Reduce Machine Stops To Limit Human Intervention In Aseptic Production

Sofia Karlén

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Examinator: Ingrid Svensson

Supervisor: Prof. Andreas Jakobsson

Assistant Supervisor: Peter Spliid Skovhus

LUND UNIVERSITY

LTH

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Author
Sofia Karlén

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Lunds Universitet
Ìnstitutionen för Biomedicinsk Teknik
Box 118
SE-221 00 Lund
Sverige

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ABSTRACT

Production and patient safety requirements are high in pharmaceutical industries where standards are set accordingly and controlled by e.g. the U.S. Food and Drug Administration (FDA). It is crucial that these standards are met without compromising the fact that production must run as effectively as possible, i.e. achieve Overall Equipment Efficiency (OEE), for the pharmaceutical companies to deliver the expected number of batches to retailers around the globe. Stops on the production lines are interruptions to the OEE and human interventions involving opening of protective glass doors following these stops are disturbing the sensitive aseptic production environment. Limiting the root causes of these stops would equal a higher OEE and increased patient safety. Proposals are made based on the two stop causes; Tipped Vials, 46.6%, and Crushed Glass, 15.6%, currently causing major interventions and delays. Belt synchronisations and material property changes suggestions are made in order to minimise the door openings with 6% and 7% respectively. With only a simple vial material change that helps increase line speed and eliminate crushed glass interventions the probability of door openings can be reduced by over 44%. Focus is on long-term stability and control, both for line flow and environment, largely following the Lean philosophy. The future of aseptic production is changing and e.g. Artificial Intelligence (AI) has significant potential as enough data is extracted and prepared, correct algorithms developed and taught accordingly. As for now, solutions built on years of studies in the fields of mathematics, physics and chemistry are needed to make aseptic production standards in the pharmaceutical industry even more efficient and, as always, with the interest of the patient as main priority.

PREFACE

Thesis Background

This M.Sc. Thesis in Biomedical Engineering has been written for Novo Nordisk A/S, a global healthcare company in Copenhagen, Denmark. From September 2019 until January 2020 I worked as a Project Management Intern at Manufacturing IT. During this internship I was looking for interesting projects within Manufacturing Intelligence and via my Manager, Kim Bach Nielsen, I came into contact with my Supervisor Peter Spliid Skovhus and Technology Innovation in Aseptic Production for which this Master Thesis has been written. This project started in February 2020.

Having studied M.Sc in Biomedical Engineering at the Faculty of Technology, Lund University, in Lund, Sweden, I have during the entire education been looking forward to writing this thesis. I did not know until the beginning of 2020 how and where this project was going to take place and what it was to be about, but as I was determined to get the chance to incorporate as much knowledge as possible which I have been fortunate to gain during my university years. Studying a very broad program with interdisciplinary foundations, I had a wide range of Engineering branches to further develop my knowledge of while working on this thesis.

Because of the COVID-19, corona virus, pandemic outbreak at the time of working on this Master Thesis project, initial plans of visiting and learning the processes at the production site for a longer time period of time as well as personally making continuous observations and measurements in real time had to be cancelled. Even so, I received excellent support throughout writing this report, from my company supervisor and from everyone I had had to stay in contact with from a distance sitting in Lund, Sweden, regardless if via Teams, email or phone. I am very grateful for the smooth cooperation from all parties during these unique and difficult times.

Thanks to

First and foremost my Manager Kim Bach Nielsen, for believing in me from the very beginning and giving me the career opportunities that got me to where I am today.

Peter Spliid Skovhus, my company Supervisor, for all the help and support I have received and who has given me everything I needed to start, work and finish this thesis.

Andreas Jacobsson, my University Supervisor and Time Series Analysis professor, my favourite course during my education.

Ingrid Svensson, my University Examiner and Head of Biomedical Engineering, who I have got to know well since I started back in 2013. My heart very much belongs to the welfare of my education program of Biomedical Engineering at The Faculty of Engineering, Lund University.

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The line to be investigated in this report is a so-called Filling Line where glass vials in two different shapes, one shorter and wider and one taller and thinner (main focus of this report) are being washed, transported, filled with insulin and sealed with a cap before going through quality control, packaged and shipped to other parts of the factory. The high level production process flow can be seen in Figure 1, where the vials come into the process from the left, into the washing machine and to the transport and waiting section (tunnel and inlet) where they move into the ”Green Area” that will be discussed later in this report. The vials are filled at the Filling station after which a cap is put on the vial and the product moves out to the right in Figure 1. Throughout this process, unwanted vials, caps or random larger debris that are unwanted are automatically removed from the process as scraps.

This line, as well as most other production lines in the pharmaceutical industry with similar purposes, sometimes experience automatic or manual stops and breakdowns followed by some human intervention because of a problem occurring on the line. On the line in question, one or more glass doors needs to be opened in order for someone working on that shift to correct the issue before the line can continue to run smoothly again. The lines are running around the clock with typically five people at each shift (four operators and one technician), but the number of people inside the aseptic area closest to these doors varies. The traditional managerial focus for a large production company making a life-saving product, is the manufacturing performance measurement OEE (Overall Equipment Efficiency), meaning utilisation compared to potential. Measures towards a decreased number of production delays, breakdowns, scraps, behaviour problems etc. have to be continuously implemented. OEE is in itself a change from the previous so called ”Up-time” focus, which is the period when a machine is running without issues, to now with OEE which includes total productivity and produce quality, [1].

Recently the focus has changed slightly again, towards achieving stability instead of only OEE. In order to combat a lack of stability on these lines and at the same time comply with FDA recommendations in aseptic production the focus as of 2020-2023 lies on preventing human interventions and eventually eliminating human presence completely in the aseptic areas. This focus has been made clear to all company production sites world-wide at Novo Nordisk. One problem is that plenty of information might still be unknown about these stops and breakdowns, for instance where the actual sources of the issues stem from, followed by the question on how to effectively prevent them. Some very experienced people on the line are supposed to have well developed observation techniques, meaning that Operators and Technicians working on the Fill Line might have a gut feeling when a problem will happen (some can supposedly even hear the problem develop) and thereby take action aligned with the correct Standard Operating Procedure (SOP). Unnecessary as well as necessary/planned interventions on the line require highly skilled workers because of the way these filling lines are set up at this moment. A deeper analysis and long-term collaboration between all local actors, suppliers and other experts could very well be needed if complete stability is ever to be achieved. Because of newly developed data gathering technologies still very few people have as of yet had the opportunity to look into the data for this specific line and taken advantage of all knowledge hidden in the numbers.

The opportunity here, on which this report is based, is that by using different line data (intervention, stop causes, door openings, vial size etc.) merged together and aligned to the date and time period for a machine stop, mathematical statistics can be used to find and prove the major factors causing the issues. The purpose of finding proof to what the major stop reasons are is to push the focus towards these and thereby achieve the greatest drop (percentage wise) in interventions. The goal is to prevent the stop causes themselves from happening in order to lower the average number of human interventions on the line per batch.

The interventions in question would be inside an aseptic production area. This is a high risk zone and the products in this zone has to be kept sterile

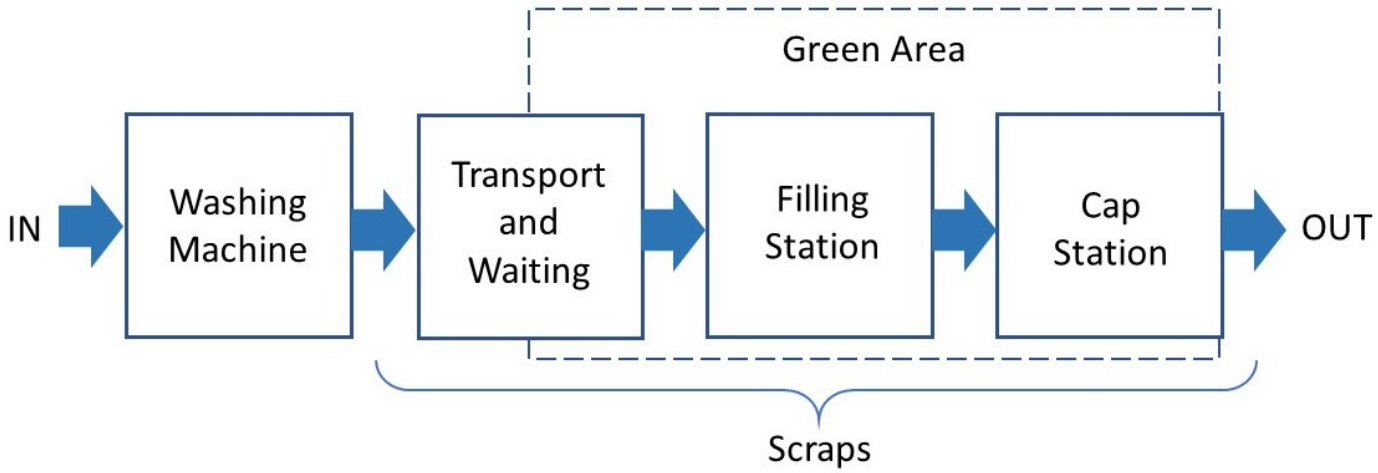

Figure 1: Production Process Flow of interest. Fill line of investigation is in the green area. *[Drawing by author from observations.]*

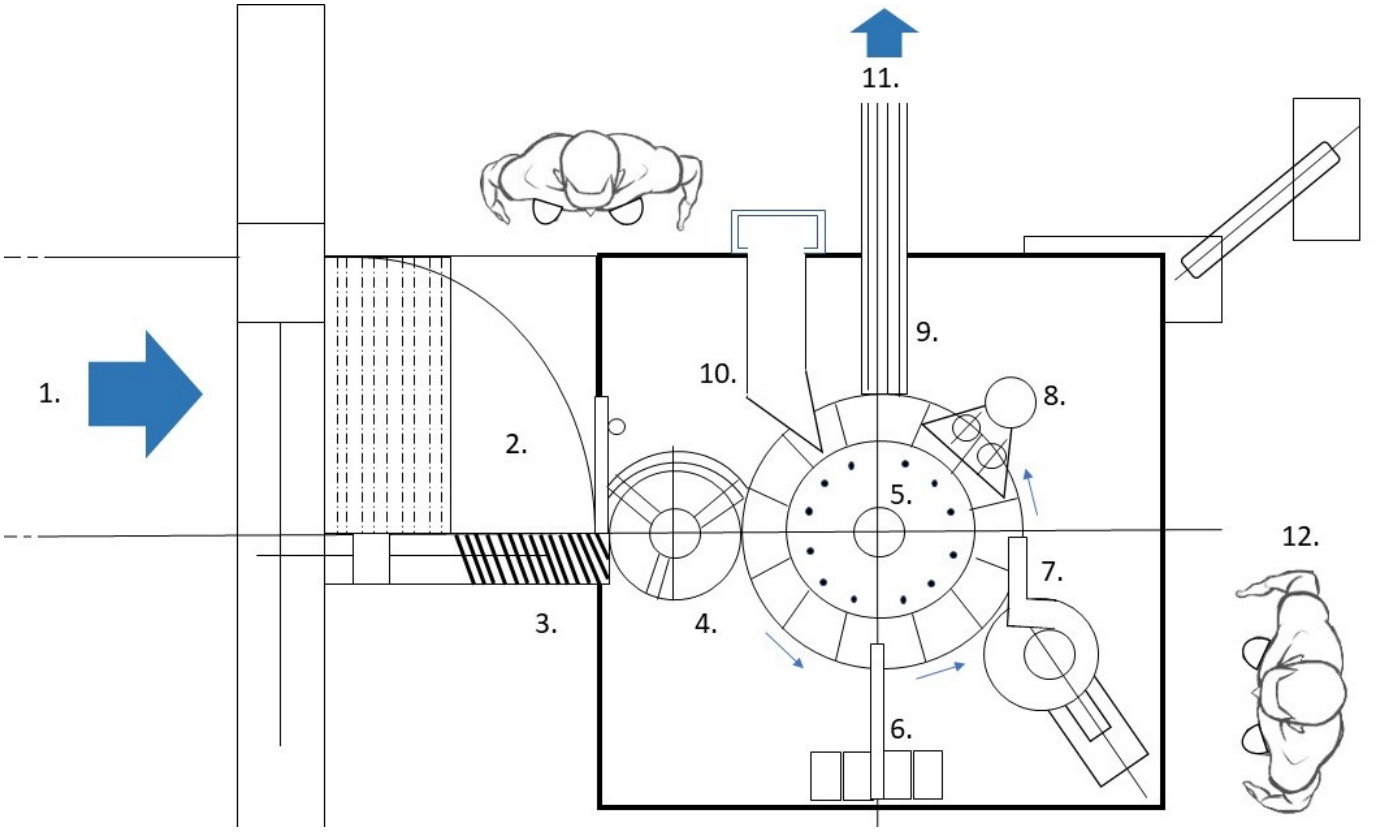

Figure 2: Illustration of the principal line of investigation. 1. In-feed, 2.Waiting, 3. Snail, 4. Transport, 5. Round table, 6. Fill station, 7. Cap station, 8. Lock station, 9. Approved produce outlet, 10. Scrap outlet, 11. Outlet, 12. Operators/Technicians *[Drawing by author from observations.]*

and with the minimum risk of microbiological contamination, such as bacteria. The number of particles larger than or equal to 5 μm has to be kept very low and the presence of people and especially people in motion exude particles of various sorts, even with the correct pharmaceutical protective wear, [2], [4], [3]. After leaving the washer where the empty vials have been thoroughly cleaned and sanitised, they are transported to be filled with insulin before a cap comes on and the sealed vials are eventually

transported away from the Fill Line (see a sketch of the Fill Line in Figure 2). Because the Fill Line is not isolated and the vials, after being transported via a conveyor belt through a tunnel, are exposed to the particles of their surrounding space, there would be a high contamination risk if the right precautions were not in place. It is not until the cap is attached and sealed to the vials, that the carefully handled finished products can be lowered and moved out of the high risk area to an area with a lower risk, i.e. less critical stages in the aseptic production, [2].

Figure 3: Vials 10 ml (two sizes) and green cap. *[Photography by author.]*

Production Process

Upon arrival at the production site the empty vials are packed out of their plastic, pallet and carton boxes and initially checked for signs of any potential damage that could have originated from either the production stage or storage at the supplier or from the packing and transportation stage at either end. The vials would be manually checked by an expert in special lighting or by use of a robot. The vials are carefully handled and either manually (most common) or automatically sent into the washing machine just outside of the aseptic area. The small glass containers are sent through the washing machine containing numerous steps for thorough cleaning and disinfection routines before being gathered together in tight rows on a conveyor belt and sent through a tunnel towards the Fill Line. In Figure 2, a sketch of the specific Fill Line in question as subject for this report can be seen. The now clean vials and cartridges arrive via a conveyor belt in a tunnel from the left hand side of the drawing in Figure 2 at ”1. Inlet station” into a curved shaped contained area (”2. Waiting”). Here they are pushed together and queued before entering the so called snail (”3. Snail”) and carefully transported (”4. Transport”) to the large wheel, the ”5. Round table”, where the vials are being held with a firm grip not to slide around and cause major issues. The vials are filled with insulin in ”6. Fill station” and a cap is put on at ”7. Cap station” and locked onto the vial not to fall off (”8. Lock station”) before they are transported away from the Fill Line at ”9. Approved produce outlet” or ”10. Scrap outlet” and out of the high risk area. The products are now ready to be sent away and packed in another part of the company. As can also be seen in the sketch of Figure 2, another factor of the Fill Line has been added, the human factor (”12. Operators/Technicians”) who are present in close vicinity to the line. They supervise the process and are prepared to take action if any problems occur during running time.

A photo of the two types of vials and a green cap can be seen in Figure 3. The vials have the same volume, but different dimensions. The caps could have different colours depending on the product. The taller slimmer vial model is the one mostly used everywhere in the world apart from in the US where the shorter wider model is more common. It has been told that the tall model of the production experience the most issues. It is very clear to the any observer that issues experienced with the taller and slimmer vial are most likely stability issues due to the shape and geometry of the vial. Having thin and tall vials creates a center of gravity located higher up which increases the probability of it tipping over. The most obvious solution to this problem would be to simply redesign the vial shape to match the ones used in the US, but it is not that simple. The problem with redesigning vial shapes is the cost of changes needed downstream since the vials are part of medical devices assembled from many different parts. The added downstream costs associated with a vial change makes the business case unattractive especially as most of the products using the tall/thin

vials are older products that might be discontinued in a few years, which does not give enough time for return on investment. It is therefore important to look at other ways to improve the vial performance by making significant changes to the filling line and downstream processes.

Should a suspicion arise of a problem occurring, there might have to be an intervention where the process is paused/stopped for a minimum period for the problem to be looked into. The thick black square line around the moving parts on the line in Figure 2 represent a transparent shield separating the line from the room. This shield is no isolator or RABS (Restricted Access Barrier Systems) and there are several doors that have to be opened for corrections during an intervention. It is important to note that they most likely do not have to be opened for all types of stops and interventions and should only be opened if necessary. There are sensors on these doors that store the data from each door opening in terms of time and action.

Batch Intervention

Current line management standards can be seen in Figure 2 by the people standing around the Fill Line in the sketch. Up to the recent decision on limiting and eventually moving the technicians and operators out of the aseptic area this management standard has also been seen as best practise. As previously mentioned, the glass doors surrounding the Fill Line often need to be opened for maintenance or interventions and on each door there is a sensor. The line is supposed to be stopped for a door to open. A scenario could be when an operator sees or hears a vial getting stuck or falling, he manually stops the line, opens the door and attends to the vial by removing it. Additional problems occur if there has been a vial breakage and with the acute risk of having glass splinters falling into the clean vials around the breakage, the whole line needs to be cleared and hundreds of vials thrown out before the production can proceed as normal. The batch usually cannot proceed again until approximately two hours after the initial intervention.

Door Opening: Four examples of batches with and without an excessive number of interventions are portrayed by the graphs in Figure 4, where in this case an intervention equals an opening of one of the glass doors surrounding the Fill Line in the aseptic part of the line. Equivalently, proof of production efficiency and inefficiency for a batch could be interpreted from just analysing the very same graphs in Figure 4. These four graphs display system data in real time from four different batches where interventions, in terms of door openings, are displayed with red dots. The blue dots however, are derived from other unspecific line data and describe other unspecific line occurrences and are not related to door openings. Graph (a) and (b) show batches smaller in size, with the cumulative amount of 500 000 vials. It can be seen that the batch (a) has quite a lot of interventions while (b) barely has any interventions. To receive the same output sum, it takes 22 hours for the batch in (a) and only 18 hours for the batch in graph (b), which means at least four hours lost in production efficiency because of stops followed by door openings. Graphs (c) and (d) in Figure 4 show slightly larger batches with the cumulative output of 600 000 vials. In graph (c) it is even more clear that, with a lot of interventions during the afternoon and evening hours of 08-07-2019, the full batch takes a long time to pass through the line, all of 24 hours. In (d), on the other hand, it does not even take 21 hours before the whole batch has passed through and only at the very end there are two separate time stamps where doors have been opened.

Interventions, particularly if they are in excess, can significantly lower the OEE, cause stability issues and consequently cause even more stops before the batch has finished moving through all steps of the production process flow. The examples of Figure 4 gives proof to the fact that achieving less stops, door openings and interventions would not only satisfy any clean area requirements, but could also improve OEE.

