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The Scientific Basis of Process Control on BFS Lines

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KYLÄHEIKKILÄ, AMANDA:
Prosessikontrollin tieteellinen perusta BFS-linjastoilla

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Prosessikontrollit ovat tärkeä osa laadunseurantaa. Niiden avulla mahdolliset laatupoikkeamat havaitaan ajoissa. Tässä opinnäytetyössä perehdyttiin BFS-täyttölinjojen prosessikontrolleihin. Työn toimeksiantajana oli NextPharma Oy, jonka Tampereen tehtaan toimintoihin työ perustui. Tavoitteena oli laatia BFS-linjastojen prosessikontrollit vastaamaan uutta EU GMP Annex 1 -vaatimusta, jossa näytemäärien ja näytteeottotaajuuksien tulisi perustua tietämykseen sekä prosessi tuntemukseen.

Näytteidenottoon ja tarkastukseen kuluu paljon aikaa, eikä tarkasteltuja ampulleja ja pulloja voida kaikissa tapauksissa enää myöhemmin hyödyntää. Näin ollen tavoitteena on minimoida näytteiden määrä, samalla varmistaen, että valittu näytemäärä kuvastaa tilastollisesti koko tuotantoerää. Opinnäytetyössä etsittiin näiden vaatimusten mukainen paras mahdollinen yhdistelmä. Oikean näytemäärän löytämiseksi työssä käytettiin ISO-2859-1 standardia.

AQL-taulukoita hyödyntäen saatiin laskettua jokaiselle tuotteelle oikea näytemäärä. Saadut näytemäärät poikkeavat toisistaan hyvinkin paljon, riippuen siitä, mitä tarkastustasoja laskennassa on käytetty. Työssä käytettiin tarkastustasoa II, sillä se tarjoaa riittävän tarkkuuden lääkkeiden laadulle ollen samalla kustannustehokas. Prosessikontrolleissa tarkasteltavien tuotteiden eri parametrien riskit otettiin huomioon tarkastustasoa ja AQL-tasoa valittaessa. Riskitekijöinä olivat vuodot, poikkeavuudet ulkonäössä ja ampullien aukeavuus.

Nykyisen tarkastusmenetelmän aiheuttama ongelma, eli kaikkien otettujen näytteiden päätyminen lääkejätteeseen, on johtanut harkintaan käyttää taaramenetelmää täyttömäärien määrittämiseksi joillakin täyttölinjoilla. Tämä päätös perustuu tarpeeseen tehdä prosessikontrolleista mahdollisimman kustannustehokkaita. Taaramenetelmän käyttö tarjoaa mahdollisuuden parantaa laadun tarkkailun tehokkuutta, sillä sen avulla voidaan optimoida täyttömääriä ja varmistaa, että kaikki valmistetut tuotteet täyttävät laatuvaatimukset ilman tarpeetonta hukkaa.

ABSTRACT

Tampereen ammattikorkeakoulu
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The Scientific Basis of Process Control on BFS Lines

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Process controls are an important part of quality control to detect possible quality deviations in time. In this thesis, the process controls of BFS filling lines were introduced. NextPharma Oy's commissioned work aims to meet the requirements of the new EU GMP Annex 1 where sample size and sampling frequencies should be based on knowledge.

Sampling and inspection take a lot of time, and the ampoules and bottles examined after this can no longer be used in all cases. For this reason, the sample size is trying to keep as small as possible. The ISO-2859-1 standard was used to determine the correct sample size. The sample quantities calculated with the AQL tables vary according to the inspection levels used. Inspection level II was chosen to balance quality accuracy and cost-effectiveness.

The thesis emphasized the ambiguity of AQL tables, requiring in-depth knowledge of the process and products. Considering the risks when choosing the inspection level and AQL level was related to the evaluation of various parameters of the products.

The problem caused by the current method, where all the samples taken end up in waste, led to consider the use of the tare method for determining filling quantities. This aims to enhance cost-effective process control and reduce pharmaceutical waste.

Key words: process control, acceptance sampling, risk management

CONTENTS

ABBREVIATIONS AND TERMS

BFS Blow-Fill-Seal Process of Manufacture

GMP Good Manufacturing Practice

WHO World Health Organization

ISO International Organization for Standardization

FDA U.S. Food and Drug Administration

ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use

AQL Acceptance Quality Limit for Product Inspection

1   INTRODUCTION

In the pharmaceutical industry, quality and safety are of prime importance. Patients' health and well-being largely depend on them having access to safe and high-quality medicines. This is also particularly important for the client of the thesis, NextPharma Oy, which operates globally and focuses on the manufacture of sterile ophthalmic drugs at its Tampere factory. Quality control and process controls are a necessary part of the pharmaceutical industry, and they ensure that products meet the strictest quality standards.

