received feedback that the Engineers found it useful to have a PMC dashboard which shows control charts of the process parameters of the last 2 working days, additionally to the PMC dashboard which shows control charts of the process parameters of the last 2 working weeks. Plotting the last 2 days of production in control charts results in less data points per control chart and thus more clarifying control charts. Also, since we discuss the control charts daily, the control charts which plot the last 2 weeks of production show only a minor deviation per day since only the last day of measurements are added to the charts. The prior 9 days of measurements are the same as the day before. Therefore, we constructed a PMC dashboard of the last 2 days of production, additional to the dashboard of the last 2 weeks of production. The Engineers have access to both dashboards during the morning meeting and can use the preferred one.

6.3 Recommendations for further implementation

Since we are not able to fully finish the implementation during the time span of this research we give some recommendations for further implementation. When Abbott follows the recommendations, the result will be a sustainable PMC procedure for every critical process parameter.

1) Add remaining critical process parameters to PMC dashboard

As explained earlier we cannot yet plot control charts for average measurements in OSI-PI. Also, the single measurements at the end of the filling PV process step cannot yet be plotted in control charts

in OSI-PI. Therefore, we recommend to also include these critical process parameters in the PMC dashboard as soon as there is time available of Abbott's Data Specialist. When this recommendation for further implementation is fulfilled, every critical process parameter that we want to monitor and control is included in the PMC dashboard.

2) Secure sustainable PMC

To secure a sustainable implementation of PMC we recommend registering the 6-month review of the control charts. When we register the periodic review of control charts, we can show (to customers and senior management) that we daily execute PMC. Registering PMC shows other people that we are currently in control or working on out of control processes. Also, registering PMC ensures that everyone knows who is responsible and accountable for the execution of PMC. This ensures that the periodic reviewing of control charts does not dilute over time, which may for example happen when employees like a Process Engineer or Manufacturing Excellence engineer rotate to a new function. One option that we recommend is to use Abbott's quality management system (QMS) to register roles and responsibilities regarding PMC. In the QMS we can register that for example a Process Engineer is responsible for revising control limits, and a Manufacturing Excellence Engineer for updating the OCAP. In this way the engineers are together responsible for the execution of PMC.

6.4 Conclusions on implementation

In this chapter we determined who needs to act in which way when the critical process parameters are out of control. We made a flow chart for the process of analyzing the control charts, as well as an OCAP which states the preventive actions that the Engineers can perform when a critical process parameter is out of control. We described the implementation that we executed so far, and finally gave recommendations to fully complete the implementation.

7. Conclusions, recommendations and discussion

In this chapter we discuss the conclusions and recommendations of our research. We start with the conclusions in Section 7.1, followed by recommendations in Section 7.2. In Section 7.3 we close the chapter with a discussion.

7.1 Conclusions

In this research we focused on applying process monitoring and control to the critical process parameters of Abbott's retort production line. We formulated the following main research question at the start of the study:

What is the best way to monitor and control the critical process parameters at the retort production line of Abbott Zwolle?

To answer the main research question we first identified the current situation at the retort production line. Next, we evaluated different solutions to the problem with help of a literature review. We proceeded with determining the critical process parameter and the best way to monitor and control them. Finally, we validated our solution, estimated the value and executed an implementation. Based on our research we draw the following conclusions.

1. Current situation

In the current situation we conclude that we do not exactly know which process parameters influence the sterility of the products. Also, we conclude that some of the process parameters are guarded with alarms, while others are not. The alarms that are present in the current situation are based on past validations and product specifications. There is no use of a tool which helps to timely detect deviations in the sterilization process based on statistics or process variability.

2. Selection of critical process parameters

With help of a failure mode and effects analysis we determined the process parameters that influence the sterility of the products. Next, in consultation with process experts, we determined the way that we want to measure each critical process parameter. To answer the sub question regarding critical process parameters and how to measure them, we summarize the critical process parameters and related measurements of the retort machines in the table below (same table as Table 4.5).

