Tampere University of Applied Sciences

The Scientific Background of In-Process Control at 3P

Amanda Lahtinen

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ABSTRACT

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The Scientific Background of In-Process Control at 3P

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This thesis was conducted at NextPharma's ophthalmology facility in Tampere and the aim was to focus on establishing a scientifically justified sampling plan for two 3P-filling machines used in the production of ophthalmic medicines. The sampling plan was based on theoretical product information and the statistic tool utilized was the Accepted Quality Limit (AQL) from ISO 28590-series. The calculations were done in Excel and executed to meet the requirements of GMP – Annex 1.

The key aspect of this thesis was the in-depth exploration of ISO 2859-1 and its application in establishing sampling schemes – normal, reduced and tightened inspection. This thesis also included working principles of both filling lines and the current method of doing In-Process Control (IPC). The results lead to invent an alternative method for process control that was not time-dependent and involved sampling at fixed intervals.

The thesis also delved into cost efficiency in IPC, highlighting the generation of pharmaceutical waste and exploring solutions for more efficient quality assurance methods without compromising safety or quality.

The calculations were executed by using AQL of 0,4 % which was based on the most critical parameter, integrity, with the inspection level II. All three sampling schemes were calculated for each product.

Key words: accepted quality limit, in-process control, GMP

TIIVISTELMÄ

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Opinnäytetyö toteutettiin NextPharman silmälääketehtaalla Tampereella. Työn tarkoitus oli perustella tieteellisesti prosessikontrollit eli näytteenottosuunnitelmat kahdelle 3P-täyttökoneelle. Näytteenottosuunnitelmat määriteltiin käyttäen Accepted Quality Limitiä eli AQL:ää, joka kuuluu ISO 2859 -sarjaan. Tulokset perustuivat teoreettisiin tuotetietoihin, eikä työ sisältänyt kokeellista osuutta. Työ tehtiin toimeksiantajan pyynnöstä, jotta GMP Annex 1 -vaatimukset täyttyisivät 3P-osaston osalta.

Työssä perehdyttiin erityisesti ISO 2859-1 -standardiin, jonka mukaan laskettiin Excelissä kolme erilaista näytteenottosuunnitelmaa, joiden välillä prosessin aikana voidaan liikkua. Työssä tehtiin riskianalyysi ja määriteltiin jokaiselle tutkittavalle parametrille oma AQL-luku, joista kriittisin parametri määritti yleisen AQL-rajan. Lisäksi määritettiin tarkastelutaso, joka oli yleinen II-taso.

Työn tarkoituksena oli myös pohtia, miten prosessikontrollista sekä muista laadunvalvonnan menetelmistä saataisiin mahdollisimman kustannustehokkaita eli miten prosessikontrollin aikana pullot saataisiin mahdollisimman laadukkaasti tutkittua ilman, että tuote joutuisi jätteeksi. Isoksi osaksi ratkaisua todettiin myöhemmin käyttöön tuleva vuototesteri sekä taarausmenetelmä.

Analyysin ohella todettiin, että nykyistä toimintatapaa käyttäen prosessikontrolleja on mahdotonta tehdä sillä taajuudella, mitä laskutulokset antavat. Vaihtoehtoiseksi tavaksi ehdotettiin tapaa, joka ei ole riippuvainen ajasta, mutta jota noudatettaessa prosessikontrollit otettaisiin aina lukumääräisesti tietyin välein.

Asiasanat: hyväksytyn laadun raja, prosessikontrolli, GMP

CONTENTS

ABBREVIATIONS AND TERMS

SOP	a Standard operating procedure
IPC	In-process control
AQL	Accepted Quality Limit
GMP	Good Manufacturing Practice
Nonconformity	non-fulfilment of a specific requirement
RR	Rachet Ring
SR	Smooth Ring
QA	Quality Assurance
RPN	Risk Priority Number
Ac	Acceptance Number
Re	Rejection Number

1 INTRODUCTION

1.1 Starting point

In this thesis, a sampling plan is established for two machines referred to as 3P-filling machines, which are utilized in the production of ophthalmic medicines, specifically eye drops. The work is executed at the ophthalmology facility of Next-Pharma, situated in Tampere, Finland. Necessary materials, including Standard Operating Procedures (SOPs), details about the production lines, product information, and access to ISO 2859-series are provided by NextPharma.

The existing sampling plan is entirely grounded on knowledge of the process. A sampling plan is a necessary component of quality control, safety and customer satisfaction. Which is why it should be formulated based on through calculations along with process knowledge. In this study, the Accepted Quality Limit (AQL) is used to determine the sample size for each batch.

The plan is individually tailored for each batch, with subsequent modifications made through the enhancement of In-Process Control (IPC) methods. Possible adjustments are deliberated with colleagues from the production departments, as well as with the Quality Assurance (QA) department and the head of the production department.

1.2 Thesis' purpose and objective

The purpose of this work is to scientifically justify in-process controls which are executed during the filling process at both – CM1 and MB2 – 3P filling machines. It is stated in the new GMP Annex 1, that a sampling plan should be used. The target of a sampling plan in this work is to calculate the frequency i.e., how many samples from a certain lot will be taken and within what time. The purpose is also to improve the method of In-Process Control (IPC) and other quality-insurance methods, to make them more cost-effective.

2 MATERIAL AND METHOD

2.1 Material

The analysis is based on batch information which is provided by the employer. The batch information includes all the product names, fill volumes, filling line, lot sizes, process control range, target fill volume, theoretical yield, and the average filling time per lot. The calculations are based on theoretical numbers and no deviants are paid regard during the calculations.