The thesis focuses on updating the process controls of the Blow-Fill-Seal (BFS) lines operating at NextPharma in accordance with the changes in the new EU GMP Annex 1. The purpose is to prepare a sampling plan based on knowledge and experience, which defines both the sample size and the sampling frequency. EU GMP (Good Manufacturing Practice) is a guideline given by the European Commission to the pharmaceutical industry on how to act to ensure product quality and patient safety. GMP requirements have been developed to prevent patient harm, such as contamination of medicines. (WHO 2015.) EU GMP Annex 1, on the other hand, contains instructions for the manufacture of sterile products (European Commission 2022).

One of the most important challenges is to determine the suitable sampling plan for the processes. The sample sizes and sampling frequencies must be selected in such a way that they represent the entire batch. Large sample sizes not only waste resources, but they also impose significant costs on companies. On the other hand, too small sample sizes can lead to inaccurate results. The ISO-2859-1 standard (ISO 2859-1 1999), which has been used as a tool in this thesis, gives clear definitions of how large a sample of the production batch should be taken and how decisions based on the sample should be made.

2 STARTING POINTS AND TARGETS OF THE THESIS

2.1 NextPharma Oy

NextPharma is a leading pharmaceutical company at the forefront of innovation in the healthcare and life sciences industry. The corporation has been operating for over 50 years and offers a wide range of pharmaceutical services, including pharmaceutical research, clinical trials, commercial manufacturing, and packaging. The company is committed to serving customers all over the world. (Pharmaceutical Technology n.d.) NextPharma places a strong emphasis on research and development, continuously investing in cutting-edge technologies and processes to stay at the forefront of pharmaceutical advancements. (NextPharma n.d.)

The company has operations in Germany, France, Great Britain, Norway, and Finland. It has more than 2400 employees and around 150 customers worldwide. In Finland, at the Tampere office, company is focused on manufacturing and developing new sterile ophthalmic products. Blow fill seal technology and 3P bottles are used for packaging eye medicines in Tampere. (NextPharma n.d.)

2.2 Background and goals of the thesis

NextPharma invests heavily in monitoring the quality of its processes by conducting regular process controls. The current number of process controls for filling machines is primarily determined by the knowledge of the process. However, the new EU GMP Annex 1, which was introduced in August 2023, sets new requirements. Annex 1 requires justification regarding the frequency and sample size, because in addition to process knowledge, there must also be a scientific basis for the size and frequency of samples. Meeting these requirements is of primary importance to ensure the highest possible quality and safety of pharmaceutical products.

The main goal of this research is to respond to these new requirements, especially regarding process controls. The purpose is to prepare a sampling plan for BFS lines based on knowledge and experience. This plan includes detailed instructions for both sample size and sampling frequency. The size of samples and the frequency of process controls should also consider the risk of the investigate parameters. In addition, the purpose is also to consider how process controls and other quality systems could be improved so that they are as cost-effective as possible.

The goal is to guarantee that NextPharma's process controls meet the strict EU GMP Annex 1 requirements. This ensures that pharmaceutical products are of high quality and safe for patients. This effort is part of a broader commitment to provide quality pharmaceutical products and adhere to the industry's highest quality standards.

3   QUALITY ASSURANCE

3.1 EU GMP

Quality and safety are of primary importance when it comes to pharmaceutical products, and regulatory frameworks are in place to comply with these standards. The EU's Good Manufacturing Practice (GMP) is the keystone for ensuring the most elevated level of pharmaceutical production. EU GMP is a collection of rules and guidelines that control the production, packing, labelling, and circulation of medicines. These regulations are designed to ensure that pharmaceutical companies consistently produce quality products that are safe for the patient. The GMP standards are applicable to the materials, tools, and facilities used along with the staff. (WHO 2015.)

EU GMP consists of several different directives and regulations. In accordance with the European Commission's text: "Directive 2003/94/EC applies to medicinal products for human use and Directive 91/412/EEC for veterinary use". These directives provide the foundation for GMP regulations and guidelines, ensuring that pharmaceutical products are consistently produced and controlled according to quality standards. (European Commission 2010.)

Meeting EU GMP standards is necessary for penetrating the European market. Pharmaceutical businesses that seek to market their products in the EU must show that they observe these standards. This conformity creates trust between healthcare providers, patients, and regulators. The sales area decides which medicinal authority's regulations to follow. The GMP regulations applicable in the EU are laid out in European laws. These laws apply to all products bought and sold in the EU and the UK, no matter if the manufacturer is established in the EU or not. Furthermore, there are further GMP guides, such as The United States Food and Drug Administration (US FDA) and the World Health Organization (WHO). (European Commission n.d.)