Process step	Process parameter	Measurement
End of filling PV	Water level PV	Single measurement
	Temperature PV	Single measurement
Come-up	Step time	Single measurement
	Flow	Average
	Water level	Average
Sterilization	Temperature PV	Continuous
	Flow	Continuous
	Water level PV	Continuous
	Pressure PV	Continuous
Cooling	Step time	Single measurement

3. Selection of method for monitoring and controlling critical process parameters

The best way to monitor and control critical process parameters at the retort production line is to use a control chart for individuals with three sigma control limits at each side of the mean. We use an empirical distribution function to calculate the control limits of process parameters that do not approximately follow a normal distribution. Every day at 8:30 a.m. the process experts of the retort

production line are responsible for analyzing the control charts. When a critical process parameter is out of control, the process experts are responsible for taking the right preventive action. Determining the right preventive action can be done with help of the out-of-control-action plan, which states who needs to act in which way when a process parameter is out of control (see Figure 6.3 for the OCAP).

4. Validation of monitoring and control method

We validated the monitoring and control method by using historical data of two process changes. For the retort v14 event we saw a significant change in the come-up time, average flow during come-up and the flow during sterilization. For the decrease in lethality for retort v15 we saw a significant change for the average flow during the come-up as well as the flow during sterilization. Since we analyze the control charts on a daily basis, we conclude that the process monitoring and control method helps detecting out of control processes within a single day, in case there is a significant change in the process. Detecting out of control processes within a day is much shorter compared to the old situation, in which it took 4 months to discover the retort v14 event, and 2 weeks to discover the change in lethality of retort v15.

5. Value of monitoring and control method

We estimate the value of the proposed monitoring and control method by estimating the time savings that we establish when we execute an implementation. Applying SPC saves the Process Engineer up to 8 hours per week. Additionally, with implementing SPC we increase the capacity of the retort production line with a total of 4 hours per week. The savings are due to obsolete batch approvals and validation runs. Also, implementing SPC significantly reduces the risk of a food safety event like the retort event as well as possible costs related to such an event. Furthermore, the value of SPC lays in the continuous improvement of the production process when applying SPC. The costs of process monitoring and control consist of a time investment which is somewhat more than 1 hour per week.

6. Implementation

We implemented our monitoring and control solution during our study. Currently, every day at 8:30 a.m. process experts discuss the control charts at hand of a PMC dashboard. When a process parameter is out of control the process experts use the out-of-control-action plan to decide on preventive actions. The dashboard contains control charts of every critical process parameter that we were able to implement during this study.

7.2 Recommendations

Based on the findings of our research we give the following recommendations:

1. Follow up on the recommendations for further implementation

We recommend following up our recommendations for further implementation, as explained in Section 6.3. We recommend adding the remaining critical process parameters to the PMC dashboard as well as documenting the PMC actions. When these recommendations are followed every critical process parameter is included in the PMC dashboard and we obtain a sustainable procedure for PMC.

2. Ideal curve

In this research we provided a procedure to monitor the process with an ideal curve. Using an ideal curve we can compare the fluctuations of a process parameter during a certain sterilization run with the typical fluctuations during historical sterilization runs. The large advantage of process monitoring with help of an ideal curve is that the people who are responsible for analyzing the process only have

to analyze one curve per process parameter, instead of multiple control charts per process parameter. For example, if we monitor every process parameter of Table 7.1 in a different control chart, we obtain a total of 10 different control charts per sterilization run. Since a curve shows us all the information that we could possibly want to know about a process parameter we can monitor the entire sterilization process with a total of 4 curves (temperature, flow, water level and pressure). Therefore, we recommend process monitoring and control with an ideal curve when this becomes a possibility in the future. To assist following up this recommendation in the future we constructed ideal curves for every critical process parameter of the sterilization process. We show the ideal temperature curve in Figure 7.1. The other ideal curves can be found in Appendix V.