The process knowledge is combined with calculated results in help of improving the method of taking the In-process Control (IPC). All the used information is collected from standard operation procedures (SOP) which are in MasterControl and can be read by an employee. The primary focus form the ISO 2850-series is the standard of ISO 2859-1.

2.2 NextPharma and Annex 1 of EU GMP

NextPharma is a pharmaceutical contract development and manufacturing organisation that provides a range of pharmaceutical services across the entire supply chain. NextPharma has nine manufacturing sites in Europe and four logistic sites. Their products range from solid and pellets, hormones, liquid and semisolid, penicillin and cephalosporins to opthalmics. Quality is regulated by FDA, EMA, and Anvisa ROW. (NextPharma.)

Good Manufacturing Practice (GMP) Annex 1 is a section of the European Union’s guidelines for especially the manufacture of sterile medicinal products. It outlines the necessary standards and practices to ensure the sterility of these products, including aspects such as cleanroom environments, contamination control, and sterilization processes. The aim of Annex 1 is to minimize the risk of microbiological, particulate, and pyrogen contaminations, making it crucial guideline for companies involved in the production of sterile pharmaceuticals and medicine devices. (ECA Academy n.d.)

2.3 Accapted quality limit

As previously mentioned, the statistical tool utilized in this context is the Accepted Quality Limit (AQL). It is defined in ISO 28590 (2017, 4) as the worst tolerable product quality level in a lot, and its primary purpose is to ascertain that the quality is acceptable to the consumer. It's important to note that there is no universal standard value for a product's AQL as it can vary from industry to another (Banton 2022).

AQL is typically expressed in percent nonconforming items, where nonconformity means non-fulfilment of a specific requirement, and nonconforming item stands for an item with one or more nonconformities. (ISO 2859-1, 3) For instance, with an AQL of 1% in a process that produces 10 000 items, it implies that up to 100 items can be defective. (Banton 2022)

2.3.1 Inspection levels

To carry out the calculations, it's necessary to choose an inspection level. There are three general levels of inspection which corresponds to a given letter code. Level II is the most used. However, if recent quality problems have occurred, a more stringent inspection, level III which involves inspection of more samples, is appropriate. (Anjoran 2021)

Level I represent the lowest level of inspection as it involves checking a much smaller number of samples. Opting for this level can be risky, potentially suggesting that quality control is less a priority to the costs or time involved in inspections. (Anjoran 2021)

In addition to the various inspection levels, there are sampling schemes in ISO 2859-1 (1999) which are combinations of sampling plans with rules for changing from one plan to another – normal, reduced, and tightened. Normal inspection is the standard level of inspection used under typical circumstances. Under reduced sampling, fewer items are inspected compared to the normal inspection. It's used when previous batches have demonstrated a good quality record, indicating a

lower risk of defects. Reduced inspection saves time and recourses but is used cautiously to avoid missing quality issues.

Tightened inspection involves stringent acceptance and rejection numbers than under normal inspection but there is no difference in sample sizes. It's applied when there have been quality issues with recent batches or when increased vigilance is necessary. Tightened inspection is more rigorous, aiming to catch defects that might have been missed under normal inspection. In summary, the inspection levels primarily determine the sample size based on the risk and quality requirements, while the sampling schemes adjust the stringency of the inspection process based on the historical quality performance of the products. (ISO 2859-1 1999)

The process starts with normal inspection but can switch to another level if the current conditions shall allow or require it. The outline for switching rules is presented in the figure 1. For example, if during the process the inspection level is switched from normal to reduced, it must fulfill three conditions which are: switching score must be at least 30; and production must be steady; and the decision to switch comes from responsible authority. (ISO 2859-1 1999) A switching score is defined as "an indicator used to determinate whether the current sampling results are sufficient to allow for a switch to reduced inspection" in the ISO 2859-1 (1999, 12). The switching score calculations are demonstrated in chapter five.

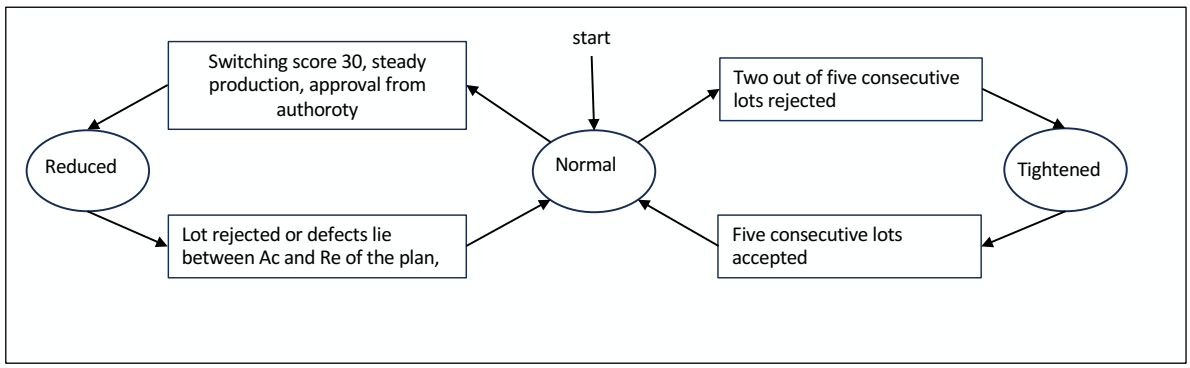


FIGURE 1. Outline from the switching rules (Edited) (ISO 2859-1 1999)

If there is no improvement in quality under tightened inspection, leading to the rejection of five consecutive lots, the inspection process must be halted. Appropriate actions must be done to improve quality before it's allowed to resume back to the use of inspection schemes. (ISO 2859-1 1999, 12)

2.3.2 Determining AQL

The acceptance quality limit informs how many defects are accepted during a process. However, during an IPC, multiple parameters are inspected and of which criticality differs. Understanding of the nature of the product, its intended use, and the potential risks associated with defects helps determine the AQL. Critical defects that affect safety or major functions typically require a much lower AQL, whereas minor defects might allow for a higher AQL. (Banton 2022)

Pharmaceutical products, due to their sensitive nature, cannot tolerate high defect rates. Even minor defect in these products could lead to severe consequences, posing significant risk to patient safety. Consequently, manufacturers of such sensitive products must adopt a less tolerant approach towards defects. Industries typically employ various tools aimed at minimizing defects in their manufacturing processes. For products of this sensitivity, the Acceptable Quality Limit is often set to 1 % or even lower, to ensure the highest standards of safety and quality. (Tetra Inspection n.d.)