Aseptic Production

To preserve product quality at the end of the value chain all finished products leaving production sites must have the right temperature, humidity, light exposure and correct packaging with mini-

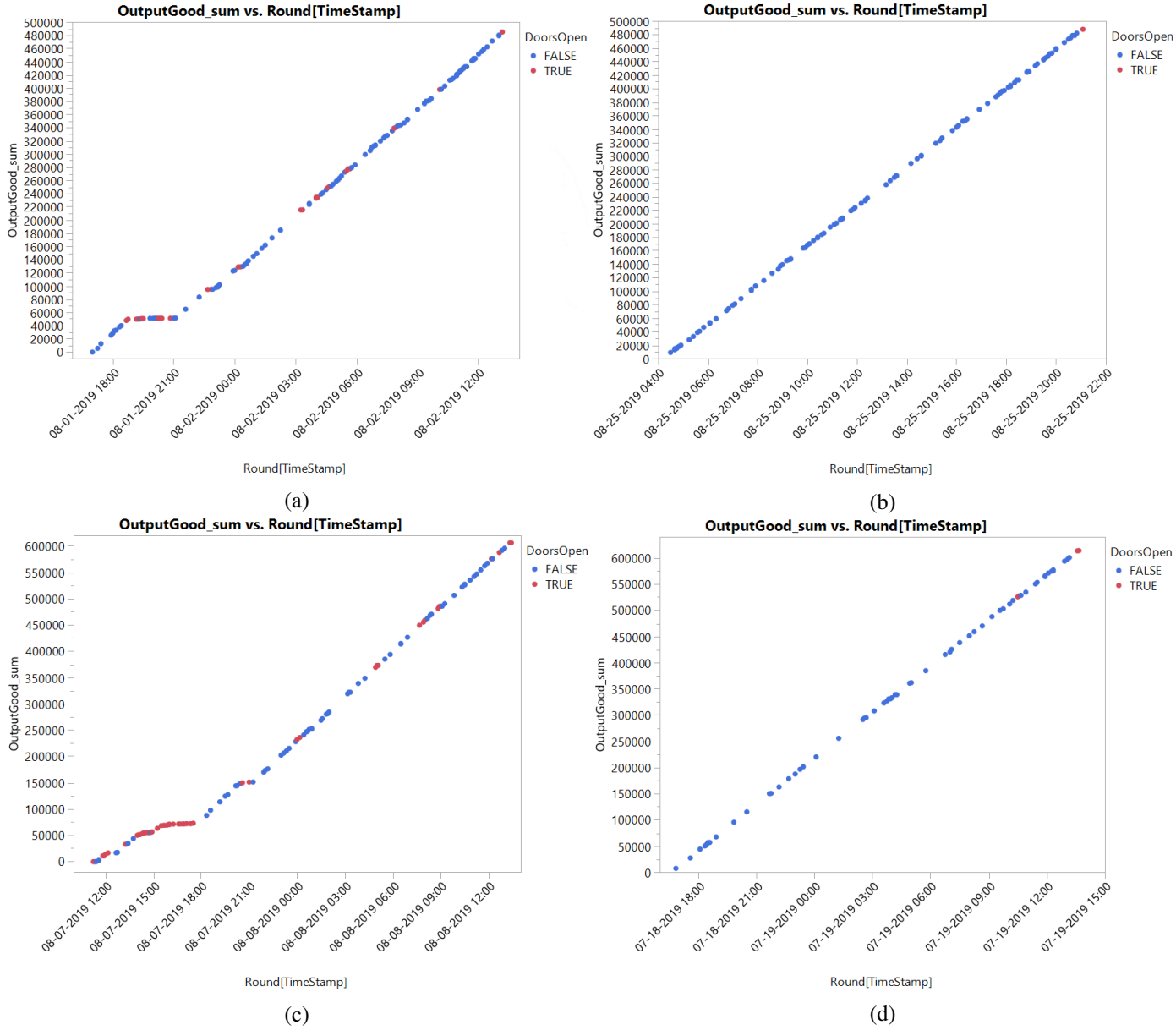

Figure 4: Door Openings vs. Batch Performance. Bad batch output (a) and (c) vs good batch output (b) and (d) for two different batch sizes. Batch output on y-axis as a function of relevant time stamps on x-axis. *[Graphs generated in JMP by author using production data from end 2019.]*

mum vibration risk. Products must be protected in all stages of the manufacturing process to avoid contamination or mix-up. Contamination could only occur if particles or microorganisms from materials, equipment or humans get into the product. Mix-up could occur if, e.g., labels from one batch end up on products from another batch or incoming materials are confused and end up on the wrong product.

With smart facility design the amount of particles in the air can be controlled, particularly in the most vulnerable areas to eliminate the risk of contamination. Production areas that need extra protection are the so called ”Classified” and ”Controlled” areas. In the Classified areas, or ”cleanrooms”, the aseptic production takes place. To keep the product pure, access to the classified areas is very strict in order to control the level of particles and microorganisms and only trained and qualified employees wearing the correct gowning are allowed to be in there. Areas like Moulding, Pre-Assembly and Packaging are controlled areas because they also require protection of products but not at the

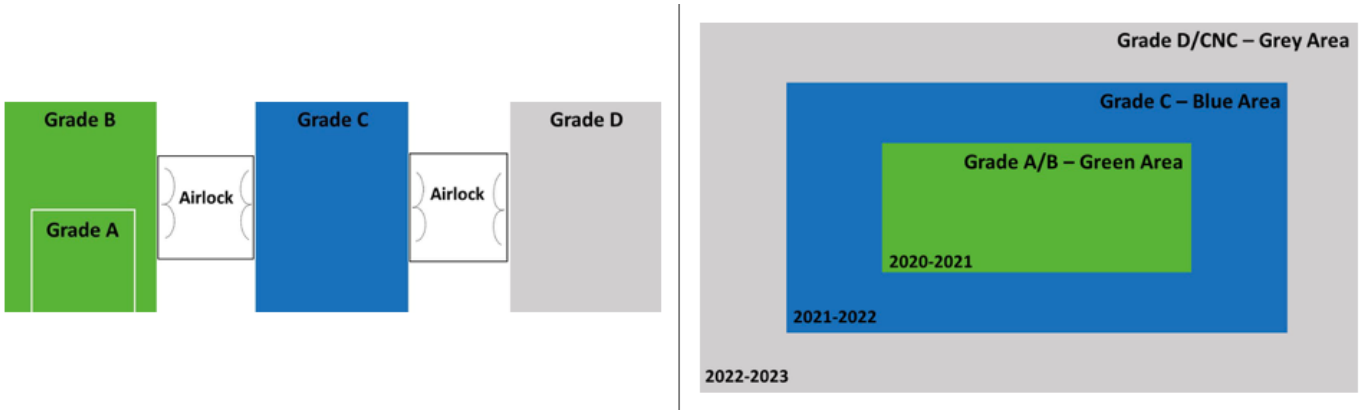

Figure 5: A, B, C and D clean room standards and an illustration of the colour layout of standard safety levels in production area. *[Drawings by author from observations.]*

same level as the classified areas.

Aseptic and sterile areas differ in the sense of aseptic meaning no contamination as well as any risk of such, whereas sterile means without all forms living microorganisms. An aseptic area has to hold a standard where organisms in the micro scale cannot be created or spread and therefore create no harm and keep the environment safe for Pharma or food, [2].

Grade A,B,C,D: In grade A area, see Figure 5, the aseptic production of insulin takes place. Here the finished products are directly exposed, e.g. in the open containers in the Fill Line as previously described. Grade A requires the most strict control of the particle levels and airborne microorganisms. Grade B is the background environment to the grade A area and here only highly trained people are involved in the aseptic preparation work. Grade B also requires a very strict control of air particles and microorganisms. People working in this area must work and move in a slow and methodical manner in order not to create additional micro particles. The airlock is an enclosed space with at least two doors, which must be designed as an interlocking system, which means that the two doors cannot be opened at the same time. The airlock helps to control the number of airborne particles and microorganisms in different areas. When you access a cleanroom from a grade B to a grade C area, this takes place via two airlocks, see illustration to the left in Figure 5. An airlock also needs to be passed when moving from a controlled area to a classified area C. The purpose of the airlock is to prevent air from flowing from area C to area D. The air pressure in grade B is higher than in grade C, and this ensures that air flows from grade B to grade C, never the other way round since the air of area B is cleaner than the air of grade C area. Different types of airlocks are used to minimise particles by controlling the flow of materials, equipment, products and humans. Facility design also helps control other important parameters like temperature and humidity through large ventilation and air filtering systems. A facility should be designed to allow production to take place in a logical order corresponding to the sequence of the operation, [2], [3].

In a grade C area the finished products are not directly exposed to the surrounding environment and requirements are less strict than in the grade A and grade B areas. Here you will find, for instance, monitoring and cleaning of equipment, [2], [3].

Grade D is a classified area with less strict requirements on the limits of particles and microorganisms than the other classified areas, [2], [3]. In Novo Nordisk controlled areas are referred to as CNC (Controlled but Not Classified). Access control for people, materials, equipment and gowning are established, but there are no limits on particles and microorganisms as in classified areas. Controlling the levels of particles and microorganisms is very important in an aseptic production facility. A cleanroom has an acceptable level of contamination that is specified by the classification of the room.

Even with smart facility design, proper gowning (See Figure 6) and cleaning procedures, particles cannot be completely avoided. It is therefore also

(a) (b) (c)

Figure 6: Gowning in Aseptic production; a) Grade C (left) and b) Grade A/B (right). An isolator is seen in c). *[Photos a) and b) taken from [5] while c) is taken from [6]]*

necessary to monitor and control the particle levels in the cleanrooms. When people move and perform activities, particles are inevitable, even in A and B areas. This is why the environment has to be monitored in classified areas by analysing samples from the air, surfaces and clothes. This has do be done regularly to control that the micro particle levels are in accordance with the requirements for that specific area. That the intended classification of the room is maintained is thereby also ensured, [3], [4].

Isolator: With the Fill Line inside Grade A/B being protected by a rigid glass shield with doors, but is neither a RABS nor an isolator, it is according to the FDA of a higher risk design where additional steps are taken to keep the area steps. New FDA recommendations states that lines in aseptic production not protected by isolators or RABS could require an even higher level of protection than what is already in place today, even though adequate safety measures continuously are being taken, [4]. It is important to note that both RABS and isolators are very expensive pharmaceutical equipment. Aseptic production using isolators separates the external cleanroom environment from the aseptic production line and thereby minimises the human exposure (see example in c) Figure 6. The isolator technology minimises human interventions in processing areas and may result in a significant decrease in micro particle contamination from the surrounding environment. There are many possible designs of isolators and transfer devices. The isolator as well as the background environment has to be designed so that the air quality that is required for each zone can be realised. Since the particle transfer in and out of the exposed area is one of the greatest potential sources of contamination, an isolator is a very important protection. In general, the area inside the isolator is the local zone for high-risk manipulations. The air classification required for the background environment depends on the design of the isolator and its application, [2], [4].

There have been projects where isolator technology has been implemented on filling machines in Novo Nordisk. The machines are then placed in enclosed spaces/containers and the inside can only be operated by humans from the outside of the isolator and only via non-movable glove holes. Apart from glove holes there is also a controlled air flow, usually unidirectional, [6]. Using an isolator does therefore minimise the particle levels towards complete elimination, but it does not change the fact that stops requiring interventions and door openings today might need the same intervention even when the isolator is in place. This might then require quite slow and tedious methods to correct the issue compared to the more open line design where doors could be opened.

When a problem occurs on the Green Area part of Figure 1, seen in Figure 2 inside the Grade A/B area, the line usually needs to be stopped. In the best case scenario the line would immediately continue moving after a quick fix away from the line, but as has been discussed before and illustrated by the graphs from batch performances end 2019 in Figure 4, this is usually not the real case scenario. Very often just one or two stops lead to a line intervention and if the problem has occurred in the Green Area, the intervention has to happen there as well which often leads to a door opening (seen by the red dots in Figure 4). That batch output vs door opening analysis made in JMP quite clearly also show another unwanted behaviour. This behaviour could be explained as ”early interventions cause more interventions”, where graph a) and b), Figure 4, have issues occurring in the beginning of the batch continue to have issues and extreme delays in comparison to b) and d), Figure 4, which only have one or two interventions at the very end of the batch, not affecting the output significantly at all. Apart from every door opening being a production stop, causing major delays and production inefficiency, every door opening could in theory also be a contamination risk.

In this report, stops and interventions in an OEE or efficiency sense are only partly dealt with and the focus lies instead rather on the preservation of the product quality and thereby protecting the vulnerable aseptic Fill Line (Grade A/B) area from any unnecessary microscopic particle exposure.

These door openings, detected by sensors placed at several positions around the doors, can quite logically be considered to be the main cause for high particle concentration risk. It is only in those moments where the doors are being opened that human particles would get really close to the exposed vials. Sometimes he or she would even have to operate above the vials themselves and the movement itself could risk particles of the micro or nano order of magnitude. The most common cause of door openings and pollution risks would be a machine breakdown of some kind, e.g. a broken or tipped vial, crushed glass, cap block, needle pop-up and general line restrains. There are also an extensive number of other possible reasons for the line to be stopped, automatically or manually (most common) and it is quite a complex labyrinth of events occurring, sometimes a few at the same time and it is hard to know exactly what event leads up to what result and the consequences.

What would happen if the doors around the Fill Line were to be kept closed at all times and is it enough to solve all intervention problems?

One would think that having the doors around the Fill Line permanently closed could be compared to having a RABS or an isolator around the line, but with humans being the major source of microparticle contamination by simply being in the same room as the exposed line, these options would create a much higher environmental safety risk with regards to air content, [7]. The glass doors are not equivalent to isolators and only partly give protection as shields to the surroundings, but there are still open airways allowing air through the doors. With human movements creating more particles/organisms only a complete elimination of human presence inside the aseptic environment, which isolator could provide, would reduce the risk.

On the other hand, there might be further risks and problems with RABS and isolators, apart from the already mentioned cost factor. The often higher air velocities inside the isolators can create vial instabilities followed by broken or tipped vials, crushed vials and jams creating queuing problems is such a risk, [7]. These issues sound very similar to some of those already occurring on the current non isolated line that needs physical intervention and usually at least one door opening. In an isolator this human intervention has to be exchanged for something else and even though an isolator has so called ”isolator glove ports” for manual operations, it is not practical when dealing with small randomly tipped vials or even worse, picking up glass splinter after crushed vials, [7].

This report deals with a three part strategy. The purpose of these is to reduce the number of stops on the line and limit the human aseptic area intervention following these stops, causing a safer and more efficient production. The three parts are:

1) Situation Analysis
    a) Problem Visualisation
    b) Statistical Analysis
2) Proposed Solution
3) Implementation Outline

This strategy has been chosen considering the complexity and variety of existing available data and the needs to process this data before making any theoretical and/or practical suggestions as of moving forward from today's situation. See a flow chart of the strategy for this report in Figure 7.

Situation Analysis

Problem Visualisation: The first part of the Situation Analysis contained in this report, the problem visualisation, is an outline of the current situation as a problem analysis from information gathered at the site, inspections, experiences and general knowledge from material on the subject. This is firstly a mere visualisation separate from any data and is mostly covered in the previous two chapters; ”Introduction” and ”Problem Definition”. Secondly there is a major Mapping step followed by Graph Building before the start of the actual Statistical Analysis, see more under ”Methodology”.

Statistical Analysis: When the problem itself on a high level has been defined and visualised there is a need to understand the problem on a detailed scale, including its magnitude and which parameters constitute the major contributing factors. A size and contribution analysis is made by using a vast variety of line data gathered during four months, from the 27th of November 2019 to the 27th of March 2020 The data is manually sorted and manipulated into more than 5000 data points of machine stops in data and time format, stop start time to stop end time, and more than 50 parameters of interest per data point serving as the information to be analysed. The choice of time period has to be as large as possible, while staying limited since a too large data set otherwise would have to be processed. Another key factor for keeping the data limited is that simple data visualisation changes can be seen around the time of end November 2019, where some stop causes common before this time do not seem to be as common anymore. This is most likely due to line optimisations that have been made at this functionality. At this time in November new interesting data is instead logged, such as door opening data, a key factor for the strategy of this report. See ”Data Preparations” under the ”Methodology” chapter for more information about this data structure.

Having the data sorted into stop times as a function of more than a few parameters creates a vast opportunity to dig deeper into this data and find the stop causes of interest. As mentioned, the data available is of a complex nature and needs thorough preparation steps and as well as a fast and simple system for sorting has to be figured out, see ”Mapping” under ”Methodology”. The reason for mapping the stop causes is to open up for very large number of statistical possibilities that could be very tedious. Some analysis would be even impossible to execute in a reasonable time span if this mapping did not exist.

Next step is to use the mapping to analyse the data using innovative methods in order to achieve the results needed for laying out a base for building solutions on. There are numerous statistical strategies that can be used for this, but focus has to be put into the direction best fit to the now mapped data. Before any mathematical statistics can come into place, the Principal Component Analysis (PCA) and Regression techniques are looked into. The main difference between these two directions are that PCA deals with the whole data set and treat the variables as independent of each other to reduce the number of dimensions, while the purpose of Regression is to find a relationship between a dependent variable and a set of independent variables.

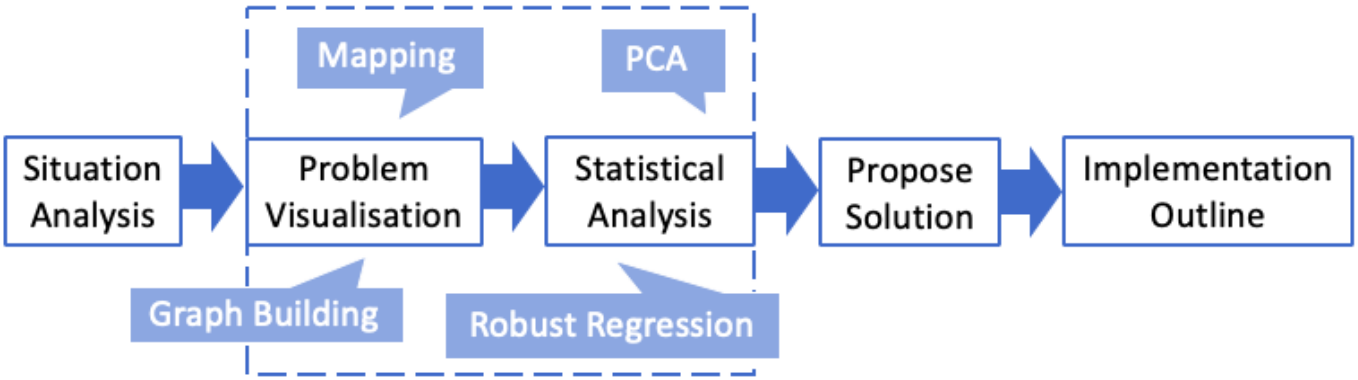

Figure 7: Strategy outline of this report. *[Flow chart by author.]*

Proposed Solution

One possibility is to create a system that can guide shop floor to make the right decisions without unnecessary interventions, but at the same time cannot be superfluous and/or distracting. One example of intervention behaviour is the phenomenon seen in Figure 4 where interventions cause other interventions. The most simple and probable cause for this being that the problem has not been fully solved yet, so one problem leads to the next. This phenomenon also follows to be investigated. No industry can sustainably afford not to be in full control, but to achieve full control data access needs to be transparent. Not only transparent, but translated into an intelligible format. The Situation Analysis should act as a foundation for proposed solutions to be built on.

To be investigated as the first step towards a solution/system could be data correlations, which are most likely hidden between the data from different parts of the line, e.g. an issue on one part of the line can cause a stop later on the line. This system should preferably be connected to Dashboards in rooms away from the Green Area as information source for happenings in the line followed by a feedback loop from the Fill Line to suppliers and Quality Control (QC). There are two problems with this idea; Firstly, there is no continuous data available, but rather time stamp based, and therefore time series analysis or similar predictive statistical processing cannot be used as easily as might be expected. The second problem is a more practical factor which is based on the actual quality and protection needed in the aseptic area. Even though human interventions might be limited while having a Dashboard controlling the situation on the line, there is still a need for intervention and door openings for the issues to be fixed and the line to continue after a stop. It has to be mentioned, however, that it is also very hard to supervise every scenario simultaneously, since the complexity and variety of situations leading up to the unwanted interruptions is fairly large, even though there might be only a handful of causes worth focusing on. This is left to be discovered and is the core reason behind the mapping mentioned above and described in ”Methodology”.

The conclusion here is that there is a need to find and solve the root causes of the stops leading up to interventions and especially door openings. There might be no obvious root causes, but nevertheless the goal is no interventions and this is the goal that needs to be strived at.

Implementation Outline

In order to put the strategy outline with analysis and proposals into action they need to be implemented. The Strategic Outline mainly gives answers to the questions ”Why?” and ”What?”, with the first answer being to limit human interventions connected to line stops and the second answer identifying the root causes to these stops and proposing effective solutions to these. The Implementation Outline on the other hand deals with questions of ”When?”, ”How?” and ”Who?”. The purpose of this report is also to try to answer these questions as extensively as possible.

Knowledge Sharing

From knowledge sharing and voices from sites it might be important and even most efficient to find the best solution for each individual site (and line). A pilot on a single site/line would more likely end up as a project ready for roll out quicker and would ideally end up as a gold standard for other lines to start implementing. This is based on the assumption that a single solution is the best strategy in this situation, but as mentioned in ”Strategy Outline” this has to be decided based on the chapter ”Statistical Result”.

Chosen area of focus is at the location of Novo Nordisk head quarter in Denmark, at a line that is running well and with investment interests. An active stakeholder interest, willingness to cooperate, a high practical need and active projects on the line are supporting this choice. The right customer is important for potential success. Personal meetings, private tours around the production facility are crucial for understanding the importance of the lines and the advanced technology in place. Engaging with people on the line, team leaders and colleagues are the main providers of knowledge and the basis for this report. Line observations at line in question are made, where the line is studied and pictures and videos taken as continuous material for this report. Standard Operating Procedures (SOP’s) regarding line management, specifically concerning line stops also make up a large portion of the background basis for this report.