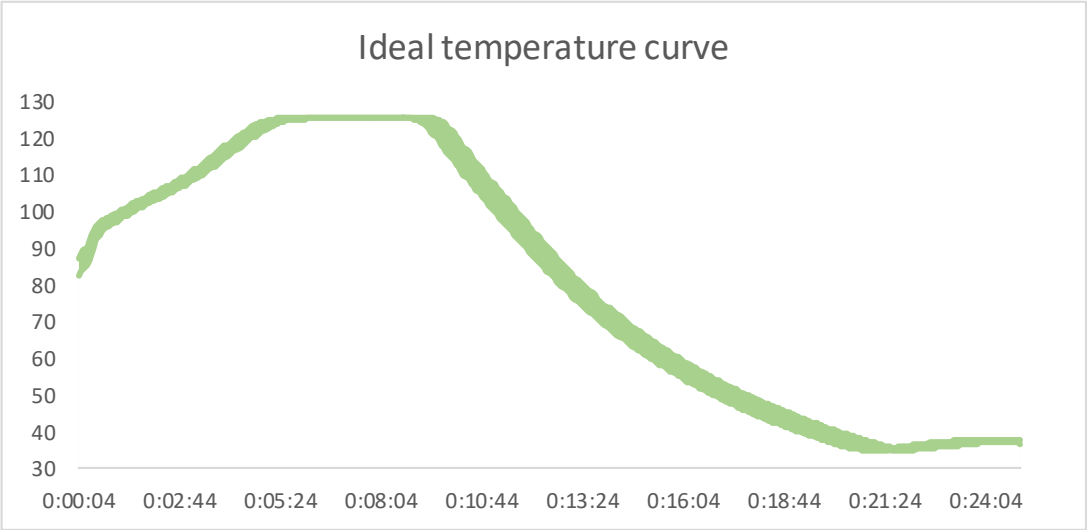


Figure 7.1 Ideal temperature curve

3. Application Phase II control charts

In our research we explained the advantages of application Phase II control charts such as a CUSUM or EWMA control chart. Phase II control charts are more robust to the normality assumption and are better in detecting small process shifts compared to the Shewhart control chart. However, despite the advantages of Phase II control charts we currently do not recommend using these control charts for the sterilization process. In the solution validation we saw that the use of a Shewhart control chart with 3 sigma control limits is sufficient to timely detect future food safety threats. Detecting smaller process deviations may only be useful when we want to detect deviations that do not directly influence the sterility of the products. Examples of these deviations are small deviations in valve settings or very small deposit build up. Before we apply Phase II control charts to detect these small deviations it is important that Abbott's employees first build up more knowledge about the process. Building up process knowledge can help to determine if it is even desirable to detect smaller process changes. In case detecting smaller process changes is not desirable we discourage the use of application Phase II control charts since the use of these charts would only cause an increase of warning/alarms. Also, using application Phase II control charts when we do not want to detect small process changes would make SPC unnecessary difficult.

4. Specification limits

In our research we only briefly discussed specification limits since SPC rather focusses on control limits. However, we do have a recommendation for further research in the field of specification limits. The way that the specification limits for the process parameters are currently determined is not always clear. For example, currently the lower and upper specification limit for the water level are 70% and

90%, respectively. However, these specification limits are based on historical knowledge and experience from, for example, validation runs. Therefore, determining specification limits lacks a fact-based procedure such as for example a design of experiments (DOE). With a DOE we can determine the relation between critical process parameters and the sterility of the products by executing multiple experiments. For example, after executing a DOE we can state how much the water level exactly influences the sterility of the product. This helps setting up fact-based specification limits for the process parameters since we then know how much a process parameter can deviate while still producing products that comply with commercial sterility standards. From a process monitoring and control point of view we can use the specification limits to determine how well our process is capable of producing products that are within the specification limits. Therefore, we recommend a study to determine the exact specification limits of every critical process parameter.

7.3 Discussion

In our research we explained the advantages of plotting continuous measurements regarding the information that we obtain from continuous measurements. Continuous measurements provide all the values that remain after an exception test, allowing us to see the stability of a process parameter in a single chart. However, during the implementation we experienced that it is difficult to apply strict sensitizing rules when we plot continuous measurements. Therefore, if we want to interpret control charts with help of strict rules it might be better to plot averages instead of continuous measurements. Plotting the average of a process parameter during a process step results in only one data point per sterilization run per process step. This is much less compared to the measurements that we plot per sterilization run when we plot continuous measurements. To tackle the problem of not seeing high and low peaks when we plot averages, we can calculate the range of a process parameter during a process step, and plot the range as a single value in a separate control chart. When the range during a process step is out of control, there was either a low or high peak, or both. When applying the described procedure, we obtain control charts like the ones in Figure 7.2. Since the process experts involved in the project initially preferred plotting continuous measurements and since plotting average measurements requires a time investment of a Data Specialist we did not implement averages