AQL tables are used to determine the sample size for batch inspection and the maximum number of defective units acceptable in that sample – acceptance number. These tables are key component of statistical sampling and quality assurance methodologies. (ISO 2859-1:1999). There are two tables. The first table starts with range of lot sizes. For each range, a corresponding code letter is assigned which is used to determine the sample size. The second table informs the sample size. Based on the code letter and the inspection level (I, II, or III), the table indicates the number of units to be randomly sampled from the batch. Lower levels result in fewer samples, while higher levels mean more samples.

3 3P-FILLING MACHINES AND IN-PROCESS CONTROL

3.1 Primary materials

The used primary materials are sterile and arrive in multi-layered packaging bags. Each bag is labelled to correspond with a specific batch number and is supplied by on operator, who places the material into designated hoppers.

A 3P-MD is made from three components, the bottle, the tip, and the cap. The used bottles are typically either 5 ml or 10 ml sizes and come in either clear or white plastic. If the product requires protection from light, the white bottle is used. The tip, positioned on top of the bottle, serves as a nozzle. It's of a standard size, compatible with every batch. The tip is covered with a cap, and there are few types of caps, Rachet Ring (RR) and a Smooth Ring, as shown in the picture 1. and picture 2. (CM1 line books 2022) Besides these two cap types, there is also a third cap type for Novelia-bottles. the design is slightly different, consisting of only two components: the bottle and a combined tip-cap nozzle, as depicted in picture 3. (MB2 line books 2022)

PICTURE 1. 10 ml RR bottle. (CM1 line books 2022)

PICTURE 2. 5 ml SR bottle. (CM1 line books 2022)

PICTURE 3. 10 ml Novelia bottle (MB2 linebooks 2022)

3.2 Working principle of CM1

A prepared formulation is sterile filtrated to the sterilized holding tank in grade A-area and the filter is integrity tested. An operator connects the hose from the holding tank to the filling machine in grade A-area. Hose has been steam-sterilized before, together with the holding tank. Before the filling starts, the air in the filling hoses is removed. (Figure 3.)

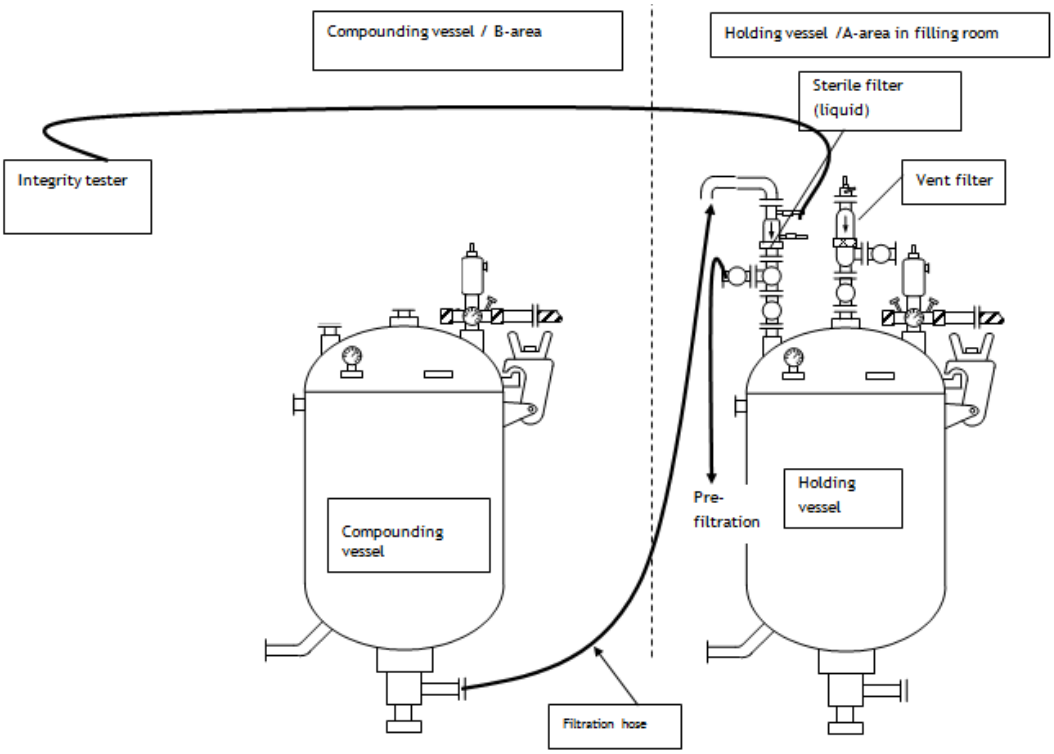


FIGURE 1. Sterile filtration (CM1 line books 2022)

The filling process of CM1 starts from the bottle feeder (picture 4). Where they travel towards to the filling unit and four bottles are filled at the same time by four needles (picture 5).