Quality standards laid out by GMP must be adhered to for both manufacture and quality control, with suitable protocols in place to ensure that production and testing are adequately validated, monitored, recorded and that staff, premises and resources are suitable for GMP production. Every action and data related to GMP must be traceable. (WHO 2015.)

3.2 EU GMP Annex 1

The European Union's Annex 1 GMP regulations provide for the requirements of good manufacturing practice for sterile pharmaceuticals and the making of sterile products. Annex 1 is included in the broader EU GMP regulation, intended to ensure that pharmaceutical companies observe the most rigorous standards to ensure the quality, safety, and effectiveness of medicines. (European Commission 2022.)

Annex 1 criteria are regularly modified to accommodate industry advancements and new regulations. Pharmaceutical companies are required to meet the current version of Annex 1 and should be aware of the latest requirements to maintain the maximum quality and safety of their products. In August 2023, the most recent annex came into effect, made in partnership with the WHO and PIC/S (European Commission 2022), and it is more in agreement with the US Food and Drug Administration (FDA) guidelines than its predecessor (NSF 2022).

The new version of the EU GMP Annex 1 significantly affects sampling and process controls in pharmaceutical production. In defining the frequency of product integrity testing, the need to be based on knowledge and experience of the production process used is emphasized. This means that the sampling frequency must be tailored to the specific features of the systems in use and the associated risks. Annex 1 pays special attention to the importance of a scientifically justified sampling plan. This requires that the plan is based on scientific principles and takes into account the reliability of the testing methods used. The sample size of the samples must be based on various information, such as the technical specifications of the packaging components and process information. Such an approach ensures that the sample size corresponds to the specific characteristics

of the tested components and the associated risks, thereby promoting the quality assurance of pharmaceutical products. (European Commission 2022.)

3.3 Pharmacopoeia

The pharmacopoeia is a unique collection of quality standards for medicaments, active pharmaceutical ingredients, and finished products. Pharmacopoeias contain standards and detailed instructions for the quality, purity, strength and identity of drugs and pharmaceutical products. These standards cover various topics such as raw materials, manufacturing processes, dosage forms and packaging. (Salo & Sinivuo 2013.)

Many countries retain their own national pharmacopoeias that determine norms for drugs within their jurisdiction. International pharmacopoeias, such as the United States Pharmacopoeia (USP/NF) and the European Pharmacopoeia (Ph. Eur.), act as commonly accepted standards and can be employed in different countries. The primary purpose of Pharmacopoeia is to safeguard public health, ensure the easy distribution of medicines, and make certain that medicines are available. (Salo & Sinivuo 2013.)

Fimea, or the Pharmaceutical Safety and Development Center, is Finland's national drug control authority and it participates in the development and maintenance of the pharmacopoeia in Finland. Fimea works closely with other international pharmacopoeias and stakeholders to develop the pharmacopoeia. (Fimea n.d.)

3.4 Risk management

Risks are associated with everything, including medicines and their use. These risks must be carefully identified, evaluated, and managed to ensure patient safety and product quality. In risk management according to the ICH Q9 recommendation, the main goal is to protect the users of the medicine, and it lays the foundation for a multi-level and systematic risk analysis in the pharmaceutical industry. (European Medicines Agency 2015.)

The production and utilization of a medicinal product inherently involve certain risks, with quality risk being just one aspect of the overall risk. A key factor in ensuring successful quality and clinical studies is maintaining consistent product quality throughout its lifecycle, aligned with important attributes. Having a strong quality risk management strategy in place is crucial for detecting and managing any possible quality concerns during the development and production stages. Additionally, employing quality risk management contributes to improved decision-making when faced with quality challenges. When implemented effectively, quality risk management leads to better decision-making, boosts regulators' trust in a company's risk management abilities, thereby positively affecting the regulatory oversight. (European Medicines Agency 2015.)

3.4.1 Risk assessment and identification

The first step in risk assessment is hazard identification and analysis, as well as exposure assessment. The first step in the quality risk assessment process involves establishing a clear problem description or risk question. By clearly defining the risk, it becomes easier to identify the appropriate risk management tools and gather the necessary information to answer any questions regarding the risk. (CRI Group n.d.)

The goal of risk identification is to prevent possible events that can make it difficult or prevent the organization from achieving its goals. It is important to ensure that accurate, relevant, and up-to-date information is used to identify risks. To identify uncertainties that could potentially impact its objectives, an organization can employ a variety of techniques. Quantitative methods can be used in risk assessment, for example a risk matrix (Table 1), which is based on an assessment of probability and severity of consequences. At the same time, measures are prioritized based on the magnitude of the risks. (CRI Group n.d.)