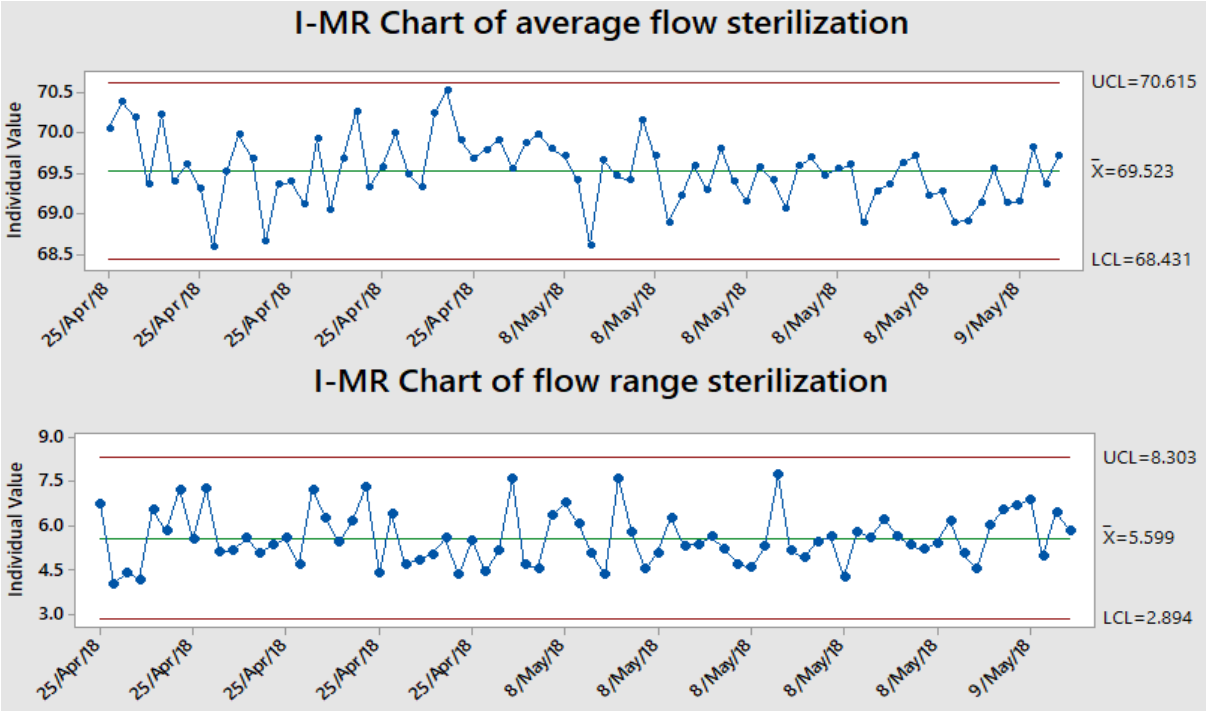


Figure 7.2 Example charts for plotting averages and ranges

and ranges in the PMC dashboard. However, we do think plotting averages and ranges is a good option if we want to obtain clearer control charts.

Another point of discussion are the critical process parameters that did not show a significant change during the validation of the monitoring and control method. When validating our method we experienced significant changes in the come-up time, average flow during the come-up process step and the flow during sterilization. We did not see significant changes in the remaining critical process parameters since we did not have information about other events occuring related to critical process parameters, other than the retort v14 event and the decrease in lethality for the retort v15. It does not mean that monitoring and controlling critical process parameters that did not show a significant change during the method validation is of less importance. The lack of significant change merely points out that food safety events due to large deviations in critical process parameters rarely occur. To prevent food safety events in the future it is important to monitor and control every critical process parameter. For example, when in the future an event occurs regarding a leakage in one of the vessels, we would maybe only see significant changes in the water level, and none in the flow. In that case it is important that we also monitor and control the water level, even if we did not see a significant change in the water level during the validation of our method.