PICTURE 4. Bottle feeder (CM1 line books 2022)

PICTURE 5. Filling unit (CM1 line books 2022)

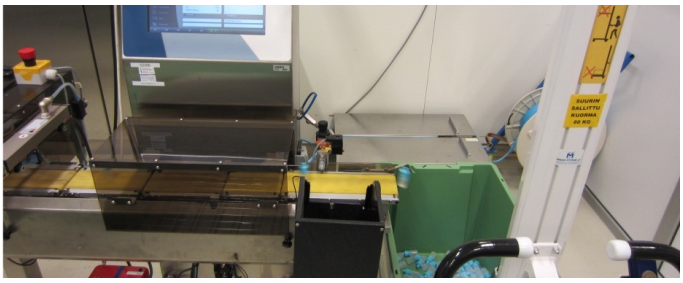
After the bottles are filled, they move to the tipping unit where the tips are fed by four shoots of vibratory feeder. At this unit, four bottles are also tipped four at a time (picture 6).

PICTURE 6. Tipping unit (CM1 line books 2022)

The tip is still loosely on top of the bottle before it is further inserted at the entrance of the capping machine. The cap is fed by a shoot of vibratory feeder and feeding plate. There are eight capping heads that inserts the cap onto the tipped bottle (picture 7). The capping heads have a closing torque set value and a control system. The force of closing the caps is depending on the type of container and cap.

PICTURE 7. Capping unit (CM1 line books 2022)

Once the cap is on, the process continues outside the clean room which is called the reception or receiving room. At the reception-line, there is a sleever-machine, but it is used for SR bottles and not for RR, as it has a tamper-proof seal. Next in line is the weight checker called Teltek scale (picture 8). The bottles are being fed at constant pitch through the checker and if a bottle is out of acceptable level, it will be rejected automatically to the reject box.



PICTURE 8. Teltek scale (CM1 linebooks 2022)

The bottles are either collected in boxes which are banded by the banding machine and a product information label is attached to the box. Or the bottles are put on trays by a robot and send to customer for secondary packing. In this case, the bottles are moved after weight check to the robot by a conveyer. Once the robot has filled a tray it will be sealed with red sealing tape and a product information label is attached to the tray. Sealed trays are packed in the shipper cases and a product information label is attached. Finally, the shipper cases are laid on the pallet which is marked with the product information and address signs.

3.3 Working principle of MB2

The MB2 filling machine differs from CM1, though they share some similarities. For instance, both machines perform sterile filtration in the same manner and use identical primary materials, apart from Novelia bottles. The notable difference between the two filling machines occurs at the filling point. In MB2 there are only two needles and two pumps. The filling process is conducted in two stages: the first needle fills half of the total volume, and the second needle completes the fill. Furthermore, MB2 has just one tipping head in its tipping unit, in contrast to the four in CM1. This design implies that MB2 operates at a slower pace, with a maximum line speed of 58 bottles/minute for RR bottles and 35 bottles/minute for Novelia. (MB2 line books 2022)

In the capping unit, a cap is fed by a shoot of vibratory feeder, and a tipped bottle is capped by one capping head. This is also different from CM1 where there are eight capping heads. The closing torque of the cap for MB2 is adjusted 18 Ncm (PP and PE bottle) or 40 Ncm for Novelia. (MB2 line books 2022)

Occasionally, the filling process may experience minor malfunctions, resulting in bottles missing a tip or cap, or having improperly placed caps. To prevent these from reaching the receiving room, a cap checker examines all bottles, rejecting those not meeting acceptance criteria. Accepted bottles are conveyed to the intermediate product box in the receiving room. All the products are sent to another destination for secondary packing. (MB2 line books 2022)

4 IN-PROCESS CONTROL

4.1 Current method of IPC

The purpose of in-process control (IPC) is to ensure that the quality of the filling process is acceptable. It is taken every 30 ± 5 minutes unless there is no production at the time. For RR- and SR-bottles the inspection during IPC is done in the following way.

In the receiving room, a qualified operator selects eight bottles – six at MB2 – in row from the table and performs visual inspection first. It's important to keep the bottles upright. The operator then checks there are no visual defects on the bottle, ensuring the cap and the tip are intact and not damaged. The functionality of the cap is tested manually by opening and closing it, and the assessment is based on feeling. The filling weight is determined by pouring the contents into a beaker placed on a scale. The scale is linked to a computer program named FreeWeigh, which facilitates easy documentation of IPC. Should any defects be identified, actions are taken following an appropriate SOP.

The inspections of Novelia bottles are performed a little differently. The filling volume is assessed using tare method and the integrity is tested by blocking the nozzle and squeezing the bottle. (TMP-DOC-0503)

4.2 Integrity testing

Currently the integrity of the bottles is tested by using methyl-thionine-chloride bath – blue bath. From each batch, 315 bottles in total are collected and placed into trays, along with two control bottles which has holes. These trays are then positioned in a holder which is subsequently immersed in a tank with a mix of water and blue methyl-thionine-chloride powder. The testing process, taking approximately 20 minutes, involves two ten-minute vacuum cycles where the pressure in the tank is alternately increased and decreased. The liquid inside the control bottles should be blue and if other bottles turn out to be blue as well, they leak. The leaking bottles are inspected and the reason for it is investigated. (TMP-DOC-0503)

However, in 2024, a new integrity tester is planned to be introduced, which will replace the blue batch method mentioned above. The significant benefit of this new tester is its ability to assess the bottles without causing damage. The tester operates through cycles designed to detect leaks or potential leaks, arising from (micro)holes or failure in the closure mechanism. This integrity testing forms part of the In-Process Control procedures. (TMP-DOC-2685)

5 ANALYSIS

5.1 Defects

The aim of In-Process Control is to detect any defects. If a bottle has a defect related to integrity it most often means the bottle is leaking. The are many reasons why a bottle would leak, one, there is no tip at all, two, the cap is not properly set, third, the bottle has been stuck and gotten broken. For the filling volume, there already exists a filling range for each product, but if during IPC an operator notices the filling weigh is out of range, adjustments are done immediately. To prevent this from happening, two operators check the filling weigh before the filling starts. This parameter is important, but if by chance an empty bottle comes through to the receiving room, it's going to be picked out by the Teltek scale.