Data Preparation

Data is accessed through local data filter systems with the purpose of mirroring and translating the data of interest from historical data. The historical data is fairly disorganised and very hard to both access and interpret while stemming from different sources. Going straight into the historical data would be like finding data called either apples or oranges, but in reality constitute the exact same type of information. Working with the local data systems is therefore necessary before any sorting and/or data manipulation steps can be taken. Some sources have the shape of sensors placed on different locations around the line and are measuring different line events. Data sources may represent actions, settings, changes and alarms are also attained as a wide variety of variables within each data source.

The data gathered for four months between the 27th of November 2019 to the 27th of March 2020 with more than 5000 rows of time stamps as function of more than 80 variables is transported into Excel whereupon a lengthy coding and data manipulation preparation period is required. A deep Excel learning experience useful for future value therefore comes about.

Adding onto previous data platform and analysis tool knowledge, new knowledge in working with the JMP Statistical Software by the SAS Institute is received and comes into perfect usage for the visual statistics of complex data. JMP, developed for Macintosh but later also Windows, contains different computer programs for analysis with focus on visual analytics. JMP is perfectly compatible with Excel sheets containing vast amounts of data and is therefore a very good choice of tool in this study. The outcome from the JMP usage can apart from the background example Figure 4, be seen in ”Statistical Result” in Figure 12, 13 and 14.

Mapping: To start the process of going from the mentioned large Excel data sheet to an interpretation possible to handle and for anyone to understand, a new system of mapping is created, see Figure 8. This illustration portrays the start and foundation of the mapping system used in this report. The mapping is based on four levels/categories of reason for a machine stop. The first reason level contains the highest and most distant level of stop type, e.g. a Production related stop, a Changeover/Setup, Breaks or Testing and Validation. By only studying the data, the visually most common cause for line breaks is ”Production”, illustrated by a larger bubble and font in Figure 8. This is quite concerning because production stops are usually compromising the Overall Equipment Efficiency (OEE) so there is a need to dig deeper

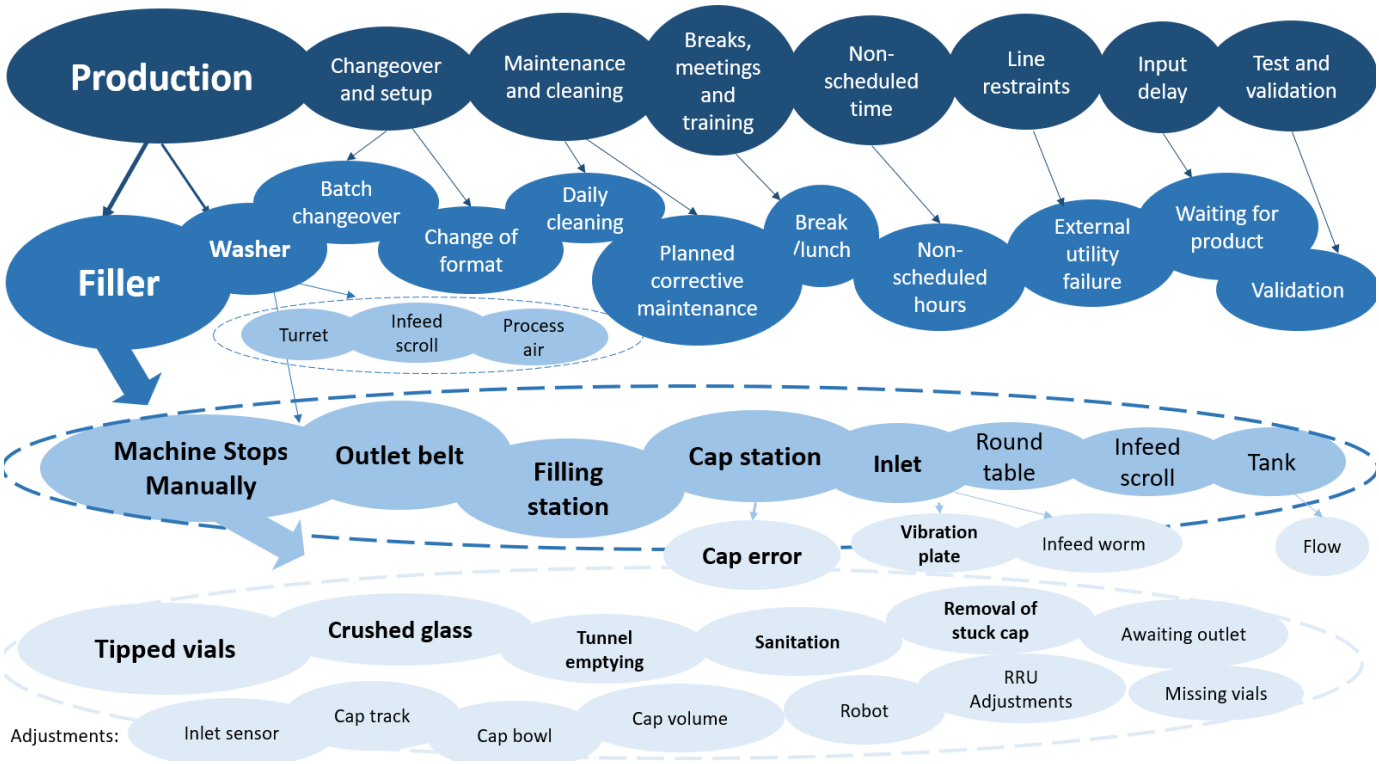

Figure 8: Mapping idea for extracted data. *[Drawing by author.]*

closer to the source of the issue to figure out the meaning of these Production stops.

The next level of reasons seen in the same figure in lighter blue colour below the first level explains in more details what that first level stop reason means. Production contains three parts; Filler, Washer and Tunnel, but issues here are usually accounted for in Filler. All other reasons at level one, except from Production, have at least one further detailed reason, e.g Maintenance and Cleaning can either be Daily cleaning or Planned corrective maintenance. The most common situations at the second level are, by far, is stops happening on the Filler, meaning the Fill Line in the Green/aseptic area and possibly in the Tunnel as recently explained. The problem could therefore have occurred on the way to the Filling part, most likely between the Washer and the Fill Line in-feed seen in Figure 2 (”1. Infeed) where the Vials are moving more freely than in Washer or at the Round Table seen in the same illustration.

Going one step further into detail to the third stop reason is now only relevant to Production related stops, since the other reasons do not exhibit any further complexity than to the second level. Within the reasons connected to the Fill Line, Manual Stops are by far the most common stop and this reveals that someone must have noticed a problem and had to stop the machine in order to attend to the issue and very likely some of these would also include an intervention and a door opening. This conclusion can be taken since we are now, from reason level two, inside the Green area. Many of the other possible third level reasons are stemming from the Filler and are most likely due to manual stops as well, but remains to be investigated. Examples are seen in Figure 2 as Outlet belt issues, Cap station etc.

The forth reason level contains the most important information, but is not enough on its own to explain a stop time stamp without the connection to the three previous levels further away from the source. Looking into the data rows of Manual Stops, Tipped Vials and Sanitation, Cap error and Tunnel emptying are found as fairly common stop reasons. Most of these are due to Manual Stops, but some of them, such as Cap error is directly connected to the Cap station.

The purpose of these combinations is to create a number of unique codes based on a systematic

alphabetic coding system where each one of the 56 different codes describes a different stop reason looking at the line as a whole. Figure 9 shows the mapping system originally created in an Excel legend. For each stop cause level the alphabetic sequencing starts over making it easy for filter functionalities in Excel and in other platforms. This is very important in order to use these codes in further analysis relative to other factors and thereby find information on a more detailed level that would otherwise be unknown.

Statistical Analysis

The above described Mapping system, data manipulation and graph building using basic mathematical statistics serves as remarkably good visualisation techniques for the specific purpose of finding the major stop causes, the parameters of importance, to propose solutions on. Without knowing the most important reasons causing the majority of stops, interventions and door openings and/or which would have the most impact on the rest of the data if removed/limited, it would be very hard to continue with this project.

The question now is what statistical methods have the most value under the circumstances, based on the data structure, the mapped information and particularly the purpose of this report.

Principle Component Analysis: After data preparation it is obvious that there is a lot of data with a large number of variables that has to be dealt with and preferably fewer dimensions would make this mapped information more clear to study and visualise. The variables in the data (here: the two to four letter codes serving as descriptions of stops) are probably not all of much relevance and it is very likely that quite a few of them are causing stops connected to interventions of interest. An assumption can be made about the independence between the variables, but it would be very interesting to analyse their relative correlation apart from identifying all variables responsible for most variation in the data set.

To achieve these goals a qualitative analysis with Principle Component Analysis (PCA), i.e. eigenvalue analysis, can be used for statistical analysis. The purpose of using this analysis technique is to reduce the dimensions of the data set by lumping parameters together into pairs/groups based on their correlations. It is important to be able to visualise in a simplified way that offers analysis opportunities, like Machine Learning, without losing too much valuable information. In short: 1. Reduce variables, 2. Preserve information. This can be done by extracting new variables, which should be independent, from specific combinations of the original variables in the data while still retaining the information in the original variables. In order to understand PCA the data can then be plotted in hyperspace, multi-dimensional to represent all variables, but since only three dimensions can be handled, the data needs to be projected to a two dimensional space, i.e. the Principal Component (PC) plane. The projection to yield the maximum variance in one specific direction is then looked for and the number of variables that needs to be combined to achieve this maximum variance depends on how many variables are correlated. The line of best fit drawn through the data in the direction of maximum variance is also the first PC, the PC_1, [8].

The two dimensional data in Variable 1 and 2, having almost identical variance, i.e. the amount of information that the variable has about the given data set, can be seen to the left in Figure 10 in its original data space. The purpose of using PCA here is to try to find the axis that contains the highest variance while the data is projected onto it, see the blue and orange axis drawn through the data to the left of Figure 10 where on these axis the data has its maximum and minimum variance respectively. The drawing to the right in Figure 10 shows instead the PCA projected data in the component space with axis as the new variables extracted from the analysis, i.e. the Principal Components. If the original set of data were to be projected along these new axis the First Principal Component, PC_1, were to have the largest contribution to variance, followed by the Second Principal Component, PC_2, with the second largest data variance projected onto that axis. In the example in Figure 10 there are only two different principal components, but can be extended up to the n^{th} principal for the n^{th} dimension of a given n-dimensional set of data. With a n-dimensional data set for large n, many variable sets would be linearly uncorrelated while sorted from having the highest to the lowest variance contribution. Each

Reason 1		Reason 2		Reason 3		Reason 4	
A	Production	A	Filler	A	Machine Stops Manually	A	Tipped vials
						B	Crushed glass
						C	Tunnel emptying
						D	Sanitation
						E	Removal of stuck cap
						F	Adjustment of inlet sensor
						G	Adjustment of cap track
						H	Adjustment of cap bowl
						I	Adjustment of cap pickoff
						J	Adjustment of fill volume
						K	Adjustment of crimping station
						L	Robot
						M	RRU Adjustments
						N	Awaiting outlet
						O	Missing vials
						P	Error with 1st fill needles
						Q	Changed filling pump
				B	Inlet	A	Vibration plate
						B	Infeed worm
				C	Cap station	A	Cap error
				D	Tank	A	Flow
				E	Security loop	A	Safety button
				F	Outlet belt		
				G	Filling station		
				H	Round table		
				I	Segment wheel		
		B	Washer	A	Machine Stops Manually		
						A	Adjustment of inlet sensor
				B	Infeed scroll		
				C	Security loop	A	Safety switch
				D	Turret		
				E	Process air		
				F	WFI		
		C	Tunnel	A	Cooling zone	A	Diff.Pressure
				B	Tunnel LAF		
B	Changeover incl. setup	A	Filler	A	Cap station	A	Cap error
				B	Inlet	A	Vibration plate
				C	Tank	A	Flow
				D	Outlet belt		
		B	Batch changeover				
		C	Change of format				
C	Maintenance and cleaning	A	Daily cleaning				
		B	Preventative/planned maintenance				
		C	Planned corrective maintenance				
		D	Move circ. hose				
		E	5 weeks maintenance				
		F	10 weeks maintenance				
		G	Close Down				
D	Breaks, meetings & training	A	Break/lunch				
E	Non-scheduled time	A	Non-scheduled hours				
F	Line restraints	A	External utility failure				
		B	Problems with IT				
G	Input delay	A	Waiting for product				
		B	Gathering materials/parts				
H	Test and validation	A	Validation				
I	Scheduled unmanned time	A	Extraordinary unmanned time				

Figure 9: The final official mapping system table with every possible stop cause per reason level, to be read from top to bottom and from left to right. *[Created by author.]*

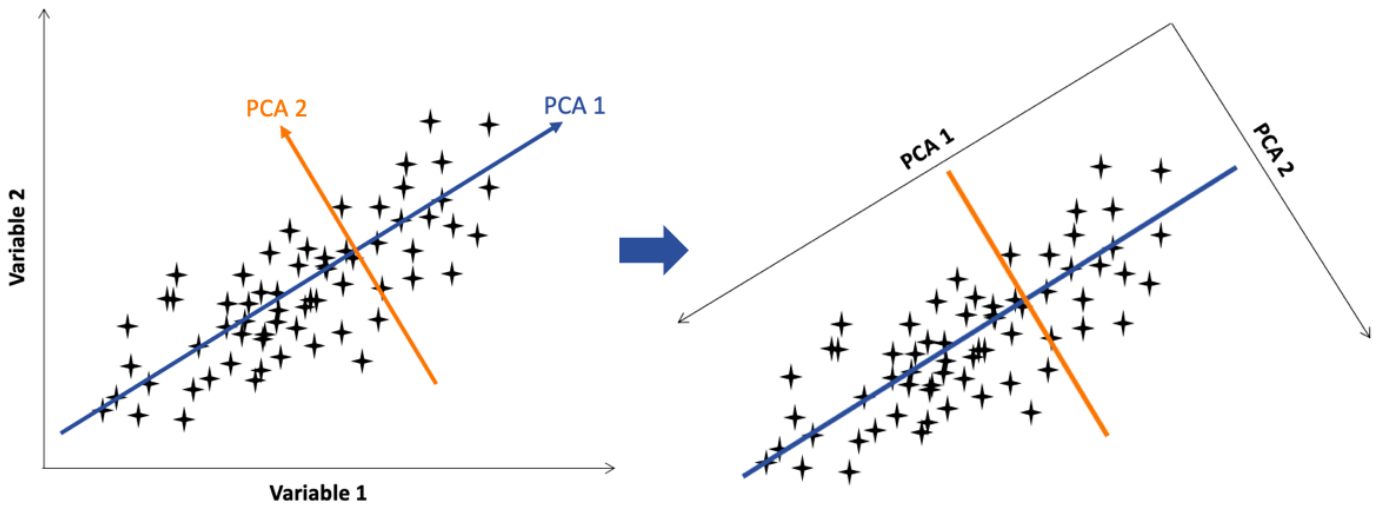

Figure 10: Original dependent variables 1 and 2 to the left and new variables (Principal component 1 and 2) to the right. The new variables are independent. *[Drawings by author.]*

succeeding "Principle Component", PC_i, will have less and less variance contribution while still being orthogonal to each other, i.e. uncorrelated. Even though the PCA model is designed to provide as many principle components as there are variables or number of samples, the system can be sufficiently described by the first three components as the rest of the succeeding components usually describe noise and errors related to signals, [8], [9].

Principal Component Analysis grasp the data content in a definite number of PCs, meaning the ones that convey the most variation in the data. Creating PCs does not eliminate values such as outliers, but the number of dimensions are reduced. The components portray the different influences, also called loadings, of the data and their causes can be traced back from the PCA plot to the sources. A normal PCA plot, as seen to the right of Figure 10, shows data clusters based on equal or non equal variations. A PCA loading plot on the other hand shows the weights/loading of each variable on a principal component (PC), [8], [9]. There might therefore be some value in trying to use a loading plot as a statistical visualisation tool in this report.

One problem with PCA using the extensive discrete data of stop causes is, as described above, that only the major stop causes, the contributions, for whatever goal is to be proven would be able to successfully describe it and all the other stop causes are disregarded as noise. It is also important to note that we do not want only to look at variable correlations, but rather the weights in terms of importance for each variable relative to another measurable variable of interest, e.g. door openings. The goal and interest of this report is to be able to measure future results based on the current situation if one, two or more stop causes would be eliminated or significantly decreased. There is likely a real purpose of having exact calculative opportunities when estimating the effects of proposed solutions for reduced machine stops. The PCA might therefore in this particular case compromise the validity of the analysis, but is still worth testing for the loading plot visualisation properties.

Robust Regression: Regression could be described as one level up from correlation. Robust regression is an alternative analysis method with the purpose of also including and not be negatively affected by values not following the observation pattern or extreme values, i.e. outliers.

A drawing of the classical linear regression as basis for this theory can be seen in Figure 11, where the variable y, the dependent/outcome variable, is a function, a linear combination, of the dependent parameters $a_0, a_1, ..., a_i$ and is linear in terms of the independent/predictor variables x_i, (plural only if multiple regression). In the simple case with only two weighting parameters we would have $y = a_0 + a_1 x + e_i$, where e_i is called the error. [10]

One common regression method is called Least

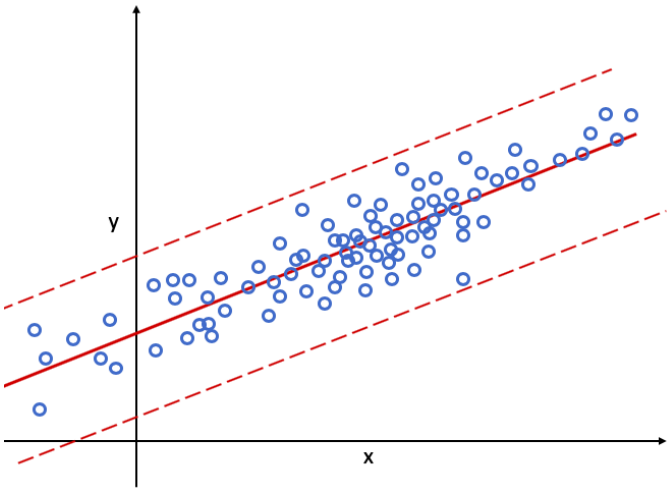

Figure 11: Linear Regression principal where the dependent variable y is a linear combination of one or many predictor variables x_i. *[Drawing by author.]*

Squares (LS), which would in the case of normal multiple regression be too sensitive to outliers and risk creating statistical errors. Even though time consuming residual analysis can handle these ”left-over” values the data assumptions have to be valid and restrictive. Robust regression requires assumptions that are less restrictive and generally present better regression results, i.e. coefficient estimates, with outliers present in the data. With normal regression there would be a distorting effect on the LS coefficients because of the outliers as well as, most significantly, a distorted weight distribution. This means that variables with an in reality quite small influence, small N shows much greater influence on the outcome of interest as they are supposed to have, which should generally be $1/N$. Robust regression finds the outliers and limits their weights/importance with iterative methods, which makes the values of importance stand out, [11], [12]. So, this regression does its own automatic residual analysis, but much less time consuming and a higher perfection in fitting the data in question to the analysis.

For the stop cause data in question, there are most likely plenty of outliers present. It is of course important always to study the data manually first, before conducting any types of statistical analysis so that the results can be properly scrutinised and validated constructively. There are several limitations to Regression and one of these is the linear relationship that is assumed between the dependent and independent variables, which often is not the case in a real situation. Another major limitation in using Regression is the binary structure of the mapping as well as the binary and/or non-numeric information of other stop time descriptors.

Academic Research

Because of restricted access to production lines during the COVID-19 pandemic and lack of specialised testing equipment, a literary study is called for under the circumstances.

With the preparation and analysis being finished, a foundation with the purpose of building solutions and opportunities on is laid out. A vast systematic investigation in the shape of an academic research constitutes a large part of this mission. Facts in this situation need to be identified, especially in terms of the latest happenings in the pharmaceutical industry. Numerous academic publications in pharmaceutical science and technology are studied to keep up to date with the latest innovations. It is also important to go through official reports on how different pharmaceutical companies, competitors, are dealing with similar situations to the objectives of the report, as described in the ”Problem Definition”.

In order to propose solutions to the problem of minimising stops to limit intervention, the strategy must be to focus on the stop causes that create the majority of the interventions. This strategy makes sense, since solving these would have a major positive effect on the project objectives. To counter the most relevant two to four letter codes, the most common stops, a solution might be needed that is either simple or, more likely, rather complex. As mentioned previously, predictive maintenance through systems connected to a Dashboard away from the aseptic production is based on correlation information. This is very interesting to look into, but there are risks that the data types, and especially the amount of data available, is as of yet not ready to be used to teach any mathematical models for predictive analysis purposes.