Table 1. Risk matrix (ARMA Reliabilit n.d.)

Likelihood \ Impact	Negligible	Minor	Moderate	Significant	Severe
Very Likely	Low Med	Medium	Med Hi	High	High
Likely	Low	Low Med	Medium	Med Hi	High
Possible	Low	Low Med	Medium	Med Hi	Med Hi
Unlikely	Low	Low Med	Low Med	Medium	Med Hi
Very Unlikely	Low	Low	Low Med	Medium	Medium

3.4.2 Risk analysis

Risk analysis offers the chance to probe more deeply into the nature, features, and level of the risk. Since an event may have many causes and consequences and effects on several goals, risk analysis requires a thorough examination of uncertainty factors. The review comprises risk origins, potential outcomes, likelihoods, events, possible scenarios, measures to manage, and their level of effectiveness. (CRI Group n.d.)

Risk analysis can be performed at different levels of accuracy and complexity, and this varies from the purpose of the analysis, the available information, its reliability, and the available resources. Analysis techniques can be qualitative, quantitative or a combination of these, and their choice depends on the circumstances and goals. (CRI Group n.d.)

Risk analysis functions as part of the risk assessment and management process, and includes the limits of analysis, hazard identification and risk assessment. The goal of the entire risk analysis is to provide a reasonable basis for decisions related to risk. (CRI Group n.d.)

3.4.3 Risk evaluation

The process of assessing risks involves comparing the identified and analysed risks with predetermined risk criteria. In conducting an effective risk assessment, the reliability of the dataset plays a crucial role as it directly impacts the quality of the outcomes. Disclosing underlying assumptions and trustworthy sources of uncertainty not only promotes confidence in the findings but also helps identify potential constraints. Uncertainty can be attributed to a mix of incomplete knowledge about a process and its predicted or unforeseen modifications. Common sources of uncertainty encompass gaps in pharmaceutical science and process understanding, potential harm sources such as process failure modes, variations in processes, and the likelihood of detecting problems. (European Medicines Agency 2015.)

The outcome of a risk assessment can take the form of either a numeric measurement or a descriptive portrayal of potential risks. Quantitative expression involves using numerical probabilities, while qualitative descriptors like "high," "medium," or "low" can be utilized, provided they are clearly defined. Occasionally, a "risk score" may be employed to refine descriptors in risk ranking. In quantitative assessments, the estimate indicates the likelihood of a specific consequence under given risk conditions, focusing on one consequence at a time. Conversely, certain risk management techniques utilize a relative risk metric to amalgamate severity and likelihood levels into a comprehensive assessment of relative risk. Quantitative risk estimation may be involved in intermediate steps within a scoring process. (European Medicines Agency 2015.)

4   SAMPLING

4.1 Process controls

Process monitoring and control in pharmaceuticals is critical to ensure that medications and associated applicators are consistent, reliable, and safe. Quality control of the process can be carried out at regular intervals throughout the entire batch or, for example, at the beginning and end of the process. Especially in the control performed at regular intervals, it is possible to prevent the creation of large quantities of unsaleable product. In this way, the pharmaceutical company's costs can be kept under control. (Process industry n.d.)

Monitoring the process is crucial for ensuring the uniform quality of the end product. This helps in maintaining s uniform appearance without any deviations, and it also plays a crucial role in avoiding the worst-case scenarios related to product contamination. Defects in process control and monitoring can be reacted to immediately and the creation of defective products and waste can be prevented. Without monitoring the process, one cannot be sure that the quality and uniformity of the final product would be sufficient. (NI Business Info.CO.UK. n.d.)

4.2 Inspection machine

Vacuum decay leak testing is a critical quality control method employed across various industries to ensure the integrity and reliability of products. From the pharmaceutical, automotive, aerospace, and electronics industries, utilizing the concept of vacuum decay leak testing is essential in finding even the tiniest of leaks in sealed components. In the pharmaceutical industry, leaking products must be removed, as the deterioration of the seal's integrity accelerates the degradation of the product's contents. (Bestech n.d.)

The vacuum leak tester creates a vacuum or low-pressure environment in the test chamber. This is usually achieved by utilizing a vacuum pump or similar mechanism. A sealed vacuum chamber ensures that no external air enters during

the test. Once the vacuum is created, the system allows the test sample to stabilize in the vacuum chamber. This allows the pressure to equilibrate with the low-pressure environment inside the sample. Several test devices have pressure sensors that detect even small changes in pressure in the product being examined. If there is a leak or defect in the test sample, the pressure inside the sample will change due to the air coming from the surrounding environment. (Bestech n.d.)