During visual inspection of the bottle, an operator ensures that the bottle is free of smudges, major dents, or other marks. And evaluates whether the defects in appearance are major or minor. However, since most products are labelled and packed in different location, it's challenging to determine if a bottle with similar defects would be accepted there as well by the inspecting operator. Inspecting the closure and opening of the cap originates from a time when the caps were so tightly fitted that opening them by hand was nearly impossible.

5.2 Risk analysis

NextPharma has used ISO Guide 51, ICH Q9 to determine risks. Risk is defined as "the combination of the probability of occurrence of harm and the severity of that harm" (European Medicines Agency 2015, 3). And Quality risk management is defined as "a systematic process for assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle" (European Medicines Agency 2015, 4). The goal of quality risk management, as outlines by ICH Q9, is to ensure the safe use of the medicine, even if in the presence of risks that cannot be eliminated. Properly implanted, risk management is an effective and beneficial aspect of decision-making, prioritization, and evaluating, as well as documenting problem situations.

NextPharma has a risk analysis tool for another production line. Although not officially sanctioned, this tool is intended for identifying potential risks during the filling process of the production line. Drawing upon insights from this unofficial risk analysis tool, table 1 illustrates a speculative example of the risks that might occur during In-Process Control. These risks are essentially estimates, grounded in the relatively recent occurrences of defects, their impacts, and how they have been detected.

The probability of each risk occurring is estimated on a scale from one to five, where one indicates an unlikely occurrence and five signifies near certainty. The severity of each risks' impact is similarly rated from 1 to 5, with 1 indicating no impacts and 5 representing a hazardous situation. Additionally, the likelihood of detecting each risk is crucial and is rated on the same 1 to 5 scale, where 1 means the risk is always detected and 5 indicates a lack of detecting control. These factors collectively determine the Risk Priority Number (RPN), which is categorized into three levels. (NextPharma)

Category A includes items with an RPN level of 60 – 125. Category B encompasses items with an RPN level of 27 – 59, while Category C includes those with an RPN level of 0 – 26. Items in Category A and B necessitate the development of mitigation plans to lower the perceived risk and RPN. RPN is calculated by multiplying the probability, impact, and detection values together. (NextPharma)

TABLE 1. RISK ANALYSIS

Risk	Probability 1-5	Impact 1-5	Detection	RPN	Risk management	Person in charge
Leaking bottle	3	4	2	24	Investigate the cause of the event, monitor & rectify	Superior, QA
Defect on appearance	3	3	2	18	Investigat the criticality	Superior, QA
Bottle without a tip	3	4	3	36	Investigate the cause of the event, monitor & rectify	Operator, maintenance, superior
Damaged cap	3	4	3	36	Investigate the cause of the event, monitor & rectify	Operator, maintenance, superior
Poor opening/closing of the cap	1	2	2	4	Measure moment, open bottles	Operator, maintenance superior
IPC late	3	3	1	9	IPC timer	Superior, QA
Filling volume out of range	1	3	1	3	Process controls before filling and during	Operator, superior

The colour codes indicate the categories based on RPN, where green is category C, and yellow is category B. Under risk management column are suggestions on how to proceed if a defected item is found. The highest Risk Priority Number (RPN) is assigned to the risk associated with a bottle lacking a tip because such a bottle becomes non-functional and it's not ingrate. The second highest RPN is attributed to the risk of defective cap. This issue has recently emerged, particularly with RR-bottles, where the tamper-proof-seal is either damaged or missing. It's also rather challenging to detect the bottles with damaged caps. One other recently surfaced issue is the IPCs being late or not taken at all. For this issue there is a timer that reminds the operator to do the IPC in time.

5.3 AQL values

While working on this thesis a meeting was arranged with people from the quality department, head of the production, and colleges from the production department. In the meeting, the progress of the thesis was discussed.

The sampling plan is determined based on specific single sampling tables which are presented in the ISO 2859-1 (1999) standard. There are two main tables, from which the first table (ISO 2859-1:1999, 19) informs a code letter which is

defined by the lot size and the inspection level. The second table (Table 2-A, 2-B, or 2-C) (ISO 2859-1:1999, 20–22) informs the number of samples, which is defined by the code letter and the AQL value. Further down in this work, the results are presented for each filling machine when the inspection level is normal, reduced, and when it's tightened.

The first calculations were carried out by using the normal II inspection level and AQL of 2,5 %. But it became apparent that it would be better to decide an AQL for each parameter based on their criticality. The overall AQL is then based on the most critical parameter. The limit needs to be greater than zero percent yet remain relatively low, as conducting a complete 100 % inspection during the process is undoable. The AQL values are determined based on the risk analysis of defects, considering the perspectives and requirements of the pharmaceutical industry. The following list presents the results and explanations for the defects and their AQL values for Both CM1, and MB2 filling lines:

1. Integrity
   - Leakage, rejected | AQL 0,4
2. Filling volume
   - out of filling range | AQL 0,4
3. Appearance, major defect, rejected | AQL 0,4
   - significant bruises in the neck of the bottle, affecting the integrity
   - dents, scratches, smudges on the bottle
   - Sealing of the RR cap not intact properly or missing
4. Appearance, minor defect, not rejected | AQL 0,65
   - erasable smudges on the bottle
   - bruises in the neck of the bottle, cosmetic flaw, does not affect integrity
5. Opening/closing of the cap
   - usability | AQL 0,65.