Another question is whether predictive maintenance is even enough to solve the issue; e.g. ”Are all or the majority of the interventions on the line necessary or not?”

TRUE or FALSE

From data accessed through a local filter, information can be extracted about whether the transparent doors in the green area protecting the lines are closed at a happening/event. This data is translated into the format of each value being either TRUE or FALSE for various discrete time stamps, similar to the situation used to create the four graphs in Figure 4. In that figure, a red dot represents a door opening while a blue dot represents another logged event, probably one of the 56 possible stop reasons retrieved from the mapping system list in Figure 9.

The door openings have a true value in this report because of their connection to interventions. The microscopic particle secretion risk mainly exists when a person moves in close vicinity to the exposed vials and having the doors open when doing so creates a more hazardous situation than by having them closed. Excluding the risk of human particles from above, a door opening might disturb the stable airflow moving from top to bottom to keep particles, glass residues and other debris locked onto the bottom surfaces. This airflow is crucial to keep the aseptic environment clean and safe. In the case of disturbances, there is a risk that particles get stuck into air vortices and land into non sealed vials.

At each glass door sensors are logging information for each opening action in time stamp. The time stamps, called TRUE, merged with the mapped information in terms of stop time periods, create a new perspective on the consequence of each stop. It has therefore been chosen to use this opportunity to quantify each stop cause relative to the state of the glass doors. A door opening being TRUE or FALSE, y, is a function of a stop cause, x. The question to be answered is; ”Has at least one door been opened during this stop?”

- If the answer is yes and the value is TRUE, it can be translated into a situation where the stop cause in question cause an intervention in the direct risk zone of the aseptic area.

- If the answer is no and the value is FALSE, it can mean one of two things:
  - No intervention at all happens and the stop has to do with, e.g. the line being filled up and some areas need to stay on hold until the process can continue
  - An intervention is needed, but not necessarily inside the aseptic area, e.g. if the stop occurs because of an issue with the Washer. If the intervention does occur inside the green area, the doors do not need to be opened until the vials are sealed and safe outside the doors.

Stop Cause Quantification

See major stop causes creating intervention as TRUE versus FALSE in regards to door openings in Figure 12. The door opening status can be seen on the y axis and the percentage of each stop relative to the 24 most common stops from the originally 56 stops on the x axis. A difference can be seen in the graph in Figure 12 between the upper half, where the stop has led to an intervention as a door opening, and the bottom half where the stop cause has not.

At the upper half of Figure 12, causing a door opening (TRUE) the five major reasons in order of importance are:

1) Tipped Vials, 46.6%
2) Crushed Glass, 15.6%
3) Manual Stop, 9.9%
4) Segment wheel, 5.0%
5) Removal of Stuck Cap, 3.3%

Tipped vials, 46.6%, as well as Crushed Glass, 15.6%, constitute together the by far largest percentage, 62.2%, of stops causing interventions as door openings in the aseptic area. Tipped Vials means that one or more vials have fallen over somewhere on the Fill Line. This might hinder the rest of the vials to continue through the process, make them fall over as well, completely get stuck and/or cause problems to the surrounding mechanical parts. Tipped Vials is very bad and inconvenient, especially since they can be both tricky to tend

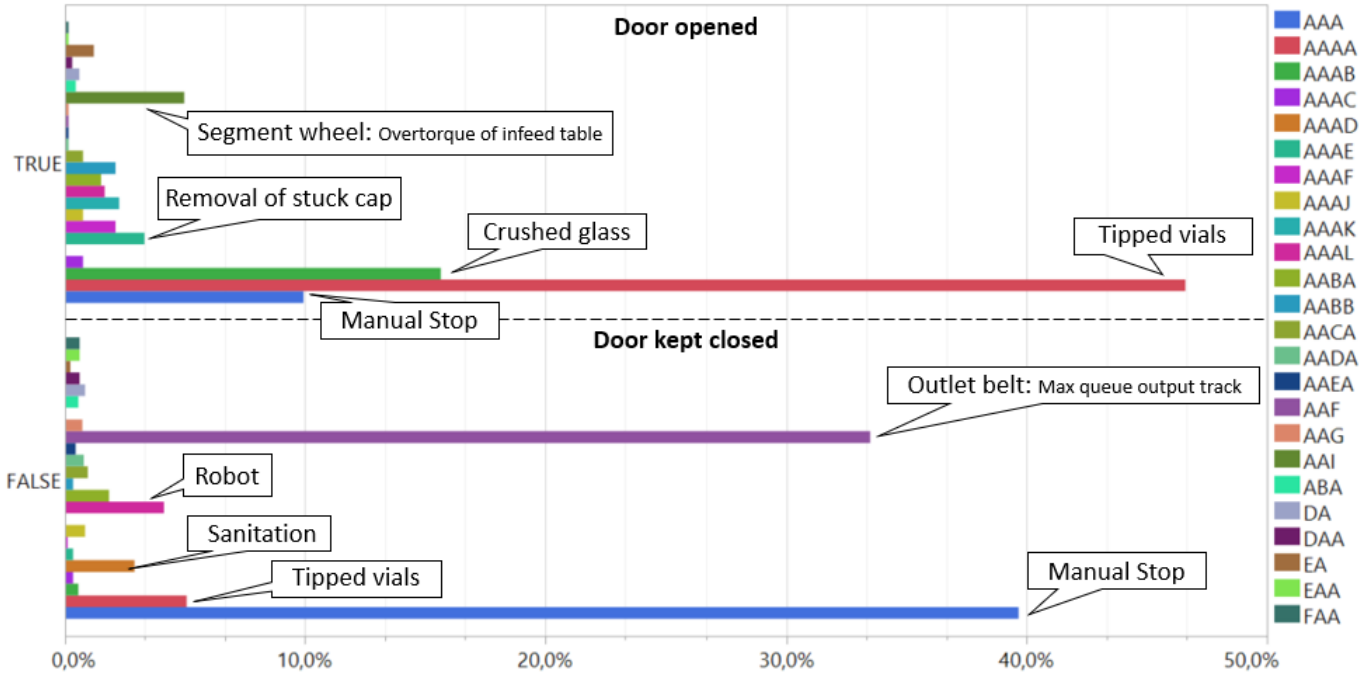

Figure 12: Door opening statistics for door open vs closed. *[Plots generated in JMP by author using production data from November 2019 to March 2020.]*

to without adding vibration to the adjacent vials, also making them to tip over. As discussed before and visualised in Figure 4 it can be interpreted that when a door opening is recorded, especially at the beginning of a batch, other door openings follow exponentially. Since, according to the statistical study in Figure 12, 46.6% of door openings are because of Tipped Vials, two conclusion can be made;

- Tipped Vial is the leading reason for interventions in terms of door openings in the risk zone.
- Interventions for Tipped Vials create further interventions, affecting the Overall Equipment Effectiveness (OEE) and the aseptic environment negatively.

Compared to Tipped Vials, Crushed Glass, 15.6%, could be considered to be even more serious in terms of consequences. The Standard Operating Procedure (SOP) states that while the line is stopped because of a crushed glass inside the A/B grade room, the entire area close to this chipped or crushed vial(s) need to be cleared and cleaned. The surrounding vials, often located in the waiting and transport areas 1. In-feed and 2. Waiting area seen in the drawing of Figure 2 need to be scrapped as safety precaution. The amount of vials needed to be thrown out depends on how far from the Fill Line in Figure 2 the breakage occurs and how many vials are involved in the crash. The further into the Tunnel in the direction of the Washer the incident happens, the more vials need to be scrapped and the longer the procedure will take. Often, the line cannot be started up again and the current batch continued up to two hours after the first stop. This decreases the OEE quite significantly for the batches where this occurs and without the meticulous cleaning being performed today, glass particles could serve as a contamination risk.

At the bottom half of Figure 12, not resulting in a door opening (FALSE) the five major stop reasons in order of importance are:

1) Manual Stop, 39.7%
2) Outlet Belt, 33.5%
3) Tipped Vials, 5.1%
4) Robot, 4.1%
5) Sanitation, 2.9%

Manual Stops (AAA) constitute all of 39% of line stops not resulting in a door opening. To understand from where the Manual Stop originates, it can be found in Figure 8 as being the third level of event in the series: Production → Filler →

Manual Stop. This could therefore technically mean any of the Reason 4 stops, A $\rightarrow$ Q, in Figure 9, but not necessarily. The stop is manual, meaning it occurs during production and is connected to the Fill Line, but could also be a required meeting break, shift change, unplanned maintenance, calibrations or any machine adjustments. It is therefore very hard to use information regarding Manual Stops for practical use, but can in this case be used to compare the previous door situation (TRUE) to this one (FALSE). The second most common stop not causing a door opening, the Outlet Belt, 33.5%, is interesting. The Outlet Belt stops, according to production accounts, usually means that there is a maximum queue on the output track and therefore the line needs to be stopped until the output has been further emptied. This same stop reason for the TRUE situation, for a door opening, equals 0%, as seen in Figure 12. This means even though a stop caused by Outlet Belt issues might lower the overall OEE and stall the production flow, it has nothing to do with human interventions on the line and is consequently not considered a contamination risk in the aseptic production.

Statistical Visualisation

For statistical visualisation of the machine stops with regards to the situation of door being opened versus the door being kept closed, Figure 12 gives a clear picture of the differences between them and the magnitude of each stop cause respectively. This graph is created from data preparation, where especially the mapping described in ”Methodology” plays a major role in making this possible.

Principal Component Analysis: The mathematical analysis technique Principal Component Analysis (PCA), has the purpose of reducing the dimensions, the set of variables, of a large data set into fewer dimensions easier to overview, while at the same time not eliminating important information from the data set. The goal of using this method is simplifications, but also to determine which variables in the data set that explain the largest part of the data variation. The Principal Components (PCi) described previously in ”Methodology” are ordered by the amount of variation of the data each one of them explains. Even though the PCA model is designed to provide as many principle components as there are variables, or number of samples, the system can be sufficiently described by the first three components as the rest of the succeeding components mostly describe noise and errors related to signals, [8], [9]. PC1, PC2 and PC3 are therefore enough to explain most of the data, not 100%, which also equals a major dimension reduction. The fact is that PC1 and PC2 usually represent the absolute majority of the variability, so in practise a 2D graph would be enough.

Using a loading plot is one way of visualising the result of a PCA analysis. Loading plots in this case has several usage; to study correlations, understand the impact of the different stop causes and if the square is taken of a loading it indicates in percentage the variance explained by the stop in the original variables, see Figure 10. Outliers, the non common stop causes and extreme values, have been removed from the data set not to dominate or skew the results of the PCA analysis. This is why only the 24 most common stop causes have been used in this analysis and not the original 56. The loading plot in Figure 13, shows how strongly each stop cause influences the principal components PC1 and PC2. If the influence, or loading , by a stop cause is close to -1 or 1, the limit of the unit circle, this stop cause carries a strong influence. If the loadings on the other hand are located closer to the unit circle center, these stop causes have a very low influence. Apart from influence in terms of the amount of data variation descriptively the different loading magnitudes of the plots in Figure 13 portray, correlation between the variables can be studied. If the stop causes are grouped closer together in the loading plot, they are likely to be positively correlated. Also, if the numerical value of one variable changes the same way and simultaneously as the numerical value of the other variable this indicates a positive correlation. If negative correlation is suspected, the loadings would instead be found opposite each other in the unit circle. An angle between two loadings greater than 90 degrees indicates a negative correlation between these two loadings.

Figure 13 shows the PCA loading plot for a) Door opened (TRUE) on the left hand side and b) Door kept closed (FALSE) to the right. The plots show from the previous stop cause mapping visualisation a fairly expected result, knowing the

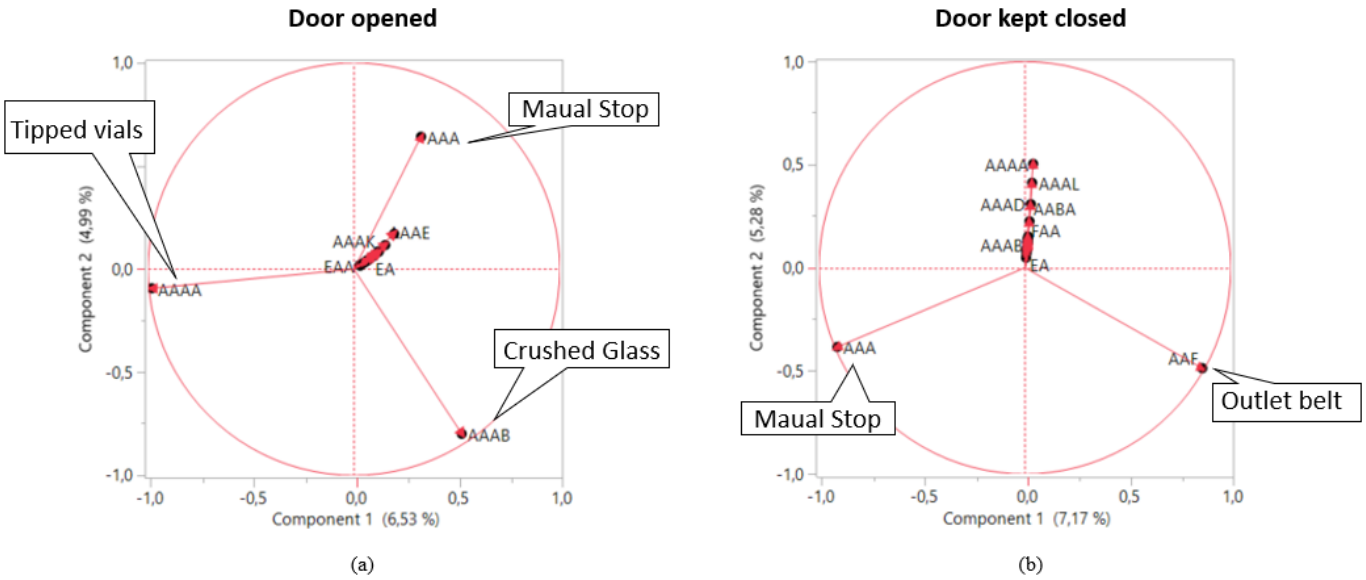

Figure 13: Door opening statistics. PCA loading plot for a) door open vs b) closed. *[Plots generated in JMP by author using production data from November 2019 to March.]*

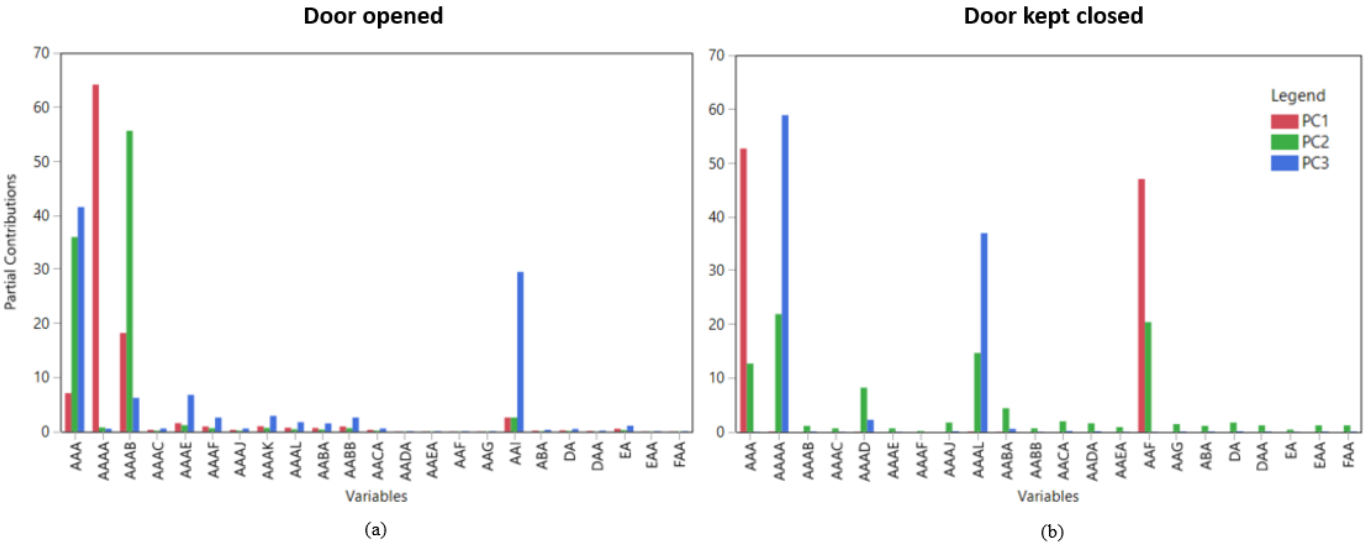

Figure 14: PCA Partial Contribution. *[Plots generated in JMP by author using production data from November 2019 to March 2020.]*

possibilities and limitations of the PCA analysis in this situation, but these results provide an extra dimension to the current situation analysis. In a) we see Tipped vials having a very large negative impact on PC1, almost exactly at -1, and close to 0 for PC2, while Crushed glass has a slightly lower negative impact on PC2 and a positive impact on PC1. Studying the diagram a) in Figure 14 the third principal component can be examined and in this partial contribution plot it is quite obvious that PC3 describes the other less important, but still contributing stop causes for open door interventions. These are e.g. the Segment wheel with the over torque of the in-feed table and general Manual Stop. Equivalently, for the situation of a stop leading to a non intervention, or at least an intervention without a door opening on the line, b) in Figure 13, both the Outlet Belt stop and the Manual Stop, discussed previously, have high absolute loadings on PC1. The rest of all the stop causes are very

clustered together, more and more closely to the unit circle centre, indicating fairly low impact as well as possible correlation. Quite interestingly, in diagram b) of Figure 14 for the partial contribution diagram display, the stop causes Tipped Vials as well as Robot issues are heavily described by the third principal component, PC3.

Preferably, each variable (stop cause) should show a distinct loading factor in the loading plots of 13 on only one principle component with an absolute value close to 1 and 0 for the other components. A rule of thumb is not to consider only the loadings above the absolute value of 0.5 as being significant in the analysis. Should the stop caused called Manual Stop be excluded from the discussion, because of its unclear background, there are in Figure 13 a) only two significant stop causes left with probably a slight negative correlation, the Tipped Vials and Crushed Glass.

Robust Regression: As mentioned for PCA above, the outliers for this statistical technique has to be removed in order not to skew the result of the analysis and show too much influence in the result. Robust Regression on the other hand has the purpose of including extreme values (outliers), an iterative method separated from the classical Least Squares regression that can identify and suppress their impact without removing the outliers in advance.

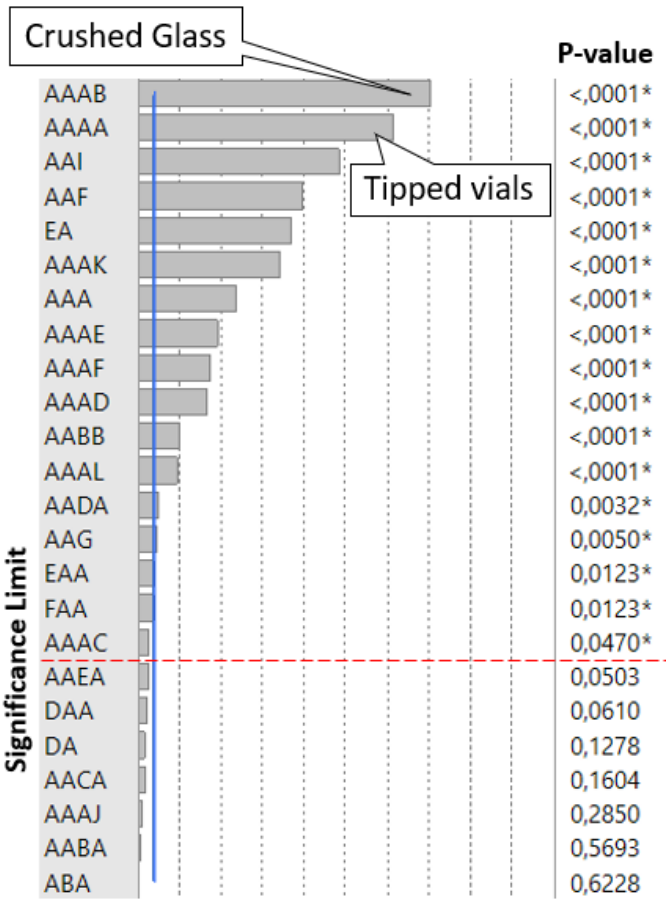

Figure 15: Effect summary ordered by P-value with Robust Regression. *[Graph generated in JMP by author using production data from November 2019 to March 2020.]*

For the analysis shown in Figure 15 the focus is now on the actual number of door openings caused by the different stop causes (variables) and not the TRUE versus FALSE scenario. The results in this plot is sorted according to the P-values. The purpose of the P-values are to determine the result significance and the red dotted line visualises the general rule of thumb that a P-value ≤ 0.05 is statistically significant and > 0.05 is not, meaning a proof of the null hypothesis and a rejection of alternative hypothesis. In recent days though, a higher value, 0.20, is often used as a cut-off value, [11], [12]. Because of the amount of variables in this analysis, previous visualisations made and the fact that focal point going forward needs to be narrowed down to the essential issues a cut-off value is chosen at 0.05. 17 out of 56 (30%) of the stop causes surpass this limit (see the red dotted horizontal line and the blue vertical line in Figure 15 separating the variables according to significance).The Robust Regression shows a slight different order of significance than the previous analysis methods with Crushed Glass as number one before Tipped Vials and stops due to the Segment Wheel. What this statistical analysis has in common with previous techniques and visualisations is without a doubt to prove that Tipped Vials and Crushed Glass by far are the most frequent stop causes to result in the highest number of interventions involving door openings.