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Appendix I – Process report

.h: 87690NR/V16/1

Documentnr: VI-101-1
Revisiedatum: 09-10-2017

.uid Blik 250ml: Proces rapport

Abbott Nutritionals

.rttijd 27-03-2018 02:46:13 Eindtijd 27-03-2018 03:09:13 Operator Dirk Dalhuisen

Programma naam	323	Product naam	Ensure vanilla non fsmp
Programma nr.	323	Product nr.	3250.5140
Geprog.door	Astrid Smit	Geprog.op	19-01-2007 11:20:37
Gewijzigd door	Leendert Baak	Gewijzigd op	23-12-2016 12:46:09
Vrijgegeven door	Leendert Baak	Vrijgegeven op	23-12-2016 12:46:14

Prg. 323 Stap 1 Fase Opw.Bov.K 27-03-2018 02:46:14

	Input		Output		Onder tol.	-	Boven tol.		Goedkeuring
Tijd	0: 0 : 0		0 : 9 : 0	Sec.		-		Sec.	☑ Voldoet
Temp.	125.00	°C	126.26	°C		-	3.00	°C	☐ Voldoet niet
Druk	1.50	Bar	1.55	Bar		-	0.30	Bar	
Rotatie	0	RPM	0	RPM		-		RPM	

Prg. 323 Stap 2 Fase Vullen 27-03-2018 02:48:08

	Input		Output		Onder tol.	-	Boven tol.		Goedkeuring
Tijd	0: 1 : 30		0 : 1 : 55	Sec.	-1	-	25	Sec.	☑ Voldoet
Temp.	0.00	°C	81.99	°C		-		°C	☐ Voldoet niet
Druk	2.50	Bar	0.16	Bar		-	0.35	Bar	
Rotatie	18	RPM	18	RPM		-	2	RPM	

Prg. 323 Stap 3 Fase Opw Ond.K 27-03-2018 02:53:45

	Input		Output		Onder tol.	-	Boven tol.		Goedkeuring
Tijd	0: 0 : 0		0 : 5 : 37	Sec.		-		Sec.	☑ Voldoet
Temp.	125.30	°C	124.87	°C		-	2.70	°C	☐ Voldoet niet
Druk	2.50	Bar	2.45	Bar		-	0.35	Bar	
Rotatie	18	RPM	18	RPM	-2	-	2	RPM	

Prg. 323 Stap 4 Fase Steriliseren 27-03-2018 02:57:55

	Input		Output		Onder tol.	-	Boven tol.		Goedkeuring
Tijd	0: 4 : 10		0 : 4 : 10	Sec.	-1	-	1	Sec.	☑ Voldoet
Temp.	125.00	°C	125.61	°C	-0.20	-	3.00	°C	☐ Voldoet niet
Druk	2.50	Bar	2.54	Bar	-0.35	-	0.35	Bar	
Rotatie	18	RPM	18	RPM	-2	-	2	RPM	

Prg. 323 Stap 5 Fase Koelen 27-03-2018 03:09:03

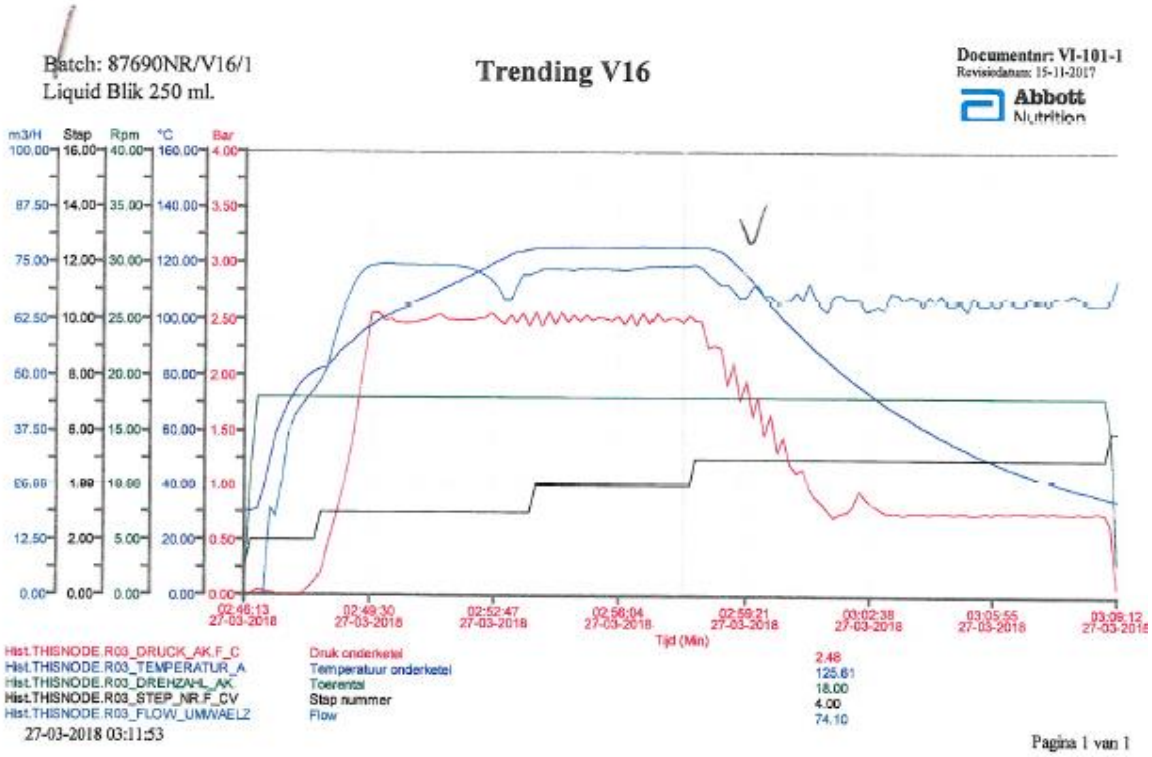
	Input		Output		Onder tol.	-	Boven tol.		Goedkeuring
Tijd	0: 5 : 0		0 :11 : 7	Sec.		-		Sec.	☑ Voldoet
Temp.	35.00	°C	35.46	°C		-		°C	☐ Voldoet niet
Druk	0.75	Bar	0.74	Bar	-0.35	-	0.35	Bar	
Rotatie	18	RPM	18	RPM	-2	-	2	RPM	