In conclusion, the AQL is set to 0,4 % with the initial inspection level being general II. based on the implemented sampling schemes, there is a potential for a shift in the inspection level to either reduced or tightened inspection, depending on the specific requirements and outcomes of the sampling process.

5.4 Sampling calculations

When a sampling plan is based on AQL, it often involves the use of sampling schemes, which are switched depending on the situation. The purpose of switching is to protect the consumer by implementing a tightened inspection but is conducted at the expense of the producer. On the other hand, the producer's interest can be pursued by using a reduced level of inspection, provided that the conditions are met, and the situation allows for it. (ISO 28590:2017)

All the necessary information from each batch produced currently at CM1 and MB2 are collected to tables. There are three separate tables for each filling line. The first table consists of calculations based on normal inspection, the second table is based on reduced inspection and the last is based on tightened inspection.

The second last column on the right informs acceptance number (Ac) and rejection number (Re). In instances where the number of defected items within the sample is equal to, or less than the specified acceptance number, the batch is deemed acceptable. Conversely, if the number of defected items is equal or exceeds the rejection number, the batch is possibly rejected. In conclusion, they both inform the maximum number of defected items allowed within the sample. (ISO 2859-1:1999) To avoid rejecting the entire batch, the sampling inspection is done during the production process, and adjustments are done once quality level appears to decrease. Due to the confidentiality requirements, the names of products are substituted with numerical identifiers, ranging from 1 to 9. The sampling frequency is calculated and displayed in the column labelled "pcs/30 min", indicating that the sample size is divided by the average filling time.

5.4.1 Sampling plan for CM1

The inspections start with normal inspection and the results are presented in the following table 2.

TABLE 2. CM1 sampling plan under normal inspection

Product	Lot size	Av. filling time	Code letter	Number of samples	Ac | Re	Pcs/30 min
1.	37383	6	M	500	5 | 6	42
2.	37383	6	M	500	5 | 6	42
3.	31925	6,5	L	315	3 | 4	24
4.	28938	6,5	L	315	3 | 4	24
5.	21463	5	L	315	3 | 4	32
6.	41121	6,5	M	500	5 | 6	38
7.	21256	5	L	315	3 | 4	32
8.	60177	10	N	500	5 | 6	25
9.	62385	10	N	500	5 | 6	25
Average						**31**

From the table, it can be observed that if samples are taken according to the normal inspection level, the quantity of samples required would be substantially higher compared to the current approach. In practical terms, this is almost impossible to implement following the existing sampling method. It is noted from the table that the number of samples remains constant despite differences in batch sizes exceeding 20 000 units. The acceptance number varies between 3 and 5, and rejection number between 4 and 6.

To be able to switch from normal to reduced inspection, switching score needs to be at least thirty. In the beginning, the switching score is set at zero, and updated as batches of products are inspected over time. The score is based on the inspection results, specially whether the batches pass or fail the quality criteria. When the acceptance number (Ac) of a lot is 2 or more, and it would have been accepted under tighter AQL, three points are added to the switching score. This indicates that that the quality of the lot is quite high, as it passes not just the current AQL but also a more stringent one. However, if the lot would have not been accepted under a tighter AQL, the switching score is reset to zero. This indicates that the quality might not be consistently high as it only meets the current, less stringent level. Over time the score cumulates.

When the Ac is 0 or 1, two points are added to the switching score if the lot is accepted – meaning the quality standards are met. If the lot is not accepted, the switching score is reset to zero. The reset indicates a failure to meet even the

basic quality standards, suggesting that the quality control process might need more stringent inspection. In table 3. results based on reduced inspection are presented.

TABLE 3. CM1 sampling plan under reduced inspection

Product	Lot size	Av. filling time	Code letter	Number of samples	Ac | Re	pcs/30 min
1.	37383	6	N	200	3 | 4	10
2.	37383	6	N	200	3 | 4	10
3.	31925	6,5	M	125	2 | 3	6
4.	28938	6,5	M	125	2 | 3	6
5.	21463	5	M	125	2 | 3	8
6.	41121	6,5	N	200	3 | 4	10
7.	21256	5	M	125	2 | 3	8
8.	60177	10	N	200	3 | 4	10
9.	62385	10	N	200	3 | 4	10
Average						**9**

The table allows to deduce that the quantity of samples for process control more closely aligns with current practices, even though the intention is not to adhere strictly to the existing sample collection model. This nonetheless provides a good indication as to whether the current method corresponds with the results obtained. It is also observed that there is less variability in the number of samples for process controls as compared to what is seen in normal inspection scenario. The acceptance number varies between 2 and 3 and rejection number varies between 3 and 4.

The inspection requires tightened inspections if two of five (or fewer than five) consecutive lots are not accepted. Switching happens always through normal inspection. It's impossible to switch straight from tightened to reduced inspection. Below is table that consists of results based on tightened inspection (table 4.).

TABLE 4. CM1 sampling plan under tightened inspection

Product	Lot size	Av. filling time	Code letter	Number of samples	Ac | Re	pcs/30 min
1.	37383	6	N	500	3 | 4	42
2.	37383	6	N	500	3 | 4	42
3.	31925	6,5	M	315	2 | 3	24
4.	28938	6,5	M	315	2 | 3	24
5.	21463	5	M	315	2 | 3	32
6.	41121	6,5	N	500	3 | 4	38
7.	21256	5	M	315	2 | 3	32
8.	60177	10	N	500	3 | 4	25
9.	62385	10	N	500	3 | 4	25
Average						**31**

The difference between normal and tightened inspections are the values of acceptance number and rejection number. There is no variation in sample sizes whatsoever. The same acceptance/rejection criteria are used in the reduced inspection, but the sample sizes are then again different.