Crushed glass is overall not as common as Tipped Vials, but the consequences are more time consuming. Both situations require interventions in the aseptic area and reduce the output of the filling line and lower the amount of medicine accessible to the end user, the patient. Solutions for a potentially more economically stable situation will be discussed in the following two chapters.

Belt Synchronisation

One of the major problems observed during go-look-see of the filling line and experiences, described in ”Knowledge sharing” of chapter ”Methodology”, is vials tipping and causing line interventions, which is also aligned with what the statistical analysis clearly states as the most common cause for door openings. These line interventions often require the whole line to be stopped meaning the conveyor belt transporting the vials from the washer, through the tunnel, all the way to the filler has to be turned off. The operators on the line have made comments that with any intervention, even those that are not related to vial problems, when starting up the conveyor belt again additional vial related interventions usually follow. This explains the high frequency of tipped vials, especially when closely succeeding each other, registered in the log system. This is also logical since any intervention or disturbance along the line, whether it be a line stop or airflow disturbance, could sometimes be followed by a tipped vial. The airflow disturbance might be difficult to mitigate as a physical intervention by an operator in the clean area will always change airflow dynamics, [7]. The conveyor belt, however, could be improved.

The conveyor belt is finely tuned to allow a steady transport speed of vials along the line without too many vials accumulating at one point causing a bottleneck or a lack of vials causing the filler to starve. Vials are also kept close together with pressure arms that have pressure sensors controlling the force applied to keep the vials together. All these controls work very well under steady state operation. This, until the line is stopped and spaces between vials starts opening up. These spaces between the vials are especially difficult to observe in the Tunnel area, see Figure 16, which means that an operator might only notice it when the vials come out of the tunnel, maybe already tipped or broken.

In Figure 16 two specific areas are pointed out which could be called high risk areas. The first one is located at the end of the Washer part of the line where the vials move from individual fixation in the circulating washing cylinders to being disengaged and touching each other, while in a queuing motion being transported through an orifice onto the Tunnel conveyor belt. The second area of interest is the entrance area to the Filler, where the vials come out of the Tunnel packed in disorganised rows before they are supposed to change direction and all make their way towards the screw conveyor (called ”snail” in production) with the help of an elastic curved wall. See visualisation of this area at 1. Infeed, 2. Waiting and 3. Snail in Figure 2 and 17. This transition in the second area between Tunnel and Filler does not always seem to be perfectly smooth and two problems can be identified; The first one being desynchronisation between the two areas when, as mentioned before, the machine stops and is started up again. This problem very likely results in tipped vials. The second problem has to do with the vials becoming too tightly packed together in the corner marked by a red circle in Figure 17 with a definite risk of glass breakage as a consequence (read more about this issue in the chapter after this one, ”Proposal 2: Material Properties”).

It is between these two areas highlighted in 16 that, according to observations and production accounts, that almost all of the vial problems occur. The location of these high risk areas makes sense as both the entrance to the tunnel from the Washer and the in-feed of the Filler are areas where there is either a sudden change in vial transport speed or where vials are grouped together under pressure. The cause for this problem is most likely the sudden jerk that the vials experience when the conveyor belt is started up after a stop and/or intervention. This step increase in conveyor speed causes vials with empty space behind them to fall over backwards (especially the longer and slimmer vials that have a high centre of gravity, see Figure 3). A simple and obvious solution to this tipping issue would be to change the geometries of the vials to achieve a lower centre of gravity, but for this study it is assumed that the vial design is fixed due to downstream finished product design. See ”Discussion” for more information on this subject. An inspiration for a solution to this problem can be found by looking

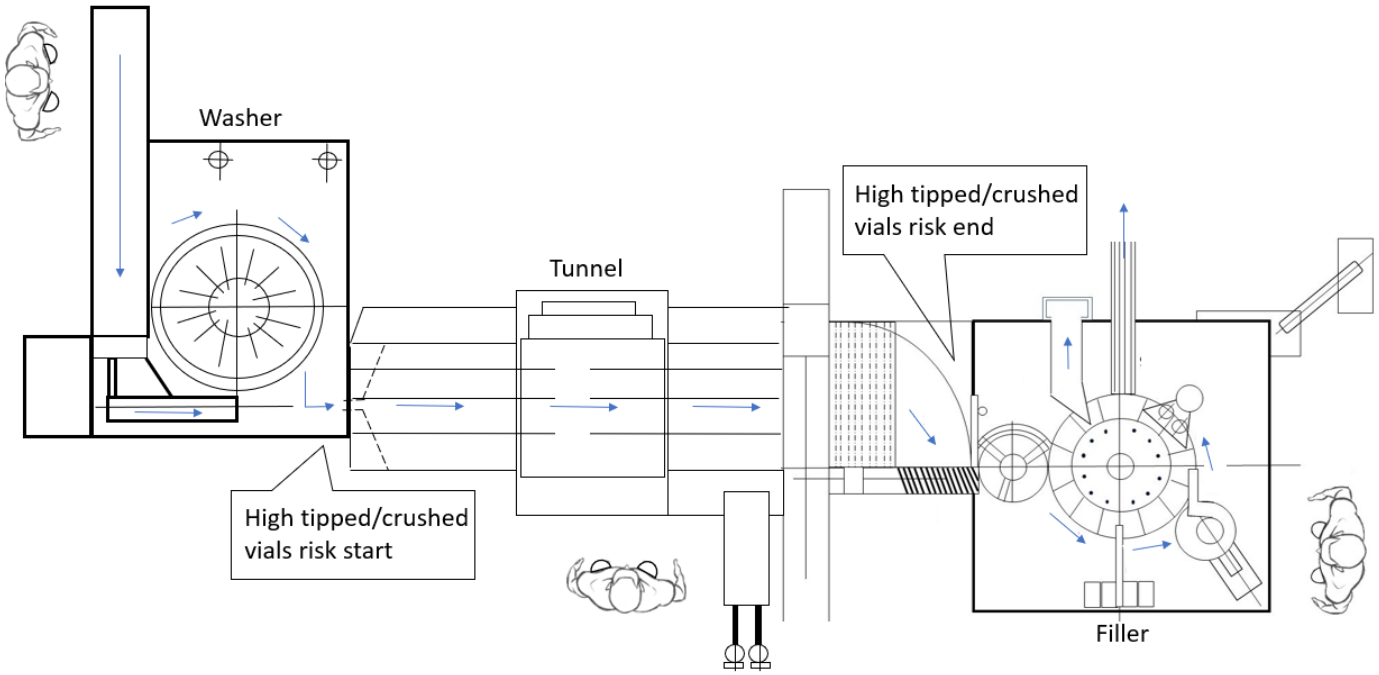

Figure 16: The whole line (Washer, Tunnel and Filler) and the subject of this report with the high risk areas of the stop causes Tipped Vials (and Crushed Glass) pointed out. *[Drawing by author from observations.]*

at the way modern filling lines are operated.

Modern Filling Line Designs: Modern filling lines have a more computerised control system that monitors the speed of each conveyor belt, screw conveyor, i.e. the snail, filler revolutions per minute (rpm) etc. to have a complete overview of all the moving parts. The data obtained from the sensors are used as input to an algorithm that automatically synchronises all the different parts of the transport network to avoid any bottlenecks or lack of feed, but also compensates for any disturbances caused by line stops or manual interventions. These are standard solutions that are offered by some companies and carry extra costs, but is worth considering if line stability is a high priority in terms of patient safety or protecting operators from hazardous substances.

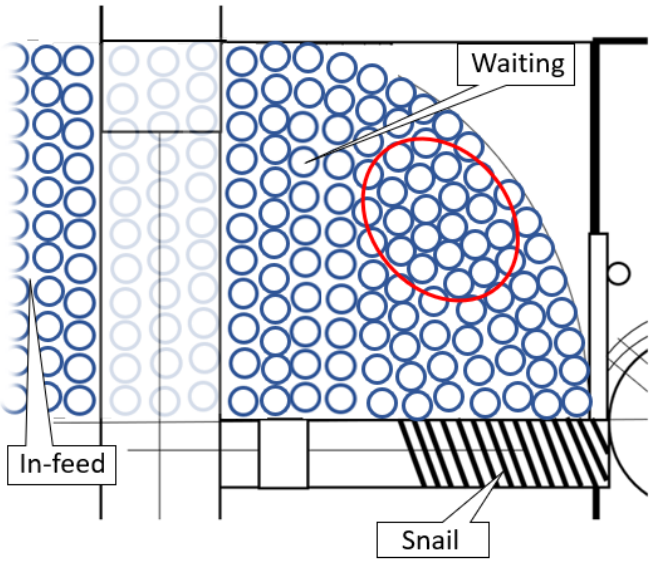

Figure 17: Vials (visualised by blue circles) being packed tightly in the area between Tunnel and Filler, see Figure 2 for context. Red marking indicate the area where vials have a tendency to be packed too tightly, most likely because of geometry. *[Drawing by author from observations.]*

Modifying Legacy Lines

An additional improvement to the off-the-shelf feature some equipment suppliers provide would be to look at how the controllers are activating the conveyor belt motors when the line is started or stopped. Programmable Logic Controllers (PLC's) of pumps and and electrical motors are sometimes

programmed to have a slow ramp-up of speed to avoid causing too much shear stress on certain mechanical parts. This concept could in theory be applied to legacy filling lines where a controller could be connected to the electrical motor for the conveyor belt where at every stop and start, the current applied to the motor would have a ramp function instead of a step change as is the case presently. This would mitigate the sudden acceleration of vials on the belt causing them to tip over. The implementation of this solution would not be easy, since the filling line would have to be taken out of operation for a long time in order to conduct tests and to tune the controller to each part of the line.

Reducing Unnecessary Interventions: The purpose of modifying legacy lines is reducing unnecessary Tipped Vials by enhancing line stability. As mentioned above, line instability issues occur when the line, or parts of the line, is stopped because of one of the reasons from Figure 9. Alternatively, the e.g. Washer needs to be paused because of sensors notifying that vials are packed too tightly in the Tunnel/Filler area and the vial moving parts of the Filler need more time to transport the vials through the line and out of the green area. No matter the reason for the stop, the vibration from the jerking motion of conveyor belt stop and start moments seem to be critical enough for vials to tip over as an unwanted effect.

The question now is; ”How many interventions including door openings in the aseptic area are due to unnecessary Tipped Vials?” In a) of Figure 18 the distribution of TRUE and FALSE stemming from the analysis made originally for Figure 12 can be seen and as expected, there are quite a lot of stops that do not end up as critical interventions, but also several door openings. In this particular analysis a local filter is introduced for the two major stop causes responsible for these (AAAA - Tipped Vials and AAAB - Crushed Glass) and their influence in terms of percentage can be adjusted respectively. While adjusting the amount of stops due to these two reasons, the relative percentage of interventions due to door openings (TRUE) and not due to door openings (FALSE) is automatically adjusted.

See more in the ”Discussion” chapter, but for this first proposal a hypothesis can be made by,

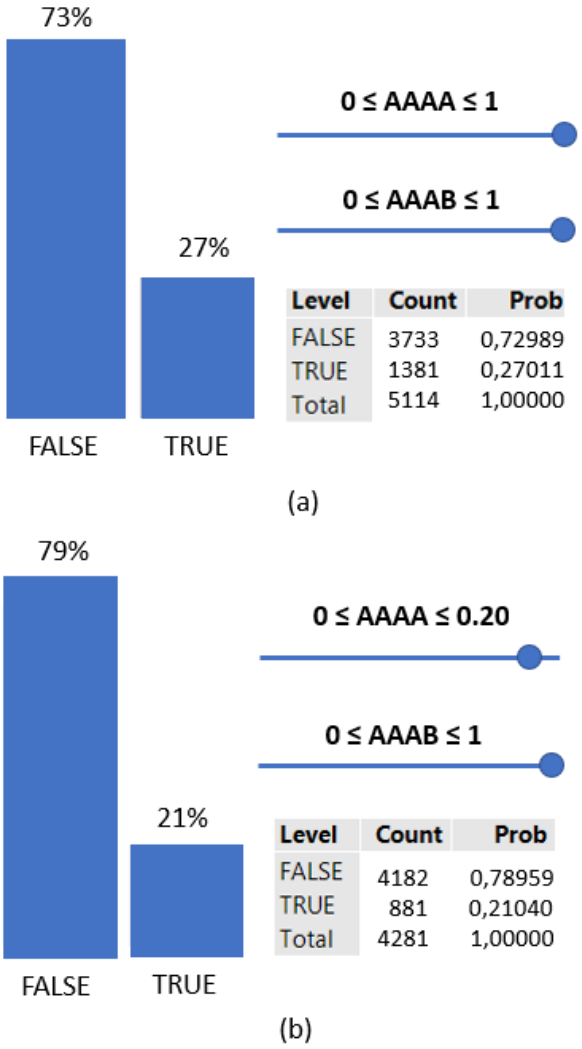

Figure 18: Distribution of intervention versus no intervention; a) without line stability modification and b) with line stability modification. *[Graphs generated in JMP by author and edited for visual purposes using production data from November 2019 to March 2020.]*

apart from experience (see ”Knowledge Sharing”), looking at the data when the tipped vials occur in terms of stop time stamps in relation to other stops. As an absolute maximum value, 80% of the tipped vials are due to jerking because of line instability after other unrelated line stops. This percentage would yield to the graph in b), Figure 18, which, compared to a) results in a 6% decrease of all door openings.

Glass as the Source of Many Problems

Manual interventions during filling line operation could potentially pose as some of the greatest risks of particle and microbiological spread in the filling line through human skin particles, moisture, fabric from clothing etc., but by far the most particles generated by amount are glass particles, [14] [13]. These glass particles are generated through the frictional forces between glass-glass and glass-wall surfaces and can even in some cases lead to cracks (causing vial leakage) or breakage (causing line stops and manual interventions), but more of this will be discussed later. There are of course ways to reduce these forces on the vials through various techniques such as making the back-pressure exerted onto the vials more gently and controlled. However, this does not fix the root cause of the problem, since there will always be unpredictable and random forces at play during vial transportation from the washing machine, through the tunnel and on to the filling section. Not only is the glass material selection important for minimising glass breakage on the line, but also from a quality perspective due to particle generation. This poses a problem, because even if one is able to completely remove manual interventions and have the whole line inside an isolator, you would always have a problem with glass particles potentially contaminating the glass vials. A common occurrence on filling lines is when the laminar air flow is interrupted (either by vials tipping or mechanical parts moving) causing dormant glass particles on surfaces to be agitated up and depositing in open vials, [15]. Frequent visual inspections are needed to ensure there are no particles present in the system that poses a risk to the patient using the drug. This poses a constant quality risks and therefore a material should be selected based not only on reducing glass cracks or breakage, but also scratch resistance. According to cGMP (current Good Manufacturing Practice) regulated by the FDA, states that ”quality should be built into the product, and testing alone cannot be relied on to ensure product quality” (FDA, 2004), [16]. It is for this reason that the focus should not be solely on quality control and corrective actions, but more on removing the risk altogether.

Glass Properties: Material properties of the vials could give some clues to the mechanisms at play that cause vials to generate particles and cause instability on the line. Before we consider the specifics of the glass material used in the process under investigation, it is good to start with evaluating what is known about glass properties and what makes it an ideal material for injectable medicines. Some of the advantages of using glass is due to several factors: chemically resistant to most substances, non-porous, transparent, easy to manufacture into various shapes and resistant to deformation, [17]. The disadvantage of glass can sometimes be that it is too brittle or prone to scratches for the application it is used for.

The chemical structure of glass is often represented via a random network model which describes the 3D structure not having any patterns of atoms/units repeating at regular intervals, [18]. The main component of glass is silicon oxide SiO_2 that is responsible for forming the bulk network structure. Alkali silicates such as NaO_2 are added to the network to provide charge neutrality and to increase the oxygen ions in the network, [18]. These oxygen ions are known as modifiers and changes the number bonds the oxygen atoms are connected to thereby reducing the number of oxygen atoms participating in the network, [18]. Figure 19 below illustrates schematically how the glass structure can be represented. The properties of glass can be further modified by adding more elements to the glass network. This is where different glass materials can be divided into classes that reflect the dominant element present within their network, e.g. Borosilicate glass.

The strength of glass is highly dependent on the composition and even if the composition is perfectly formulated for its application, small defects on the surface or the molecular structure can lower the actual strength of the glass by several magnitudes, [18]. The flaw within the glass acts as a stress concentration point from where a crack, fracture or breakage can rapidly propagate throughout the

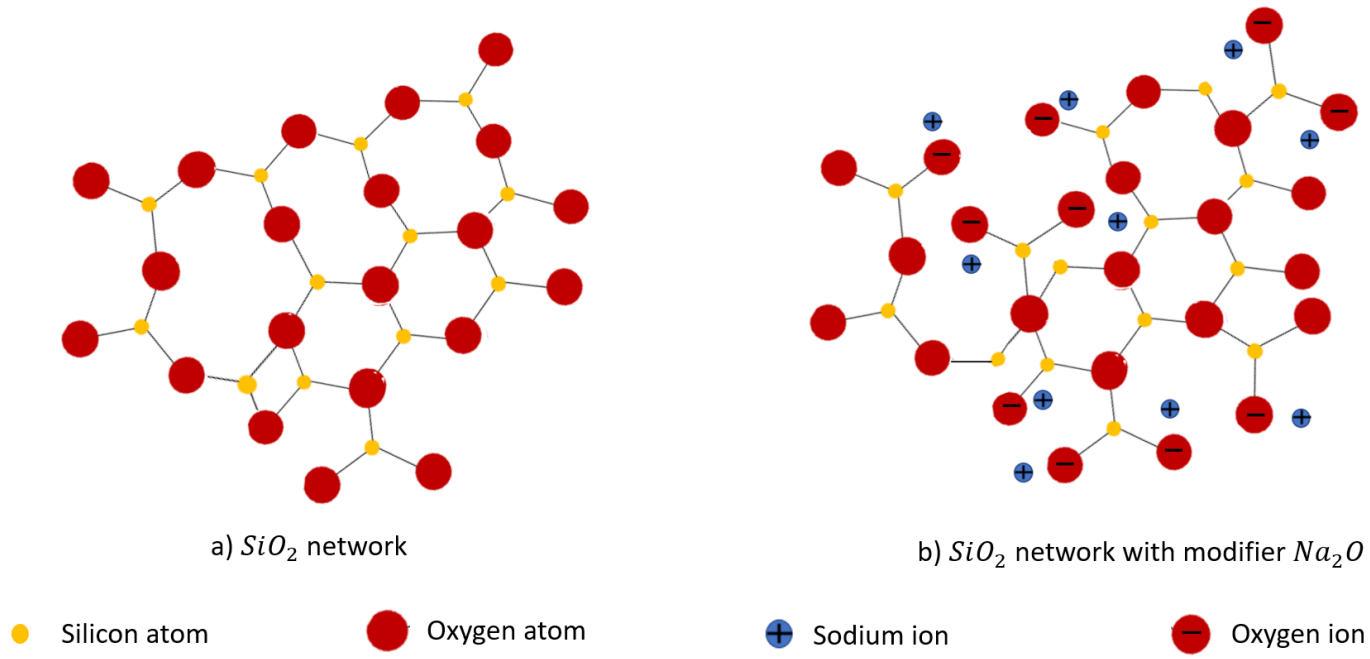

Figure 19: Chemical structure of glass. *[Drawings by author, adapted from [18].]*

glass. These flaws can be caused by many different ways within in the manufacturing processing (rapid cooling/heating) or during glass handling (contact with hard surfaces), [18]. Glass defects are still to this day a major problem within industry and is one of the highest risk factors during injectable drug manufacturing.