Testing of leaks is a key part of the process controls at NextPharma. On BFS 6 machine, leaks are detected thanks to pressure sensors. On the other hand, leaks of products tested on other BFS machines are detected as leakage points with absorbent paper.

4.3 Sampling size selection

Several factors must be taken into account when choosing a sample size. First, it is necessary to define which process variables one wants to find out precisely. At the same time, the costs of sampling must be weighed in relation to the benefit to be achieved from the measurement results. The initial information about the sample, the distribution of the investigated property in the process, and the feasibility of practical sampling must also be taken care of. (National Institute of Standards and Technology n.d.)

An important factor is the accuracy of the results, which should be combined with the estimated sample size. This unifying equation, or probability expression, helps to optimize the sample size so that the accuracy of the results is maintained, but the cost of sampling and the sample size can be minimized. A large sample size improves the accuracy of the results and reduces the risk that the sample taken does not represent the entire population. (National Institute of Standards and Technology n.d.)

If the law and the desired quality allow, the costs of sampling should also be taken into account when choosing the sample size. Therefore, when choosing the sample size, it is necessary to evaluate whether a particularly high accuracy is needed for the results, as it can increase the sampling costs. It is also useful to use previous information about the process, such as mean and variance estimates, in

the optimization of sampling. (National Institute of Standards and Technology n.d.)

To obtain a comprehensive assessment, sufficient observations of the sample are needed, but at the same time care must be taken that the sample size remains practical. It is important to assess the risks associated with the chosen sample size. It is necessary to consider whether maintaining a large sample size is necessary for the accuracy of the results or whether it would be possible to reduce the sample size and at the same time accept a possibly increasing number of errors in the results. (National Institute of Standards and Technology n.d.)

5 PROCESS DESCRIPTION

5.1 BFS lines

The BFS process is a very advanced and efficient method, which is used especially for aseptic packaging of liquid medicines. The process offers several advantages over traditional packaging methods, including reduced risk of contamination, longer product shelf life and better product integrity. The BFS process combines three key processes – blow, fill and seal – into one continuous operation that ensures sterile production. (FDA 2004.) These main steps of process are shown in figure 1.

The first step of the BFS process involves pressing the tubular thermoplastic into shape. With the help of sterile compressed air, cavities of the right size are formed in the mold. When the pipe is long enough, the mold closes, the blank is cut, and its bottom is pressed shut. The mold moves to the filling station, where the product to be packed is fed into the container using aseptic techniques. Precise dosing and filling mechanisms ensure the right amount of product. After filling, the upper part of the container is heated, which softens the polymer and enables it to be sealed airtight. The molds in the presses open and have formed a tight and safe container that prevents microbes from entering, preserving the integrity of the product. (Reed 2004.)
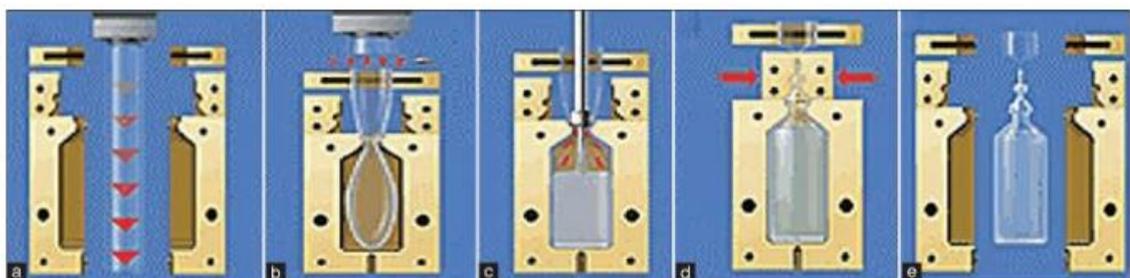

Figure 1. Blow-Fill-Seal process (Reed 2004)

During the entire procedure, sterile air is used to form the shape of the pipettes and bottles. During the procedure, there are several stages when the product has the opportunity to be exposed to particles in the environment. These critical steps

are cutting the blank, moving the blank to the blowing stage, and the moment just before closing the blank when the spindle is removed. BFS machines must be designed in such a way that pollution from outside does not hinder production. In particular, the contact surfaces must be completely sterile. (Reed 2004.)

The success of the BFS process depends on many different factors, such as the thickness of the wall, the compatibility of the materials and the assurance of sterility. If the wall is too thin, the thread to be manufactured may be damaged and thus lead to leakage and a non-sterile product. (Hroncich 2016.)