Tijdstip	*Stapnr. en foutmelding*	*Status*

Datum: 27.03.18 Operator: DDalhuisen AMS 0 MAP

27-03-2018 03:12:00 Pagina 1 van 1

Appendix II – Process graph



Appendix III – Factors for constructing control charts

Observations in sample, *n*	Charts for averages				Charts for standard deviations					Charts for ranges				
	Factors for control limits			Factors for center line	Factors for control limits				Factors for center line	Factors for control limits				
	A	A2	A3	c4	1/c4	B3	B4	B5	B6	d2	1/d2	d3	D1	D2	D3	D4
2	2.1210	1.8800	2.6590	0.7979	1.2533	-	3.2670	-	2.6060	1.1280	0.8865	0.8530	-	3.6860	-	3.2670
3	1.7320	1.0230	1.9540	0.8862	1.1284	-	2.5680	-	2.2760	1.6930	0.5907	0.8880	-	4.3580	-	2.5740
4	1.5000	0.7290	1.6280	0.9213	1.0854	-	2.2660	-	2.0880	2.0590	0.4857	0.8800	-	4.6980	-	2.2820
5	1.3420	0.5770	1.4270	0.9400	1.0638	-	2.0890	-	1.9640	2.3260	0.4299	0.8640	-	4.9180	-	2.1140
6	1.2250	0.4830	1.2870	0.9515	1.0510	0.0300	1.9700	0.0290	1.8740	2.5340	0.3946	0.8480	-	5.0780	-	2.0040
7	1.1340	0.4190	1.1820	0.9594	1.0423	0.1180	1.8820	0.1130	1.8060	2.7040	0.3698	0.8330	0.2040	5.2040	0.0760	1.9240
8	1.0610	0.3730	1.0990	0.9650	1.0363	0.1850	1.8150	0.1790	1.7510	2.8470	0.3512	0.8200	0.3880	5.3060	0.1360	1.8640
9	1.0000	0.3370	1.0320	0.9693	1.0317	0.2390	1.7610	0.2320	1.7070	2.9700	0.3367	0.8080	0.5470	5.3930	0.1840	1.8160
10	0.9490	0.3080	0.9750	0.9727	1.0281	0.2840	1.7160	0.2760	1.6690	3.0780	0.3249	0.7970	0.6870	5.4690	0.2230	1.7770
11	0.9050	0.2850	0.9270	0.9754	1.0252	0.3210	1.6790	0.3130	1.6370	3.1730	0.3152	0.7870	0.8110	5.5350	0.2560	1.7440
12	0.8660	0.2660	0.8860	0.9776	1.0229	0.3540	1.6460	0.3460	1.6100	3.2580	0.3069	0.7780	0.9220	5.5940	0.2830	1.7170
13	0.8320	0.2490	0.8500	0.9794	1.0210	0.3820	1.6180	0.3740	1.5850	3.3360	0.2998	0.7700	1.0250	5.6470	0.3070	1.6930
14	0.8020	0.2350	0.8170	0.9810	1.0194	0.4060	1.5940	0.3990	1.5630	3.4070	0.2935	0.7630	1.1180	5.6960	0.3280	1.6720
15	0.7750	0.2230	0.7890	0.9823	1.0180	0.4280	1.5720	0.4210	1.5440	3.4720	0.2880	0.7560	1.2030	5.7410	0.3470	1.6530
16	0.7500	0.2120	0.7630	0.9835	1.0168	0.4480	1.5520	0.4400	1.5260	3.5320	0.2831	0.7500	1.2820	5.7820	0.3630	1.6370
17	0.7280	0.2030	0.7390	0.9845	1.0157	0.4660	1.5340	0.4580	1.5110	3.5880	0.2787	0.7440	1.3560	5.8200	0.3780	1.6220