Glass within the Pharma Industry: Containers used within the pharmaceutical industry are carefully regulated and it is each pharmaceutical company's responsibility to comply with the standards outlined in the regulations that specify best practices for container design and use. The containers regulated are those that are in direct contact with drug product and depending on the critical nature of the contents, different degrees of protection are defined. According to the The European Pharmacopoeia, [19], there are 3 different types of glass containers. These 3 type are categorised according to the hydrolytic stability and is defined as the degree of resistance a glass has to release soluble minerals when in contact with a solution. This is measured by titrating the solution after a test to determine the amount of alkali compounds released, [19]. Based on the hydrolytic resistance, the 3 categories can be classified [19]:

Type I: Neutral glass (usually Borosilicate) having high hydrolytic resistance due to the chemical make-up of the glass. This glass is inherently resistant to leaching without any additional surface treatment. Suitable for uses up to most critical such as parenteral drugs (injectable medicines).
Type II: A soda-lime glass with surface treatment which gives it high hydrolytic resistance. Suitable for aqueous solutions and to some extent also parenteral applications.
Type III: Mostly used for powders and non-aqueous parenteral applications, but excludes freeze dried substances.

The vials in question for this study are of Type I and it is therefore important to know about the requirements within the pharmaceutical industry with regards to containers before investigating alternative materials. The glass materials that will be in focus for this study are Alkali Borosilicate, which is currently in use, and Alkali Aluminosilicate glasses.

Borosilicate Glass

Alkali Borosilicate glass has a structure similar to that in Figure 19, but with the added boron trioxide molecule (among others) as an extra glass constituent. The composition of Borosilicate glass are approximated to be 81% SiO_2, 13% B_2O_3,

4% $Na_2O + K_2O$ and 2% Al_2O_3, [21]. One of the most sought after features of silica glass containing boron is that is has an exceptionally low thermal expansion coefficient. This low thermal expansion property is very useful for cookware and one of the famous brands in this field is known as Pyrex, [20]. Apart from household application, the thermal properties of this glass is highly sought after in the pharmaceutical industry due to the thermal stresses parenteral glass vials are subject to during filling. These thermal stresses are most prevalent when the vials are cleaned in the Washer and then enters the Tunnel where the vials are subject to a sudden increase in temperature when they are dried. Borosilicate glass is also strong and a container can be dropped on the floor without breaking, but if dropped from a height cracks might occur.

Problems with Borosilicate Glass: The cracks and breakage of parenteral vials can compromise the sterility of the contents and the propensity of glass breaking from cracks or other causes are greatly increased with flaws on the exterior surface of the vials, [22]. The origin of the flaws might have different reasons, but by far the most common are flaws induced by vials in contact with each other where the applied surface-to-surface force induces tensile stresses propagate from the glass defects, [22]. The surface properties of glass, especially regarding friction properties, draws a lot of focus from glass manufacturers, but this will be discussed later.

Another problem with Borosilicate glass is delamination. This is a phenomenon that is prevalent across many different glass types, with some more prone to others. Glass delamination is a type of corrosion occurring on the surface of the glass whereby glass flakes are produced [22]. Although delamination is not that common in the pharmaceutical Borosilicate glass containers, recently there has been a significant increase in occurances within the industry, [23]. There have been studies made ([24] [25]) to explain this phenomenon better and there were strong evidence to suggest that this is likely due to the chemical nature of Boron present in the glass network. What was suggested in these studies is that phase separation occurs whereby the boron is evaporated out of the glass during a high temperature process whereby in some areas of the glass there forms two distinct composition interfaces making the glass heterogeneous instead of homogeneous, [22]. As mentioned before, any imperfections or non-homogeneity within the glass structure can significantly impact the strength of a glass container.

There are of course other problems with some Alkali Borosilicate glasses such as chemical durability. This is relevant to hydrolytic test, but for this study the focus will be more on the strength and durability of the glasses and all glass types discussed in this study would comply to the requirements of a hydrolytic test. Now that the issues and shortfalls of the well-established Alkali Borosilicate glass have been highlighted, one can start to look at the latest breakthroughs in glass technology within the pharmaceutical field.

A New Glass Material

One of the exciting breakthroughs in recent times was that of alternative glass compositions that are inherently safer and exhibit better performance in terms of line stability for aseptic production. One of the most notable ones is alkali aluminosilicate glass. Although this type of glass has been in existence for for some time, it was the breakthrough in the glass manufacturing process that made this glass a viable alternative for the pharmaceutical industry, [17]. Not only has this glass improved strength, but also better surface properties that make a significant difference in improving line stability. The basis for this improved line stability ultimately comes down to a combination of two features unique to the improved alkali aluminosilicate glass: 1) No trace of boron, thereby eliminating the issues typically experienced by alkali Borosilicate glass. 2) A very low friction factor coefficient, which indirectly brings many additional benefits. Apart form the increased strength and lower risk of flaws within the glass crystal structure due to the total lack of boron (as previously discussed) which would significantly reduce the breakage of vials on the filling line and therefore contribute to reduce manual interventions and increase patient safety, the low-COF (coefficient of friction) is what is the most interesting feature to consider. Before drawing conclusions on how a low-COF would benefit line stability and lower manual

interventions, it is important to first understand the physics of friction and it correlates with stability of vials on a filling line.

Physics of Friction on Vials

As a start it is good to begin understanding the physics of friction from a fundamental perspective. The fundamental concept of friction is the forces at play when two surfaces of two objects are moving against each other whereby the relative motion of the surfaces causes energy to be transferred and dissipated because of the shear forces acting against motion, [26]. While friction can play vital roles in certain applications in industry, for this study frictional forces will be treated as a detrimental factor at play during aseptic filling as in this case frictional forces can lead to vibrations. The cause of these self-induced vibrations can be simply explained: when the energy transferred is larger than the energy dissipated, [26]. These vibrations, especially on glass surfaces, are in most cases very apparent even to the human ear as the excess energy is converted into sound that can be categorised as a "groan" (representing a low frequency) or a "squeal" (representing a high frequency), [26]. These sounds are very loud and constant in any conventional filling line which can be confirmed by anyone witnessing the filling line first-hand. One of the ways to model this self-induced vibration is to approximate an expression that correlated the frictional forces with the frequency of what is known as stick-slip oscillations.

Equation of Motion: To simplify understanding a diagram representing a simplified physics experiment is shown in Figure 20 with an equivalent representation of how the same physics experiment from ref. [26] can be applied to two vials moving against each other. The diagram represents the stationary object at a given mass m, a spring of stiffness k used to counteract the frictional forces, the relative velocity v_0 of the moving surface and x representing the sign convention for the direction of movement. It is furthermore assumed that the friction force is proportional to the normal force F_N between the two surfaces since there is a close to constant pressure being exerted on the vials when grouped together. The friction coefficient is denoted as μ and is a function of the relative velocity between the two vials as $v_r = \dot{x} - v_0$,. One can therefore express the equation of motion as follows, see Figure 20 as reference to equation:

$$m\ddot{x} + kx = -\mu(v_r)F_N sign(v_r) \tag{1}$$

Law of Friction: When the the relative velocity between the vials are zero, the two surfaces stick together and the displacement of the initially stationary vial increases in the positive x direction until the friction force achieves the maximum static friction force [26]. The slipping action occurs when the force of gravity in combination with other external forces acting on the glass surface exceeds the static friction force. The following continuous slip friction law can be used that was developed by Thomsen, 1999 [27]:

$$\begin{aligned} \mu(v_r) &= \mu_s v_r / v_s, \quad |v_r| \leq v_s \\ &= sign(v_r)[\mu_k + (\mu_s - \mu_k)exp(-20(|v_r| - v_s))] \end{aligned} \tag{2}$$

where μ_k is the kinetic friction coefficient and v_s is the relative velocity of the maximum coefficient value. The above equation is not that relevant for this study, but could be used for future in-depth investigations. The focus is this study is, however, to simply understand the relationship between friction and vibration.

Consider the case where the two vials stick together due to the high friction coefficient, which would imply that Equation 1 would be as follows [26]:

$$\dot{x} = v_0, \quad \ddot{x} = 0, \quad kx = \mu_s F_N \tag{3}$$

Therefore the maximum displacement of the stationary vial for a stick motion would be x_0 and calculated as follows:

$$x_0 = \frac{\mu_s F_N}{k} \tag{4}$$

Once the two vials slip from each other, the relative velocity of the one vial would be $v_r = \dot{x} - v_0$, and therefore be negative. When v_r is negative, Equation 1 becomes:

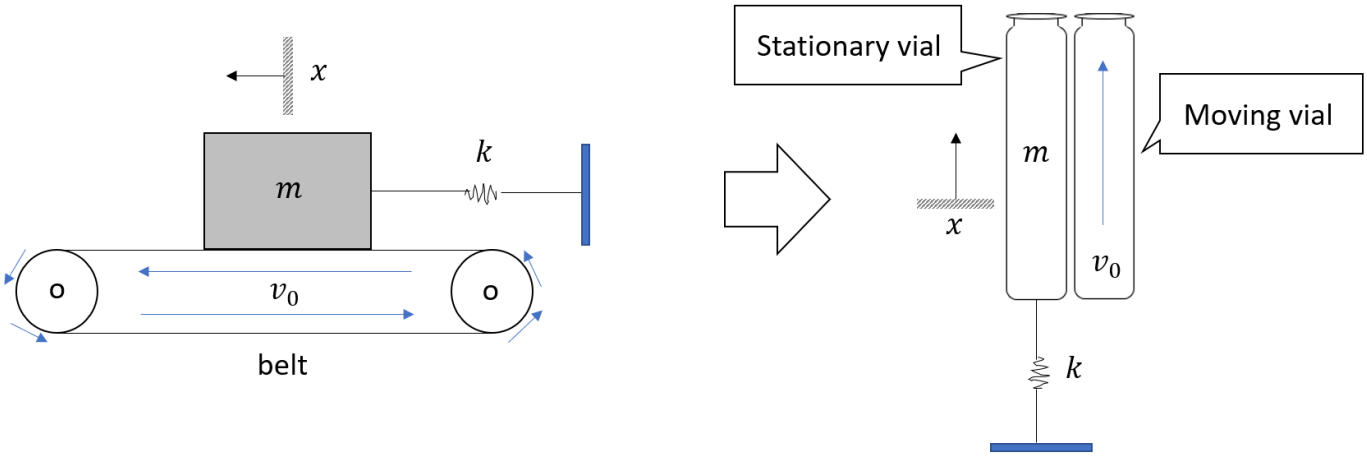

Figure 20: Vial moving something. *[Drawings by author from theory, [26]]*

$$\ddot{x} + \omega_0^2 x = \frac{\mu F_N}{m}, \quad \omega_0^2 = \frac{k}{m} \tag{5}$$

and this would make the corresponding solution:

$$x(t) = \frac{\mu F_N}{k} + C\cos(\omega_0^2 - \varphi) \tag{6}$$

where C and φ are determined by initial conditions

If the slipping motion is happening during a semi-static process, the slipping deflection,

$$\Delta = \frac{(\mu_s - \mu)F_N}{k} \tag{7}$$

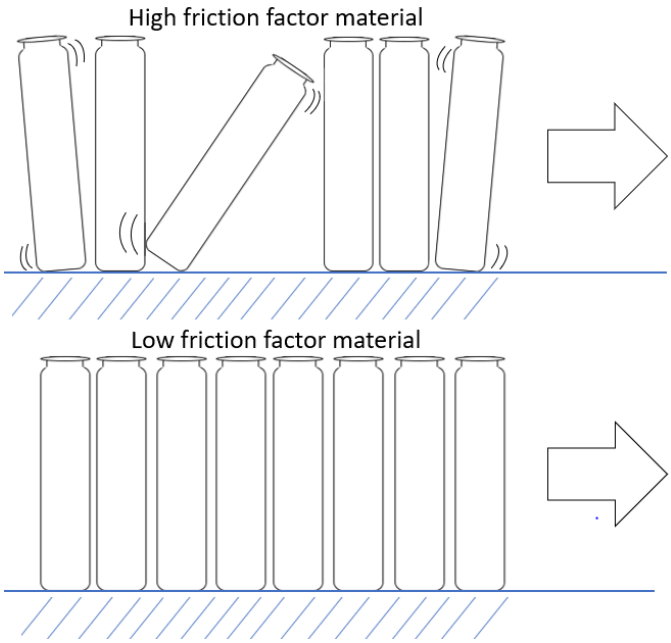

Figure 21: Friction *[Drawing by author.]*

is proportional to the difference between the maximum static and kinetic friction forces. It can therefore be concluded that with an increase in the coefficient of friction (COF) of either surface in contact with one another, there would be an increased displacement which translates to vibrations at higher amplitudes, leading to vials vibrating more violently when closely packed together. This is illustrated in Figure 21 where it can clearly be seen how this would work in reality and therefore by using vials with lower COF, you would be able to significantly reduce tipped vial events and hence manual interventions.

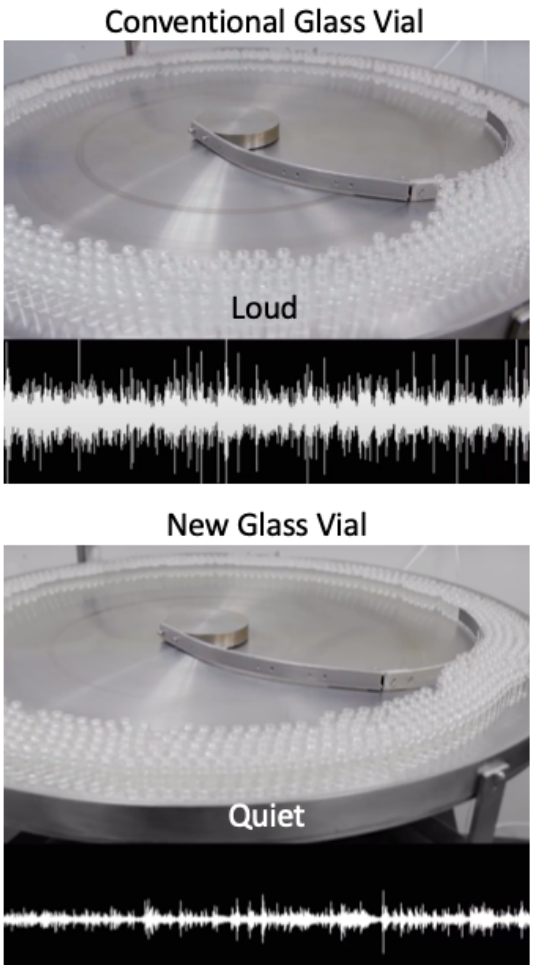

Figure 22: Conventional Borosilicate glass noise level (top), new Valor® glass noise level (bottom).*[Taken from source, [29].]*

Valor® Glass, setting a new standard

For this investigation a new vial that is already on the market and recently approved by the FDA (October 2019) [29] will be used as case study to demonstrate that the theory discussed in the preceding sections is what formed the basis for companies such as Corning (manufacturer of the new Valor® glass) to improve vials used in the pharmaceutical industry. This glass has the composition and properties that was demonstrated theoretically in the previous section to be able to improve glass performance. The Valor® is an alkali aluminosilicate glass with chemically treated surface to give a very low COF.

The Sound of Friction: As demonstrated in the previous section, there is a clear cause-effect relationship between the COF of the glass surfaces and the vibration of the vials against each other. To prove this phenomenon one might think to that this can only be done by directly measuring the vibration of the using sensors on the vials. This is an expensive and tedious exercise requiring the line to be stopped and risking contamination on an already validated production line. A simpler and easier way of determining the effect of friction is by simply making audio recordings of the line in operation close to areas where there is substantial movement and where glass vials are closely packed together. These types of studies have been made by glass manufacturers and is used to evaluate the increased performance of a new glass compared to a benchmark/baseline type of glass. As can be seen in Figure 22, the new improved glass was compared to conventional Borosilicate glass, [29], by measuring the frequency and amplitude of the sound waves originating from the glass vials vibrating. The reason for looking at the sound waves is to validate the new glass as being an improvement and one can directly relate the vibration movement of the vial to the sound, specifically the amplitude of the sound waves.

It can therefore be concluded with reasonable confidence that this reduction in vibration would significantly reduce line interventions.

Reduction of Particles: As can be seen in Figure 23, there are significant reduction in particles caused by glass contact whereby the most notable reduction was that of 2-10 μm. It is these particles that make up the bulk particle contamination that could occur on filling lines.

This significant reduction in particles is what ensures that drug products can be manufactured in a safe and efficient process that ultimately reduces the risk to the patient.

Improved Strength: A strength test of the Valor® glass can be seen in Figure 24 whereby a mechanical force measured in kg weight was applied to the sides of both the Borosilicate and the aluminosilicate (Valor® glass). The force was steadily increased until the vial breaks which was 20kg for the Borosilicate glass. When doing the test on the aluminosilicate vial, a weight load of up to 454kg was applied and even at this high load the glass did not break. This is a significant improvement to glass strength of over x20. Having

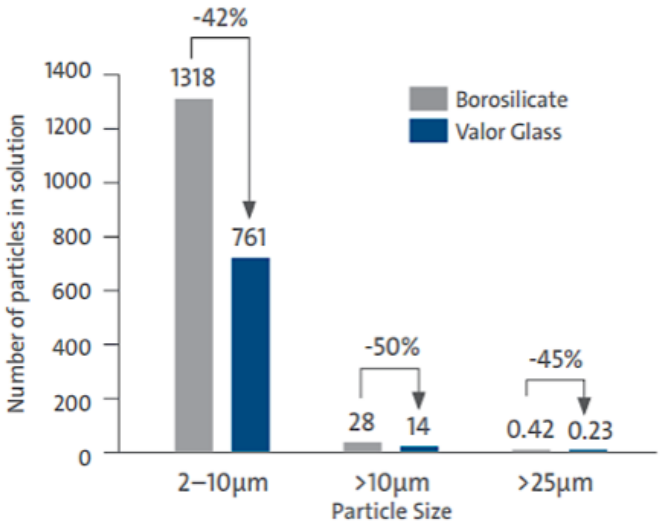

Figure 23: Particle reduction with Valor® glass. *[Taken from source, [30]]*

such as strong glass on the filling line reduces the importance of having packed vial pressure control as well as preventing glass breakage due to line stops.

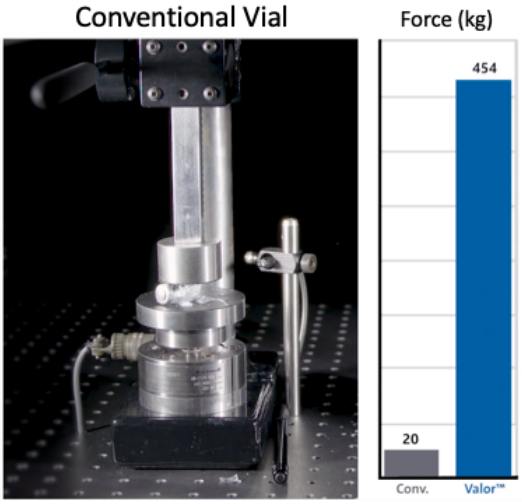

Figure 24: Improved force load of Valor® glass compared with Borosilicate glass. *[Taken from source, [29]]*

Although it is advantageous to have a strong glass vial, it is just as important to have vials without cracks being packaged as a product after filling since a leaking vial compromises the sterility of the medicine. It is therefore important that if there is a flaw in the vial, the vial should break under minor force to avoid it from potentially being overlooked by inspections. If the vial should break more easily it is also important that this glass breakage does not result in many splinters and smaller glass shards scattering all over the line. To ensure the glass only breaks into large manageable pieces that would make it easy for an operator or a robotic arm to pick up, the glass properties would have to specifically be designed for this. The way the Valor® glass achieves this, is by manufacturing a glass with internal tension and compression forces which can be seen in Figure 25. As soon as a deep crack starts within the vial, the stored internal energy (tension layer) ensures the vial to break whereas when there is a minor surface flaw the compression layer ensures it does not propagate into a deep crack.

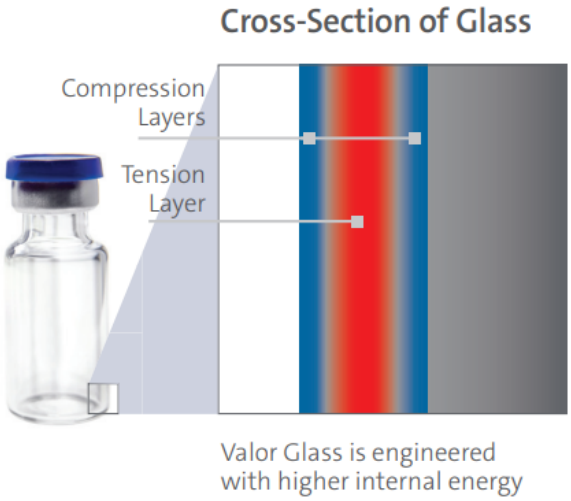

Figure 25: Particle reduction with Valor® glass. *[Taken from source, [30]]*

Business Case: Selecting a new material is easy enough once a clear benefit from a quality perspective can be realised, but the cost associated with such a change needs to be balanced with other benefits that would be able to give a return on investment for a more sophisticated glass material. Such ad-hoc benefit that would contribute to the return on investment would be the increased throughput of glass vial on the filling line. With a lower COF, vials would move more quickly on the line by having less resistance and causing significantly lower interventions. To prove this hypothesis, several studies were done by Corning [30] on commercial filling lines under controlled conditions to demonstrate the financial benefits of having higher line efficiencies. Figure 26 taken from the study [30] shows the improved performance achieved with strength-

ened low COF vials (Valor® Glass) compared to conventional Borosilicate glass vials. The average increased throughput ranged between 25 and 62 percent between 3 different commercial filling lines. Even when taking the lowest throughput increase of 26 percent, this is still a significant increase in OEE for a filling line and the financial gain a manufacturer can realise would significantly decrease the payback period for investing in a new glass material.