5.2 Ampoules and bottles

Nextpharma has a total of four BFS filling lines, all of which have the same operating principle. In this work, the focus is on lines 3, 4 and 5. The BFS 3 filling line focuses on the production of individual bottles. The filling machine has six needles, so six bottles are produced during one cycle. BFS filling lines 4 and 5 specialize in the production of ampule stripes. Ten filling needles are used in these filling lines, which means that each set consists of ten ampoules.

Ampoules are small, closed vials made of glass or plastic that are used to store and administer liquid medicines. They are a common and essential form of pharmaceutical packaging, as they are able to maintain the stability and sterility of the contents. Range of volume goes from 0,2ml to 0,5ml. (Medic College 2020.) NextPharma is focused on producing 0,2ml to 0,3ml filling volume. Due to the airtightness of the ampoules, the packaged liquid remains free from contamination. Ampoules are typically designed for single-dose use. This eliminates the risk of cross-contamination, as each ampoule contains a precisely measured dose and is intended for immediate use after a dose. Ampoules often have a narrow, breakable neck, thanks to which the opening can be performed safely by cutting off the neck section. This ensures that the content can be accessed without contamination. (Medic College 2020.)

BFS bottles are much larger than ampoules. NextPharma makes one filling size, which is 10 ml. The bottles get a cap at a later stage of production, which when used by the customer, makes a hole at the top of the bottle.

6   MATERIALS AND METHOD

6.1 Material

The thesis has used the material received from the client, which consists of a table containing executable. The table covers detailed information about different products, including product name, machine number, filling volume, batch size, process control area, theoretical yield in ampoules and bottles, and average filling time in hours.

It is important to take into account that all calculations have been performed on a theoretical basis, without deviations during the process. This means that the calculations are based on ideal conditions and do not take into account possible changes or variations during the process. However, such an approach provides a solid basis for evaluating the theoretical performance and later comparing it with the practical implementation.

6.2 Attribute sampling plan

Attribute is a statistical sampling method that is a key part of quality control, especially for testing the presence or absence of certain characteristics or attributes in a population. This method is designed to test the presence or absence of certain characteristics or attributes in a population. (SuperfastCPA n.d.)

In attribute sampling, a sample is taken from a population, and an inspector or quality control professional tests the sample to determine how many times a particular characteristic occurs in the population. This gives an idea of the frequency of occurrence of the attributes and helps to assess the qualitative state of the population. Attributes are often evaluated based on two options, accept, or reject, which facilitates decision-making and enables a clear quality assessment. (SuperfastCPA n.d.)

6.2.1 Sampling plans

The selection of the sampling plan is influenced by the number of data items to be taken from a batch or basic set, i.e., the sample size, as well as the acceptance and rejection rates. Later, different types of sample programs are introduced, such as single-, double-, and multi-sample programs. When choosing a sampling plan, it is important to consider the following points

- lot size

- inspection level

- AQL level

- whether normal, tightened, or reduced inspection is applied. (ISO 2859-1 1999.)

In addition to the above, the critical properties of the product must be known, based on which the risk levels should be determined (ISO 2859-1 1999). Furthermore, decisions should also take into account the nature of the process.

6.2.2 Lot

A lot is a group of products manufactured under the same conditions over a period of time. As far as possible, each lot should consist of products manufactured at the same time, which is essential to ensure an acceptable quality level, especially when there are several batches to be delivered. This principle is important when introducing the concept of an acceptable level of quality. (ISO 2859-0 1995.)

Large lots have an advantage in terms of sampling inspection, as it is more economical to take a larger sample lot from a large lot. This allows better coverage between the quality of the samples and helps to ensure that the entire batch meets the set quality standards. Large batches therefore provide a more efficient way to monitor and ensure consistent product quality during the same manufacturing cycle. (ISO 2859-0 1995.)

6.2.3 Normal, tightened and reduced inspection

The ISO 2859-1 standard for switching rules is designed to help determine when to switch from normal to tightened inspection and vice versa during a sampling inspection process. Figure 2 helps to visualize the switching rules, which are part of the standard's guidelines for acceptance sampling plans. The switching rules in ISO 2859-1 provide a systematic way to adjust the level of inspection based on the observed quality of the product being inspected. (ISO 2859-1 1999.)
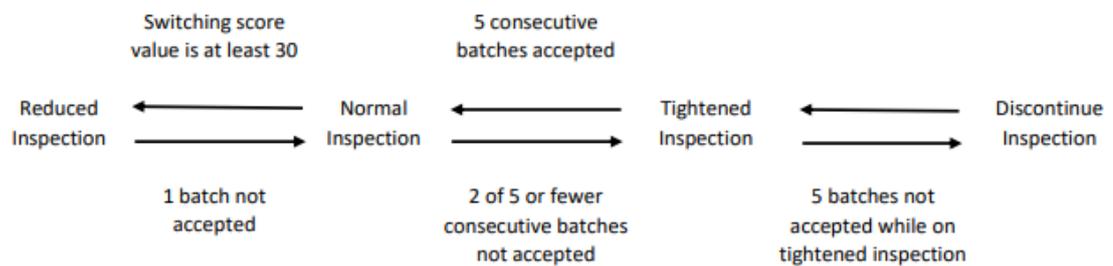