18	0.7070	0.1940	0.7180	0.9854	1.0148	0.4820	1.5180	0.4750	1.4960	3.6400	0.2747	0.7390	1.4240	5.8560	0.3910	1.6080
19	0.6880	0.1870	0.6980	0.9862	1.0140	0.4970	1.5030	0.4900	1.4830	3.6890	0.2711	0.7340	1.4870	5.8910	0.4030	1.5970
20	0.6710	0.1800	0.6800	0.9869	1.0133	0.5100	1.4900	0.5040	1.4700	3.7350	0.2677	0.7290	1.5490	5.9210	0.4150	1.5850
21	0.6550	0.1730	0.6630	0.9876	1.0126	0.5230	1.4770	0.5160	1.4590	3.7780	0.2647	0.7240	1.6050	5.9510	0.4250	1.5750
22	0.6400	0.1670	0.6470	0.9882	1.0119	0.5340	1.4660	0.5280	1.4480	3.8190	0.2618	0.7200	1.6590	5.9790	0.4340	1.5660
23	0.6260	0.1620	0.6330	0.9887	1.0114	0.5450	1.4550	0.5390	1.4380	3.8580	0.2592	0.7160	1.7100	6.0060	0.4430	1.5570
24	0.6120	0.1570	0.6190	0.9892	1.0109	0.5550	1.4450	0.5490	1.4290	3.8950	0.2567	0.7120	1.7590	6.0310	0.4510	1.5480
25	0.6000	0.1530	0.6060	0.9896	1.0105	0.5650	1.4350	0.5590	1.4200	3.9310	0.2544	0.7080	1.8060	6.0560	0.4590	1.5410

Appendix IV – Probability vs Severity matrix

SEVERITY AND PROBABILITY PROFILES	
SEVERITY	
HIGH	High impact to patient/user, system, process or other attribute
MEDIUM	Medium impact to patient/user, system, process or other attribute
LOW	Low impact to patient/user, system, process or other attribute

PROBABILITY*	
VERY LIKELY	Strong evidence to suggest it will happen (Probability > 1/100)
LIKELY	Evidence to suggest it will happen (1/100 ≥ Probability > 1/10,000)
POSSIBLE	Possible evidence to suggest it will happen (1/10,000 ≥ Probability > 1/100,000)
NOT LIKELY	Theoretically possible, but unlikely chance (1/100,000 ≥ Probability > 1/1,000,000)
REMOTE	Theoretically possible, but very remote chance (Probability ≤ 1/1,000,000)

*Both qualitative and industry standard numerical guidelines have been provided for PROBABILITY. Use the numerical guideline when data is available and appropriate for the situation.

PROBABILITY vs SEVERITY MATRIX				
PROBABILITY	**VERY LIKELY**	**HIGH**	**HIGH**	**HIGH**
	LIKELY	**MEDIUM**	**HIGH**	**HIGH**
	POSSIBLE	**MEDIUM**	**MEDIUM**	**HIGH**
	NOT LIKELY	**LOW**	**MEDIUM**	**MEDIUM**
	REMOTE	**LOW**	**LOW**	**MEDIUM**
		LOW	**MEDIUM**	**HIGH**
		SEVERITY		

Appendix V – Ideal curves