The increased throughput can be explained by looking at Figure 27 which shows that even though a filling line can have a higher line set speed, that does not fully translate to the actual vial per minute (Vpm) throughput realised. It can be seen that on Figure 27 the Borosilicate glass vial effective throughput starts to plateau as you increase the filling line set speed over 400 Vpm. This decrease in efficiency is due to glass vials having larger forces exerted on the surfaces causing vial breakage (stopping the line) as illustrated by Figure 17 and with a higher COF the frictional forces cause the vials also to move slower with them getting stuck to one another. This in comparison to the strengthened, low COF vial that does not have these limitations and can scale linearly with the filling line set speed. This also means that any other improvements made to the filling line that would enable an increased line set speed would would be able to maintain a high efficiency.

To give an example of how this increased line speed as well as the added benefit of reduced downtime and interventions translates to a reduced fill cost, Figure 28 illustrates this, taken from the same studies previously discussed [30]. It can be seen that at a fixed filling line set speed of 350 vpm, the Borosilicate vials has an effective throughput of 210 Vpm (60% efficiency) which translates to a baseline arbitrary fill cost of $0.75/unit. Simply having a better glass material can potentially increase the efficiency to 80% and reducing the cost per unit to $0.56. This is an estimated 25% reduction in operating cost, which is more than enough to offset an increased cost in vial material. It can therefore be concluded that changing the material would not only be an improvement from a quality perspective, but also from an operating cost perspective.

Now that the potential of the new vial material is well established, the next step would be to see how this potential improvement would impact the filling line under investigation by using the data from that line.

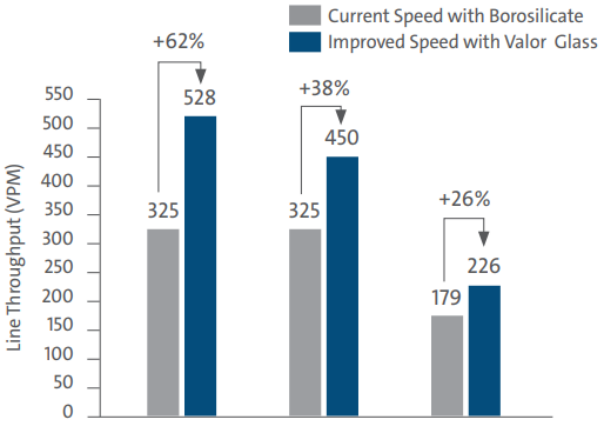

Figure 26: Controlled trial studies on commercial filling line to measure average throughput of vials. *[Taken from source, [30]]*

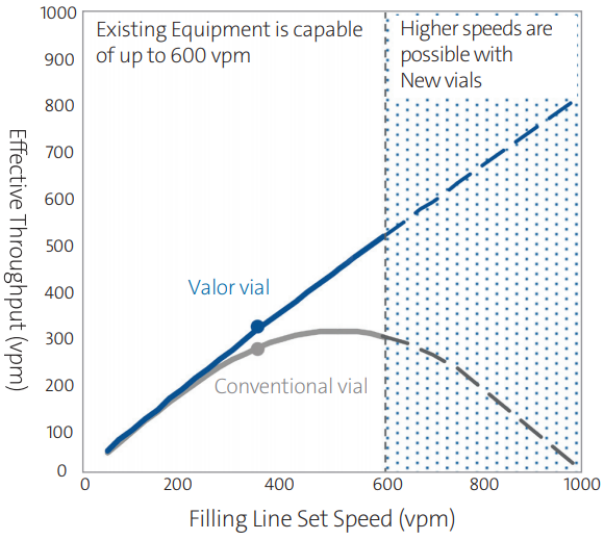

Figure 27: Comparison of vial throughput between Borosilicate and Valor® glass. *[Taken from source, [30]]*

The same intervention distribution analysis as seen in Figure 18 in the previous chapter is made for this material change scenario and visualised in Figure 29. Graph a) has the purpose of comparison to graph b) where it can be assumed that with this proposal described above, the number of interventions due to Crushed Glass would be completely dismissed changing the AAAB level from 100% to 0%. In regards to Tipped Vials (AAAA) some sources, [30], from studies do state that the overall stability

Valor vials reduce downtime and interventions

Effective Line Throughput (vpm = vials/min)		Reduced Fill Cost ($/unit)	
Conventional Vials (Historical)	210 vpm	60% efficiency at 350 vpm	$0.75/unit
Valor Glass (Baseline)	280 vpm	80% efficiency at 350 vpm	$0.56/unit
Valor Glass (Potential)	480 vpm	80% efficiency at 600 vpm	$0.33/unit

Valor vials enable higher line set speeds

Figure 28: Comparison of vial throughput between Borosilicate and Valor® glass. *[Table by authour, information taken from source, [30]]*

of the vials would improve significantly because of this new material, but in this case it has been disregarded. What also has been disregarded is the fact that with no glass breakage in tight situations and less friction between vials, it would make sense that simultaneously fewer vials were to tip over as a consequence of this alone. The only factor that has been accounted for with Tipped Vial related door openings in graph b) of Figure 29 is the 80% hypothesis discussed in the end of "Proposal 1: Line Stability". Backed up by data study and line go-look-see this hypothesis has to do with the amount of Tipped Vials that are "unnecessary", meaning those that happen because of unrelated events, e.g. other stops that on their own would not have needed any intervention. Alternatively, vials tip over as a result of attempts to pick up another vial. If all of the 80% of the stop causes due to tipped vials are because of these reasons, then 80% multiplied with the percentage of Crushed Glass in the whole set of stop causes has to be removed from the AAAA influence in the distribution.; $0.80\times \sim 0.05 = 0.04$ equals a 4% decrease. Combining the decrease in AAAA and AAAB according the theses calculations the overall decrease in TRUE door openings would be 7%, 1% more than for Figure 18, but it is more than likely that the actual decrease would in fact be much higher, since the comparison should not be made with an absolute number of decreased interventions. A better comparison would be to look at the number of interventions per vial filled since you would be able to have increased vial throughput with the new vial material. A detailed outline of this is discussed in the section "Discussion".

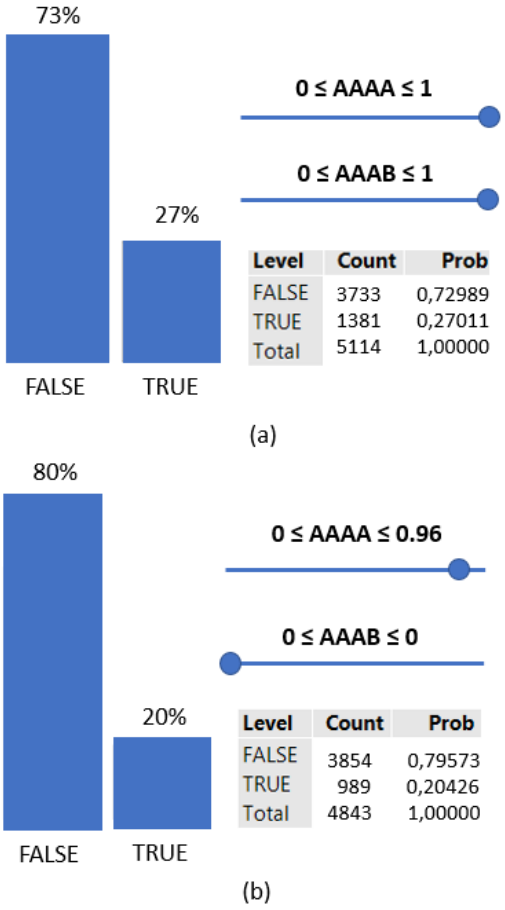

Figure 29: Distribution of intervention versus no intervention; a) without vial material change and b) with vial material change. *[Graphs generated in JMP by author and edited for visual purposes using production data from November 2019 to March 2020.]*

Machine Stops and Interventions

Throughout this project, efforts have been made in terms of trying to reach the goal of reducing machine stops to limit human intervention in aseptic production. The ”Introduction” describes the background to the title of this report; the production process flow of interest, the line of investigation (the Filling Line for Vials of two different sizes) and the design of this line and its produce. To give the reader a detailed picture of the backdrop in front of which the stops and interventions occur, this is very important. The batch intervention and the door openings that are continuously mentioned and used as a reference for separating ”bad” and ”good” interventions (or by the names TRUE and FALSE door opening scenarios as they are recognised as by now) are exemplified by the four graphs in the important Figure 4. This is based on real data, but from another line, and with the time stamps on the x-axis it gives a perfect example of just how much wasteful time those door openings add to the production. Not to confuse door openings with other stops and interventions and to explain the aseptic part of the problem, the A,B,C and D grading system is introduced, where Grade A/B also can be called the green area or the aseptic area. This is the inner core of the environment safety areas in production and the other grades have to be passed in order to get in there and without full training and gowning it is not allowed. The glass doors, when door openings are mentioned, are in here, because it is only here the vials are exposed to their surroundings during a long enough period to be contaminated should the reliable safety measurements not be in place the way they are. In the ”Problem Definition” it is stated that: ”In this report, stops and interventions in an OEE or efficiency sense are only partly dealt with and the focus lies instead rather on the preservation of the product quality and thereby protecting the vulnerable aseptic Fill Line (Grade A/B) area from any unnecessary microscopic exposure.” In addition to the aseptic area facility designs and meaning, one important background story is about isolators and RABS. Isolators do minimise the risk of particles contaminating the open vials, but the objective of this report is not just to limit human interventions, which is slow and complicated with isolators, but to reduce the stops and issues on the line to make this a reality.

The high-level strategy of this report is visualised in Figure 7 and the final content of this report is compared with the steps of the Lean strategy below in Figure 34. Below is also more information about Lean and, specifically, the Toyota Kata strategy which also to some degree has inspired the project strategy. It is the Biomedical Engineering knowledge and techniques that constitute the foundation for the entire project execution. Mapping the Stop Causes, the first step, and the table in Figure 9 both portray how the mapping is done, but also act as encyclopedia for the reader when encountering graphs where this system has been used further into the report. Without some type of mapping, any other analytical function on the data would be difficult. The main purposes of Principal Component Analysis (PCA) and Robust Regression is the overview they provide from this huge set of data, because Figure 12 could be enough to flag Tipped Vials and Crushed Glass and make the decision to focus on these two. The percentage of each Stop Cause is colourfully visualised for door opened and door kept close respectively and there is quite a remarkable difference for these two scenarios. The PCA and Robust regression analysis back up this initial result and the choice is clear; in order to limit human intervention, a.k.a. door openings since this has been highlighted as the unwanted action in this aseptic production area, the stops called Tipped Vials (AAAA) and/or Crushed Glass (AAAB) need to be reduced.

As previously discussed in this report, there are two types of glass vial designs containing the same volume; one slim and tall, which is the most common and the one used as the model in this project, and one short, wider and less sensitive to vibrations (see a photo of both in Figure 3). Changing the vial geometry to, in terms of machine stops, to the seemingly better version has two major obstacles; the cost of changes in processes and packaging upstream and downstream of the Fill Line

to align everything this size and the fact that the throughput of the wider model is much lower than the throughput for the same amount of vials with the thinner model.

Another possible suggestions to avoid AAAA and AAAB is instead of changing the vial geometry, to change the mechanical line geometries, e.g. change the design of the Washer → Tunnel interface and the waiting area of the Filler as the vials exit the tunnel, both seen in Figure 16. A suggestion on how this could be performed in the area currently designed as in Figure 17 where the vials and the tightly packed area is circled, is drawn in Figure 30. The point of this design is to avoid the phenomenon where some vials experience too much impact from the movement of the other vials coming out of the tunnel conveyor belt. These vials push some of the vials in front of them in the right direction, to the snail and into the Filler, but others are actually pushed back into the circled area and stay there for a long period. This might be critical for the risk of Crushed Glass. In Figure 30 the vials come out of the tunnel in a single file and go from being clustered together in the self-created rows of the Tunnel to a single file via the same triangle formation as what led them into the tunnel. One clever thing with this specific design would be that the side walls of the outlet areas are open at the bottom so that any vials in horizontal position are forced to leave the belt area by falling through these openings as scrap, without having to stop the line and perform interventions. This design should also reduce the amount of crushed glass, since the tightly packed area inside the arched wall in Figure 17 is now completely gone. Though very interesting, this is not considered a proposal by itself, but an interesting thought, since the objectives of this investigation involves no major changes on the line. If major changes can be made, then an isolator or RABS might have to be considered too. If in the future, on the other hand, it is decided to rebuild and redesign this filling line this could be an interesting suggestion to look into. One possible negative consequence of this design could be a slower throughput, but if simultaneously less stops happen from vials tipping or breaking, then the improved throughput would most likely neutralise and weigh up the cons to an increased throughput instead.

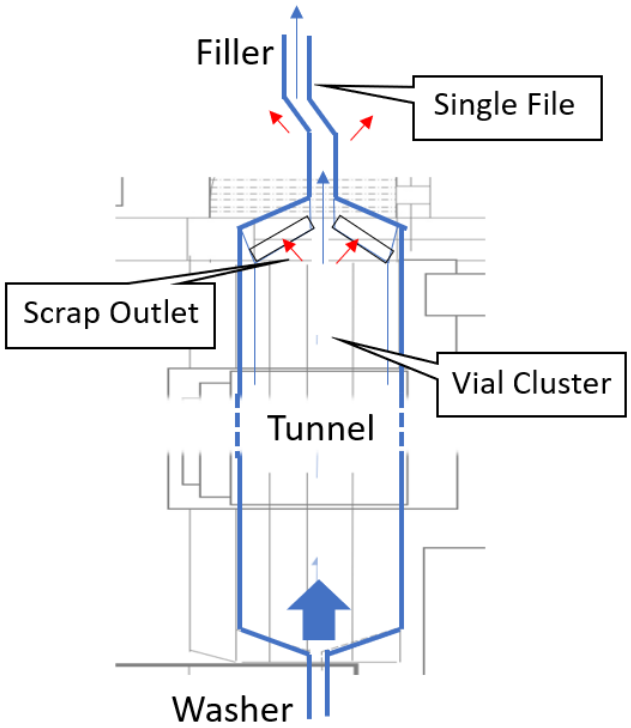

Figure 30: A new Fill Line design suggestion for the risk zone in Figure 16. The red arrows show the areas where tipped vials would roll off the line to scrap. *[Drawing and design by author.]*

An abstract, but still obvious, suggestion to completely eliminate Tipped Vials and Crushed Glass in the risk zone of Figure 16 is to mount some type of shielding device around the vials immobilising them when transported through this zone. This is probably a much better idea in theory than in practise though, because whatever is mounted to the vials needs to be moved with the vials through the Tunnel, then it has to release them separately into the snail that probably can no longer be used in this case and all this at a reasonable tempo. Most likely, a solution like this would take up too much space on the line, create much less throughput and just be very cost inefficient apart from again, the fact that, the whole line needs to be rebuilt and that is not of interest at the moment.

A smaller improvement, but still maybe with not a too simple implementation, as described later in this chapter, to the line by a common control system for line stability, belt synchronisation, slow and controlled ramp-up and ramp-down, less jerking and consequently much less tipped vials is suggested in ”Proposal 1: Line Stability”. An interesting point

is the conveyor belt surface material. It has to be smooth enough for the vial stability when the belt stops and starts, but if it is too smooth the vials would not move at all. There has to be balance with enough friction to keep the vials on the moving belt and smooth enough so that sudden jerks in the belt do not cause the vials to tip over.

What has to be considered here though is if the supplier of the equipment or the current vendor is unable to make any further changes whatsoever on the line, then the only thing left is to change the vial material itself as suggested in ”Proposal 2: Material Properties”. With regards to the benefits of replacing the vial material, it is clear that this would not only improve the filling line from a quality control perspective, but also increase the efficiency of the line via higher vial filling throughput. It is also evident that even though there might be increased operational costs involved in using this new vial material, it can be offset by the financial gain with potentially higher effective line filling speeds being possible. See further opportunities where this proposal is included below.

Using modern technology there are definitely a lot of other possibilities to create smart systems that can detect line abnormalities, e.g. vials that have tipped over and/or got stuck somewhere. Infrared cameras with machine learning technology can detect when vials are too tightly packed together, e.g. find the critical zone in Figure 17 and/or follow single vials entering the Filler from the Tunnel to see if they follow out through the snail or get stuck in the high impact zone and with time risk cracking. This is very interesting and by detecting the issues with smart systems they can in some cases be detected before the damage happens and therefore be used for preventative purposes. A notification or alarm will go out to the people working on the line, but actually to solve the issue, an intervention still needs to happen and if there is no one ready with the gowning procedures required for Grade A/B then the line has to be stopped even longer than usual lowering the OEE significantly, so without additional technology this is counterproductive. The future role of Artificial Intelligence (AI) will be described a bit later, but this smart technology must be accompanied by some automation on the line itself, e.g. by using robotic arms which then have to pick up, not only Tipped Vials, but also Crushed Glass and cleaning the whole area when this happens and a robot cannot do that as well as a human with current technology. It would probably be better if the vials do not have to crack in the first place.

Opportunities: As mentioned in the Business Case of ”Proposal 2: Material Properties”, the method for estimating the improvement in line operation and the reduction in interventions should not be done with absolute values. Since it is now known that the new vial material will have an added benefit of increasing line speeds, this will further compound the effect of eliminating the crushed glass phenomenon since the number of crushed glass per 1000 vials filled would dramatically decrease with increased line speeds. The same can be said for Tipped Vials, but to the same effect as Crushed Glass since Tipped Vial occurrences are also dependent on the belt stability. A simple calculation can be used to estimate the real probability reduction of line interventions by using both the percentage decrease in interventions (100% in the case of Crushed Glass) and the percentage increase in line throughput as demonstrated in Figure 26 and 27. This would then give a more reasonable indication of what the decrease in Crushed Glass probability would be. This is of course assuming that other interventions on the filling line would not increase with a higher line speed, since it is assumed that these interventions are production equipment related and not dependent on the line throughput. An example of this calculation can be seen in Figure 31 where data from a batch from the line with the output 146117 of finished products and with the total of 178 logged events (stops and/or interventions) is used. With a throughput increase of 33% for the new glass material a total intervention decrease in terms of probability can be as much as 44%, which is a much greater value than the original 7%. This new number is far fetched because of the assumption of no additional events for the 33% extra throughput, but it can at least show potential because Crushed Glass do take the most time out of interventions occurring while production is running. In real hours this is the most significant.