Figure 2. Switching rules (ISO-2859-1 1999)

The determination of the switching score should commence at the beginning of regular inspection, unless directed otherwise by the relevant authority. The starting switching score is established as zero and is adapted after reviewing each successive lot in the original standard inspection. For single sampling plans with an acceptance number of 2 or more, an additional 3 is added to the switching score if the lot would have been accepted with a stricter AQL. (ISO 2859-1 1999.)

The purpose of these switching rules is to allow the inspection process to adapt to changes in product quality. If the quality of the product deteriorates, the rules help in increasing the level of scrutiny, switching to tightened inspection. Conversely, if the product quality stabilizes or improves, the rules allow for a reduction in inspection intensity, switching back to normal inspection. (ISO 2859-1 1999.)

6.2.4 Inspection level

The correlation between batch size and sample size is determined by the inspection level. Table 2 is structured so that larger batch sizes typically correspond to larger sample size. This table comprised three standard inspection levels 1, 2,

and 3, and four special inspection levels labeled S-1, S-2, S-3, and S-4. The general levels, especially level 2, are widely employed, and it is recommended to use level 2 unless another level is specified. (ISO 2859-0 1995.)

Table 2. Sample size code letters (ISO 2859-1 1999)

Lot size	General Inspection Level			Special Inspection Level			
	I	II	III	S1	S2	S3	S4
2-8	A	A	B	A	A	A	A
9-15	A	B	C	A	A	A	A
16-25	B	C	D	A	A	B	B
26-50	C	D	E	A	B	B	C
51-90	C	E	F	B	B	C	C
91-150	D	F	G	B	B	C	D
151-280	E	G	H	B	C	D	E
281-500	F	H	J	B	C	D	E
501-1200	G	J	K	C	C	E	F
1201-3200	H	K	L	C	D	E	G
3201-10000	J	L	M	C	D	F	G
10001-35000	K	M	N	C	D	F	H
35001-150000	L	N	P	D	E	G	J
150001-500000	M	P	Q	D	E	G	J
5000001 ->	N	Q	R	D	E	H	K

Level 1 has a sample size slightly less than half of level 2, while level 3 has a sample size about one and a half times that of level 2. Special inspection levels are designed for situations where it is necessary to keep the sample size small. (ISO 2859-0 1995.)

6.2.5 AQL

Acceptance Quality Limit is a widely used statistical tool in quality control and quality assurance, which is used to determine the maximum allowed amount of defective or non-compliant products in a batch or sample without rejecting the entire batch. AQL helps organizations find a balance between the need for thorough quality control and the practical aspects of production and inspection costs. (Anjoran 2018.) The international ISO standardization organization has developed standard 2859-1 for this purpose, which defines AQL as the "worst tolerable

quality level". This is based on the assumption that it is impossible to achieve completely flawless production. (ISO 2859-1 1999.)

In table 3 the inspection level II is selected to use, which is the commonly used. Defects can generally be divided into three different categories, each of which has its own AQL acceptance rate. This percentage indicates the maximum acceptable number of defective products in the inspection sampling. General AQL percentages are: 0% for critical defects, 2.5% for major defects, and 4.0% for minor defects. (Anjoran 2018.)

Table 3. Sampling plan (ISO 2859-1 1999)

Lot size	Sample Level II		AQL					
			0.01	0,1	0,4	1,0	1,5	2,5
			Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re
2 ~ 8	A	2						
9 ~ 15	B	3						
16 ~ 25	C	5						0 1
26 ~ 50	D	8					0 1	↑
51 ~ 90	E	13				0 1	↑	↓
91 ~ 150	F	20			↓	↑	↓	1 2
151 ~ 280	G	32			0 1	↓	1 2	2 3
281 ~ 500	H	50			↑	1 2	2 3	3 4
501 ~ 1,200	J	80		↓	↓	2 3	3 4	5 6
1,201 ~ 3,200	K	125		0 1	1 2	3 4	5 6	7 8
3,201 ~ 10,000	L	200		↑	2 3	5 6	7 8	10 11
10,001 ~ 35,000	M	315		↓	3 4	7 8	10 11	14 15
35,001 ~ 150,000	N	500		1 2	5 6	10 11	14 15	21 22
150,001 ~ 500,000	P	800	↓	2 3	7 8	14 15	21 22	↑
500,001 →	Q	1250	0 1	3 4	10 11	21 22	↑	↑

↓ = Use the first sampling plan below the arrow. If sampling size equals, or exceeds, lot size, carry out 100 % inspection.