5.4.2 Sampling plan for MB2

The calculations are executed in the same way for the MB2 filling line as they are for CM1. The results for normal, reduced and tightened inspection are presented in the following tables (table 5, 6, and 7.).

TABLE 5. MB2 sampling plan under normal inspection

Product	Lot size	Av. filling time	Code letter	Number of samples	Ac | Re	pcs/30 min
1.	9390	5,5	L	200	2 | 3	18
2.	17241	9	M	315	3 | 4	18
3.	9390	6	L	200	2 | 3	17
4.	10732	4	M	315	3 | 4	39
5.	21463	7	M	315	3 | 4	23
6.	1942	1	K	125	1 | 2	63
7.	21359	7	M	315	3 | 4	23
8.	8738	3,5	L	200	2 | 3	29
9.	18779	11	M	315	3 | 4	14
						27

The batch sizes are considerably smaller in MB2 filling line than those in CM1, leading to smaller sample sizes. However, the average number of samples per In-Process Control remains high. The table also shows that during the filling of product number 6. a large portion of the lot is taken into process controls, which goes against of making sampling cost-effective. For small lot sizes the sampling could be executed differently.

TABLE 6. MB2 sampling plan under reduced inspection

Product	Lot size	Av. filling time	Code letter	Number of samples	Ac | Re	pcs/30 min
1.	9390	5,5	L	80	1 | 2	7
2.	17241	9	M	125	2 | 3	7
3.	9390	6	L	80	1 | 2	7
4.	10732	4	M	125	2 | 3	16
5.	21463	7	M	125	2 | 3	9
6.	1942	1	K	50	1 | 2	25
7.	21359	7	M	125	2 | 3	9
8.	8738	3,5	L	80	1 | 2	11
9.	18779	11	M	125	2 | 3	6
Av.						**11**

It can be seen from the table that the sample sizes decreased significally but so did the acceptance and rejection numbers. Table 7 presents a tightened sampling plan for the products of MB2-filling machine.

TABLE 7. MB2 sampling plan under tightened inspection

Product name	Lot size	Av. filling time	Code letter	Number of samples	Ac | Re	pcs/30 min
1.	9390	5,5	L	200	1 | 2	18
2.	17241	9	M	315	2 | 3	18
3.	9390	6	L	200	1 | 2	17
4.	10732	4	M	315	2 | 3	39
5.	21463	7	M	315	2 | 3	23
6.	1942	1	K	125	1 | 2	63
7.	21359	7	M	315	2 | 3	23
8.	8738	3,5	L	200	1 | 2	29
9.	18779	11	M	315	2 | 3	14
Av.						**27**

The same affect can be seen in this table as in the tables of CM1. The sample sizes as well as the values of each IPC remains the same but the acceptance, and rejection numbers are more stringent than they are under normal inspection.

5.5 Implementing sampling plans

The current procedure needs to be altered to enable sampling in accordance with the previously mentioned tables. Particularly, when taking IPCs under normal and tightened inspection. Additionally, these calculations are purely theoretical and may not accurately reflect the actual situation. In fact, the yield is always a little smaller and the filling time varies but is generally longer.

An alternative method for conducting process control, which is not dependent on time, involves sampling at fixed intervals. This process control method could be implemented as follows:

1. Divide the sample size (X) by 8 or 6, which implies that during the production, process control of 8/6 bottles should be taken (Y) times.
2. Divide the theoretical yield by the number Y, resulting in the number (Z). This means that process control would be taken after every (Z) bottles.

However, this method depends on whether the Teltek-scale counter at the receiving room of CM1 is operating, and whether more products have arrived from the cleanroom than have passed through the counter.

5.6 Cost efficiency of IPC

In the production of a single batch, pharmaceutical waste occurs even before the tank is even connected to the filling machine. However, the primary focus is on activities outside of the filling room, where bottles are disregarded as waste for several reasons. Waste generation includes process controls (8/6, depending on the machine), microbiological samples (10 units), several dozens of chemical laboratory samples, and 315 units for integrity testing with RR/SR caps. Waste also comes from bottles that fall on the floor and in the beginning of every batch, depending on the filling volume, “flushing” bottles are taken and disregarded as

waste. In the table 8, and 9, the percentage of samples relative to the batch size is displayed. These calculations are based on the results from table 1, to which the blue bath bottles, chemical- and microbiological laboratory-sample sizes have been added.

TABLE 8. Percentage of samples relative to the batch size, CM1

Product	
1.	2,4 %
2.	2,4 %
3.	2,2 %
4.	2,4 %
5.	3,0 %
6.	2,2 %
7.	3,1 %
8.	1,5 %
9.	1,4 %

It can be seen from the table that the larger the lot size is the smaller part goes to samples. The average percentage of samples relative to the theoretical yield is 2,3 %. The table 9. displays the same calculations but for products produced at MB2 filling line. It should be noted that only during the production of products 6,7, and 8, 315 bottles are taken to blue bath integrity testing.

TABLE 9. Percentage of samples relative to the batch size, MB2

Product	
1.	2,4 %
2.	2,0 %
3.	2,4 %
4.	3,3 %
5.	3,1 %
6.	24,5 %
7.	3,1 %
8.	6,3 %
9.	1,8 %

It can be seen clearly that a relatively high number of samples are taken during the production of product number 6, compared to the small yield. The table shows

as well that not only should IPC be done cost effectively but also all the other quality insurance methods. It's understandable that laboratory inspections cannot be altered or influenced.