There is no denying that both Tipped Vials and Crushed Glass have to be decreased significantly and with a combination of proposals mentioned thoroughly in this report and/or mentioned briefly

	Borosilicate	Valor® Glass
Batch Size (OutputGood)	146117	146117 + 33% ≈ 194823
Number of Interventions for Crushed Glass	48	0
Total Number of Interventions per Batch	178	130
Number of Interventions per 1000 Vials	≈ 1,2	≈ 0,67
Decreased Intervention Probability	—	≈ 44%

Figure 31: Total estimated benefit in terms of decreased intervention percentage from ”Proposal 2: Material Properties” during one batch from the line in question with the longer, thinner vial model. *[Table by author.]*

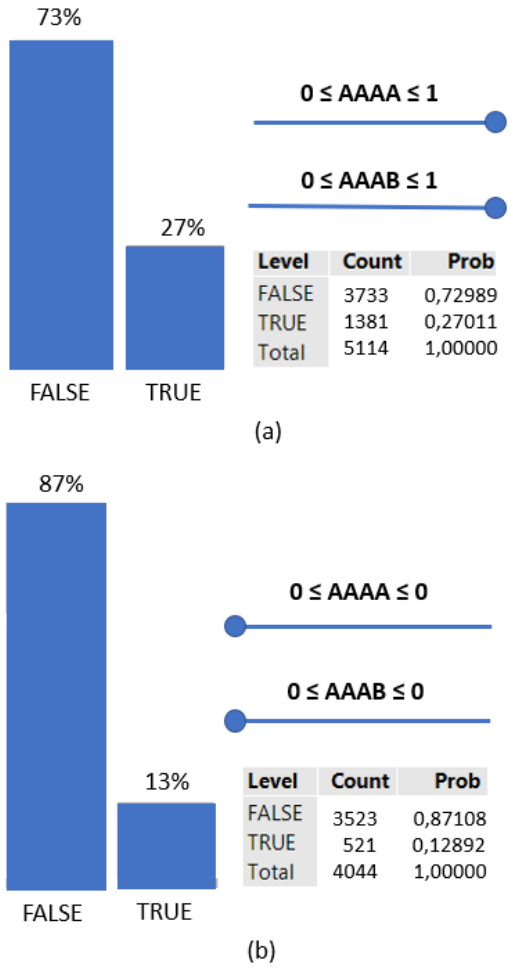

Figure 32: Distribution of intervention versus no intervention; a) without no reduced machine stops and b) with completely reduced machine stops for Tipped Vials and Crushed Glass related interventions. *[Graphs generated in JMP by author and edited for visual purposes using production data from November 2019 to March 2020.]*

in ”Discussion” it would be possible to disregard them both completely in the future. Figure 18 and Figure 29 visualise the distribution of stops on the line that belong to either the interventions involving door openings (TRUE) or stops/interventions that do not (FALSE) and here are considered of a lesser ”risk” and better align with the objectives of this report. The TRUE bar in these graphs should be as small as possible relative to the FALSE bar and in the b) figures the decrease of TRUE is 6% and 7% respectively compared to the no change scenario in a). The assumptions leading to all of 44% decrease mentioned above will not be possible using the methods from ”Statistical Result”, but even without this throughput increase; ”What is the most realistic maximum decrease percentage in door openings if one or more proposals of this report are successfully implemented?” The realistic maximum impact of the machine stop decrease when focusing on Tipped Vials and Crushed Glass is 14%, meaning an almost or complete elimination of these two stop causes, see Figure 32. This number occurs when AAAA and AAAAB are removed from the statistics and the distribution portrays only the rest of the 54 different stop reasons and it has already been shown that some of them do result in interventions and door openings, most clearly in Figure 12, but these need to be taken care of in other ways than what has been proposed in this report. To achieve an overview of this situation, where Tipped Vials and Crushed Glass are removed out of the equation, the previously used PCA loading plot, see Figure 13, is again used in Figure 33. To recap the meaning of these plots, loading plots are used to study correlations between the different variables and their

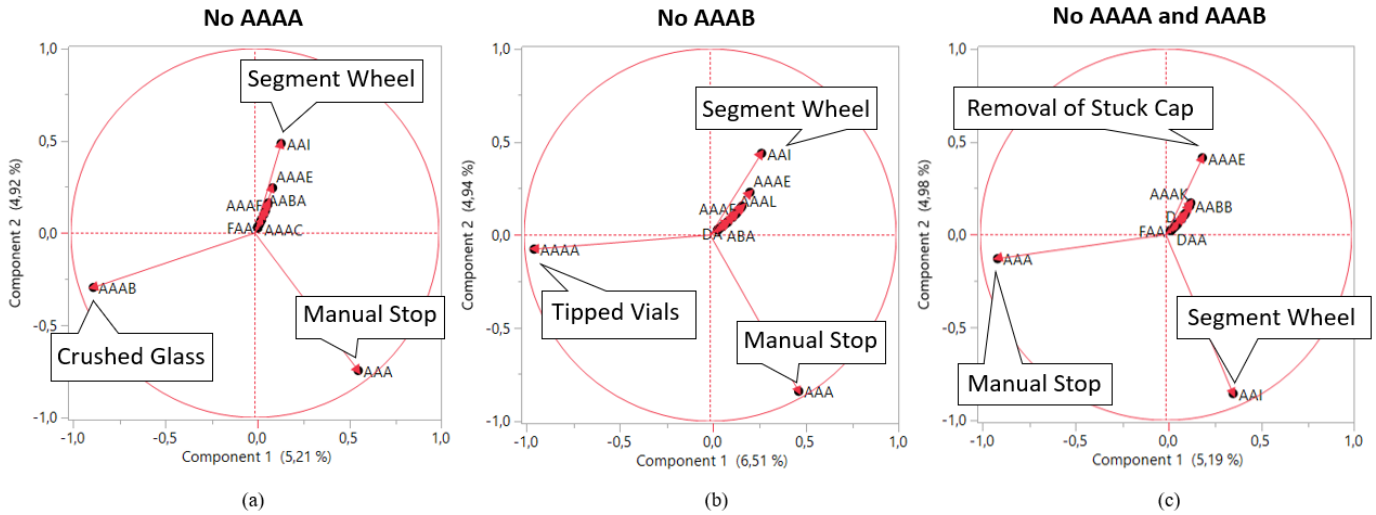

Figure 33: Distribution of intervention versus no intervention; a) without no reduced machine stops and b) with completely reduced machine stops for Tipped Vials and Crushed Glass related interventions. *[Graphs generated in JMP by author and edited for visual purposes using production data from November 2019 to March 2020.]*

individual impact, how much variance in the data that is explained by each variable. In plot a) in Figure 13 the original situation with both AAAA and AAAB are part of the data can be seen and these two, as expected, carry the largest loadings. Now in Figure 33 a) and b) show more or less the same situation but for no Tipped Vials and no Crushed Glass respectively. This, because of the equal great impact of these two, meaning equal in terms of loading more than the exact percentage because then Tipped Vials carry 31% more of all door openings. In these two plots the stop cause Segment Wheel (AAI) is described more by both PC1 and PC2 more than in the original loading plot. This is logical, since the segment wheel is in the centre of the Fill Line, not possible to be reached without opening a door. The rule of thumb though is that only loadings above the absolute value of 0.5 are considered to have a statistically significant impact and the AAI loading is just on that limit, so while one of AAAA and AAAB is still present as a reason, the focus should still lie on them. In c) on the other hand the interesting situation of Figure 32 with no AAAA and AAAB is visualised. Previously the stop cause called Manual Stop has been disregarded because of its unclear background, but this plot clearly shows a strong description of AAA by the first principal component and of Segment Wheel by the second one (PC2). This means that after Tipped Vials and Crushed Glass have been successfully eradicated, to make a proper study on this and try decreasing them could very well be the road to take as Next Target Condition, see Figure 34.

Implementations: Depending on which proposal and/or combination of ideas for improving the current situation, the objectives of this report, end up as the preferred choice, the implementation will be different. Regarding the first proposal being discussed, ”Proposal 1: Line Stability”, it deals with belt synchronisation between the Washer, through the Tunnel and out into the Filler in the aseptic area, see Figure 16. The suggestion is a centralised control system to avoid jerking and instabilities between the parts of the line during starts, stops and interventions. This would ideally limit all of 80% tipped vials and a 6% decrease in human intervention in the cleanroom. To implement this solution the controllers activating the conveyor belt motors have to be accessed to learn how these are programmed. Thereafter, measurements can be made based on the theory presented in this report and adjustments can be made directly on the line, when no batch is running, e.g. during scheduled Sanitation and Maintenance hours. At least in theory, this seems to be a fairly simple and very cost effective implementation. The risk to be taken into account when deciding to implement this proposal

is that all details on the functionality of the belt controllers have not been disclosed and it might therefore not be as easy to find and reprogram the internal parts of interest as hinted by this report. The line would have to be taken out of operation for a long time in order to conduct tests and tune the controller for all parts of the line. External automation/engineering consultants might have to get involved and suddenly the implementation becomes a little bit more complicated and more expensive than expected.

Implementation in regards to ”Proposal 2: Material Properties” on the other hand actually has the possibility to be quite straightforward. This is because all lines, machines and settings are supposed to remain unchanged. Exchanging the material itself does not change the shape of the vials and all machine geometries and packaging equipment dealing with the vials before and after the Filling Lines can remain the same as before. To perform the implementation, a stability study first needs to be executed, before a vial material change request is made to the FDA for the drug product in question. The fact that this new material has already been approved by the FDA for the pharmaceutical companies Merck and Pfizer for same or similar usage and this vial has become the FDA’s preferred future vial material, the application process should be very smooth, [36].

Any further implementation of improvement suggestions for the objectives of this report has to be individually considered.

Ethical Analysis: ”Can machine stops be reduced to limit human intervention in aseptic production?” ”Yes”. Reasonable strategies to achieve the goal of reducing machine stops to limit human intervention in aseptic production has to be proposed. This, while making sure that the production flow is improved and not hindered in any way, including creating new work opportunities and still saving money. When standard procedures in production have had the same structure, maybe a very well thought out structure, for a long time it could be both hard and time consuming for all parties involved to change this normal practise. All industries and companies within them need to evolve, slowly but steadily, towards perfecting what sometimes might seem to be mere details, but could actually turn out to be crucial factors for a company’s competitiveness.

Changing standard procedures could possibly make some current tasks and positions superfluous. Many traditional jobs will probably in the near future have to be somewhat adjusted to current needs anyway, but there is understandably a certain resentment in some production areas for major changes. One part of that is as described an underlying scare of personal involuntary career changes, but by far the largest part is the knowledge that the specialists have in their own areas and the fact that they know better than anybody what ideas from management would or would not work. Most of the time good advice is to share knowledge before making any analysis or come up with any suggestions for solutions, since if these do not work as intended in actual production the people supposed to be using them will not use them and we are back to square one again. Front-line personnel should not be forced to have additional things to monitor if not absolutely necessary and they often have more than enough already. The exception is only if this new solution makes work more efficient and/or provides a better overview than they had before, the solution has a true value.

Another option would be if standard procedures are not actually changed, but rather the means by which the standard procedures of today are met are modified or exchanged. This, as suggested by Figure 32, could still be enough to achieve the goal of efficiency and safer environment where standard practice and design would not have to experience a significant change. There might still be resentment to these changes and as mentioned before, a quick-fix solution is likely not possible, but it is about evolving with care. It is about taking small steps in the necessary direction while continuously evaluating the ethically important questions, i.e. ”How will the situation for the employees evolve as structural changes are made?” and ”Is the patient always in focus?”. To ensure a well thought out manufacturing improvement perfectly aligned with changes and with the patient as main focus, a fitting strategy needs to be followed.

Lean Strategy

The Toyota Production System (TPS) is based on the two concepts of direct production stop as answer to an issue and no part of the production line overproduces for continuous flow without unnecessary stops, [37]. This system can be used to describe the Lean philosophy and originates from how the Toyota manufacturing process is uniquely based on stability and with a high production rate, low costs and high product quality, [38]. The core focus for Lean production strategies are on creating customer (here patient) value, while concentrating on the value making chain. Even though the result from a lean strategy might be production optimisation, lean strategies in general focus far less on this and more on the production flow as a whole, the stability. To achieve stability, there has to be a continuous consistency on all production levels and in all areas. To really save time, money and increase quality waste has to be reduced from the manufacturing processes, e.g. overproducing, transporting, storage, incorrect processing, waiting time, too much motion and defects. In non-lean production, waste is eliminated at certain places, but with Lean, waste is continuously removed in lesser volumes. This results in lower production costs, less human interventions and higher Overall Equipment Efficiency (OEE). Part of the stability is to estimate the output from a set of inputs, as there should exist deeper knowledge about the production flow with using Lean. If e.g. the production goal is increasing OEE, then every part of the process should be adjusted accordingly. On the other hand, if the objective instead is greater patient safety with less interventions, then all adjustments should be made according to this goal, [37]–[39].

The Lean strategy can be applied in the biomedical industry as well as in any other industries when developing competitive products and first and foremost patient safety. Biomedical Engineering contains interdisciplinary engineering sciences and principles for strategic problem solving and design using biomedical applications to advance healthcare, e.q. the pharmaceutical industry. Mathematics, statistics and IT are tools that combined with basic anatomy, material chemistry, and physics can be used to understand vastly different situations. This report shows Biomedical Engineering problem solving following the Lean philosophy. The Lean steps that have been followed throughout this report and how they are identified can be seen in Figure 34. The Lean idea of problem solving is for setting high-level goals that can be executed in a strategic and fairly agile way. Both Lean and agile focus on continuous process evaluation and value in terms of the customer, or patient, are considered most important. In Figure 34, Lean can be called a set of steps and/or a philosophy, but to solve the problem in question a Lean strategy, like Kata, can be used.

Improvement Kata: One Lean strategy is the Toyota Kata strategy with the purpose of keeping up with the pace of change in any level, on production level as well as on industry level. This is a problem-solving strategy to create continuous cumulative improvements by reiterating a four-step routine seen in Figure 35, where the official four steps of the so called Improvement Kata Model is drawn. This set of practices/steps should teach a scientific mindset and a overall logical approach to solving unknown problems. The first three steps constitute the Planning Phase where the direction/challenge of the task at hand firstly needs to be understood as well as, subsequently, today's situation in this subject. As the final step of the planning phase, the target conditions for the next step in the process can be established. Throughout the forth Kata step, the Executing Phase, an iteration of the same procedure is made for each process step with the help of five coaching questions seen in Figure 35.

Good management practise according to the Toyota Kata is described as: "the systematic pursuit of desired conditions by utilising human capabilities in a concerted way." (Rother, 2009, p. 15), [39]. Rother here means that it is not about the solutions themselves, but rather the routines with which they are elaborated through unknown and unforeseen waters. It is important to note that Kata cannot be implemented, only practised. The definition of an issue is defined as the gap between phase 2. and 3. in Figure 35, between the current situation and the target condition, [38]. Not to be too vulnerable to change, but rather absorb it, understand it, and learn to use it to one's advantage might be encouraged by the Kata model and this is something very important for the future of all processes and environments, in this case for the future of Aseptic Production.

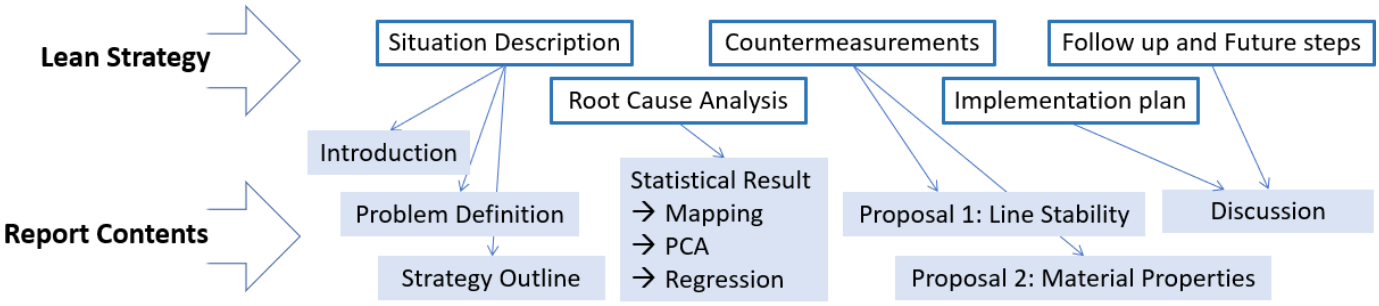

Figure 34: Following the steps of Lean in this report. *[Graph by author, Lean structure from source, [38], [39]]*

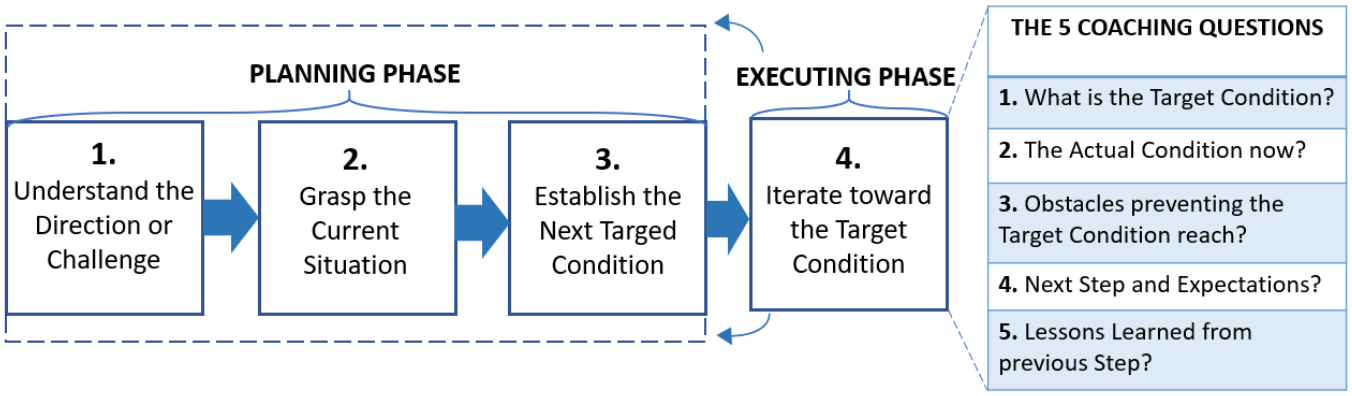

Figure 35: A Lean Strategy: The Toyota Kata Model. The four steps of the Improvement Kata Model for systematic problem solving as good manufacturing practise. *[Drawing by author inspired by source, [39]]*

The Future of Aseptic Production

The end goal is to achieve an even safer healthcare for patients and FDA is one of many administrations in the pharmaceutical industries ensuring that every company comply with rules aligned to this goal. People with chronic illnesses have to take their medication every single day/week or on similar regular basis and if they cannot trust the quality of their life saving medications for their chronic illness as well as the integrity of the company providing the drugs, it would be a catastrophe for the patients as well as for the company in question.

The future of aseptic production is constantly changing, being modernised and moving forward in various ways. Artificial Intelligence (AI) and Machine Learning are used in fantastic ways, often with the purpose of preventing problems by finding them in advance. This only works when enough data has been gathered and sorted and the correct algorithms developed and taught accordingly. In the meantime, we need solutions built on years of studies in the fields of mathematics, physics and chemistry to make aseptic production standards in every pharmaceutical company even more efficient, safe and as always with the interest of the patients as number one. A future recommendation is to carry out a proper investigation based on this report, e.g. aligned with the Kata model in Figure 35 where the AI goal is set up as the first step. Data requirements, cost benefit analysis and targets should also be part of the planning phase.

The Role of AI: In most cases, no off-the-shelf Artificial Intelligence (AI) solution exists but there are definitely building blocks available ready to be introduced. To develop an AI system, a very deep technical knowledge of the engineering processes as well as the overall company and industry structures

is crucial when using data mining techniques. The events responsible for the logged data points and the connections between them and has to be understood for the AI system to work aligned with, and not against, standard operating procedure's (SOP's) and general decision making together with strategy objectives. It is quite likely that a team needs to be appointed, maybe to a project, with the sole purpose of gathering data, preferably through a data translation filter so that the data can be read in the same format and have the same structure. Both historical and current data has to be collected, longer periods than the four months of stop time stamps used in his report. The data used for a good AI system in itself has to be of good quality. If this input data is disorganised, the output will be even more disorganised and potentially have adverse consequences if used blindly. Cost efficiency plays a large role when companies choose to use AI since predicting and avoiding issues is in the end cheaper than trying to find the problem and propose solutions, as has been done in this report. Earlier issue identification is a less tedious process with lower impact, but also for any evaluation of past happenings. An AI system can provide good access to historical data and hopefully evidence for the series of events leading to the issue in question and the system could help ensure that it never happens again by evaluating options for change, on any level.

AI might very well provide an innovative solution to the intervention issues on the line and/or serve as support to Proposal 1 and 2 discussed previously in terms of a broader variety of data knowledge to ensure the actual benefits of the proposals in a more accurate way in terms of cost and impact. The main usage example of AI for the purpose of this report is predicting and preventing machine stops from ever occurring. It is very important always to be one step ahead of future requirements from the market and/or organisations like the FDA as well as company structural changes and developments.

Conclusion

Machine stops can be significantly reduced to limit human interventions in aseptic production. For a sustainable production in terms of efficiency, value creation and patient safety in all areas there is a continuous need for, and interest in, new innovations. This report shows that this reduction is most effective when different methods targeting the root causes of the most crucial and time consuming stop causes are combined. The goal to decrease or completely eliminate stop causes called Tipped Vials and Crushed Glass should be considered Target Condition in the Lean Strategy. Out of the two proposals, changing the vial material, would be the most feasible and with the best line improvement relative to the effort of implementing it.

The background knowledge gathered and every analysis made for identifying these two stop causes as different and more pronounced from the many background issues, can later be reused in the second iteration step towards the new Target Condition. This report presents a number of innovation prospects and these may possibly be considered by any project with objectives aligned with solving line instability issues and breakage problems among small glass containers, e.g. vials or cartridges for parenteral use. This future project does not have to be connected to the same line types, area or company, but most likely this report is of most interest within the pharmaceutical industry.

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