The exploring on how to make quality assurance efficient and cost-effective started with pondering how an operator could detect a flaw and other issues during the IPC without opening the cap. Currently, issues that can't be detected without opening the bottle cap, leading to wastage after inspection, include missing droppers, the condition of the sealing surface, and the cap's opening/closing functionality. Bruises on the bottle neck can occur during capping. Although it's concluded that bruises don't contribute to leakage and are more of a cosmetic flaw.

A protentional solution may be found in a new leak tester scheduled for implantation in 2024. Its purpose is to test the integrity of the bottle during in-Process Control without damaging the bottle. If a bottle is missing a dropper, the tester would identify it as leaking. If the cap is poorly fitted and not visually identifiable, the tester would also mark it as leaking. The criticality of testing the cap's opening/closing functionality during IPC could be re-evaluated as it is done due to an issue that is currently perhaps not that critical or relevant as it was a while ago. This tester would also eliminate the blue bath testing, and at the same time, save 315 bottles per batch.

Currently, fill volume is measured by pouring the product into a decanter glass on a scale. However, this method has a drawback: some product inevitably remains in the bottle and not all can be extracted, with results largely dependent on the operator pouring. A solution could be to use a tare bottle which is already in practice when the Teltek scale is not operating due to an issue. Before a batch starts, a specific tare bottle is weighed on the scale before weighing the filled bottles. Although there may be minor variations in material mass, these are negligible during weighing. If the said tare practice is adopted, it should be also noted that the absence of a dropper could possibly be detected during weighing. Even though there is a filling range for each batch, it would be useful to determine if the mass of the dropper affects the weight significantly enough to make the bottle underweight.

6 DISCUSSION

This thesis emphasizes the role of AQL in determining the inspection level and the number of samples. This approach ensures that the quality of the pharmaceutical products is maintained while balancing the practicalities of the manufacturing process. The decision to set the AQL to 0,4 % reflects a commitment to high quality, but also understanding the requirements of the industry, and acknowledging the challenges of conducting a 100 % inspection.

Furthermore, the thesis introduces a refined approach to AQL, where its adjustment is based on the criticality of various parameters, of which are inspected during in-process control. This strategy demonstrates a nuanced understanding of quality control, ensuring that the most critical elements of the production process are prioritized in the quality assessment. Such an approach not only enhances the precision of quality control but also aligns it more closely with the specific needs and risks associated with different stages of the manufacturing process.

Additionally, the adaptability of sampling plans in response to the varying conditions of the manufacturing environment is a key highlight of this thesis. The ability to switch between normal, reduced, and tightened inspection levels, contingent upon the situation, showcases a quality control system that is not only efficient but also highly responsive to the varying quality levels of product batches.

The thesis also addresses the aspect of cost efficiency in quality assurance. By exploring new methods and equipment, such as the proposed leak tester and the use of tare bottle for more accurate fill volume measurements, the study provides practical solutions to reduce waste and improve yield of the production process. The exploration of alternative methods for process controls would lead to more efficient and accurate quality process, reducing waste and enhancing overall product integrity.

It’s important to note that this his thesis can be used as a base and introduction for efficient sampling, but it’s advised to do more further research, specifically

based on accurate and real-time data. Continuing determining an official risk analysis is highly recommended, and to make the entire filling process cost-effective, all the pharmaceutical waste should be considered starting for the compounding and filtration of the product.

REFERENCES

Anjoran, R. 2021. How The AQL Inspection Levels In ISO 2859-1 affect sampling size. QualityInspection. Blog. Read on 26.10.2023. https://qualityinspection.org/inspection-level/

Banton, C. n.d. Acceptable Quality Level (AQL): Definition on How It Works. Website. Updated 09.12.2022. Read on 27.11.2023. https://www.investopedia.com/terms/a/acceptable-quality-level-aql.asp#toc-what-is-acceptable-quality-level-aql

ECA Academy. n.d. EU GMP Annex 1: Manufacture of Sterile Medicinal Products. Read on 14.08.2023. https://www.gmp-compliance.org/guidelines/gmp-guideline/eu-gmp-annex-1-manufacture-of-sterile-medicinal-products

European Medicines Agency. 2015. ICH guideline Q9 on quality risk management. Database. Read on 6.12.2023. https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-ich-guideline-q9-quality-risk-management-step-5-first-version_en.pdf

ISO 28590. 2017. Sampling procedures for inspection by attributes. Helsinki: Suomen Standarditoimisto SFS. Read on 20.11.2023. Requires access right. https://online.sfs.fi

ISO 2859-1.1999. Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection. Helsinki: Suomen Standarditoimisto SFS. Read on 03.11.2023. Requires access right. https://online.sfs.fi

MasterControl. 2023. TMP-DOC-0503 REV 04. Document. Read on 27.11.2023. Requires access right. https://www.mastercontrol.com

MasterControl. 2023. TMP-DOC-2685 REV 01. Document. Read on 27.11.2023. Requires access right. https://www.mastercontrol.com

NextPharma. n.d. About NextPharma. Read on 12.08.2023. https://nextpharma.com/group

NextPharma. 2022. CM1 line books. Database. Read on 27.11.2023. Requires access right.

NextPharma. 2022. MB2 line books. Database. Read on 27.11.2023. Requires access right.

NextPharma. n.d. Risk-1 Filling machine. Excel-table. Read on 1.12.2023. Requires access right.

NextPharma. n.d, Riskienhallinnan perusteet. Database. Read on 1.12.2023. Requires access right.

Tetra Inspection. n.d. How to choose a suitable AQL level. Website. Read on 6.12.2023. https://tetrainspection.com/aql-level/