↑ = Use the first sampling plan above the arrow.

Ac = Acceptance number

Re = Rejection number

Setting an Acceptable Quality Level does not guarantee that lots of poorer quality will not be accepted. This is because the AQL is focused on the average quality. Some batches might fall below the AQL, but as long as the overall average remains above it, they could still be accepted. Furthermore, if the average quality being provided falls slightly below the AQL, it is possible that several batches will be approved before a switch to stricter inspection is necessary. Additionally, there may still be some level of acceptance even after the switch has been made. (ISO 2859-0 1995.)

6.2.6 Single, double, or multiple sampling plans

ISO 2859-1 presents three different types of sampling plans, single, double, and multiple (ISO 2859-1 1999). Single sampling involves the random selection of one sample from a batch of items, and the final disposition of the batch is based on the data gathered from that single sample. In the double sampling plan, there are three options after testing the first sample. Either the batch is accepted, rejected or there is no decision. Multiple sampling is an expansion of double sampling plans, requiring more than two samples to make a determination. The benefit of multiple sampling lies in the reduction of sample sizes. (National Institute of Standards and Technology n.d.)

Choosing between single or multiple sampling plans with satisfactory characteristics involves a decision-making process. This process includes evaluating whether the average sampling efficiencies achieved by different multiple sampling plans outweigh the increased complexity and the unpredictability of daily sampling and inspection levels. (National Institute of Standards and Technology n.d.)

7 RESULTS

7.1 Determine the AQL level

The selection of the AQL level based on the greatest risk is an important part of quality assurance and defining the sampling strategy. AQL represents a level of acceptable quality, and its selection must consider the characteristics of the product, the nature of the process and the greatest risk factors. In this case, the selection of the AQL level was based on a risk analysis, which evaluated the effect and possibility of different risk factors. Table 4 examines the possible risks for ampoules, which include leakage, abnormalities in appearance and ampoule opening. For each risk, the degree of impact and probability were determined.

Table 4. Risk assessment for ampoules

Defect	Impact	Likelihood	Risk
Leak	Risk severity: medium Extent of risk: one person	Unlikely	Low Medium
Abnormality in appearance	Risk severity: low Extent of risk: one person	Unlikely	Low
Openness	Risk severity: low Extent of risk: one/more persons	Possible	Low medium

By evaluating the risks of ampoules and bottles in separate tables, it is possible to distinguish potential risk factors and aspects that may vary between these two types of products. This allows for more specific and focused risk management for each type of product. This improves the effectiveness of risk management and helps ensure that all relevant risks are considered in the context of each product. Table 5 presents the risk of bottles produced on the BFS 3 line, and their effects.

Table 5. Risk assessment for bottles

Defect	Impact	Likelihood	Risk
Leak	Risk severity: medium Extent of risk: one person	Unlikely	Low Medium
Abnormality in appearance	Risk severity: low Extent of risk: one person	Possible	Low Medium

When evaluating the probability of products leaking, it was taken into account that all the ampoules are leak tested. This provides a strong basis for assessing probability of defect unlikely, as leakage events are systematically detected and corrected. On the other hand, on the BFS 3 line, which has proven to be reliable, leaking products are very rarely detected. On the BFS 3 line, leak testing is done at the beginning and in the middle of filling. This reflects the trust between the process and the desired quality.

In the assessment of the severity of the consequences, it was emphasized that the possible consequences of leaked products for the consumer can be significant, such as contamination or receiving the wrong dose of the active ingredient. This can directly affect the health and safety of the consumer. In the selection of the AQL level, the magnitude of the possible risks was considered and based on the considered possibilities. The AQL level was set at 0.4, which reflects the balance between risks and production requirements. At this level, it is ensured that risks remain under control while meeting production requirements as efficiently as possible.

The risks of openness were assessed as low. The problem may sometimes appear that the neck of the ampoule does not break, which can prevent the use of the ampoule. Typically, out of ten ampoules, only one does not open properly. The fact that the ampoule does not open, however, does not pose a risk to its user. Based on this, an AQL level of 1.0 was chosen, which reflects an acceptable level for such quality features.

The consequences of the risks of visual defects were assessed as low, as they do not pose a significant risk to the user of the product. For example, plastic may have accumulated at the end of the ampoule, which prevents the liquid from draining properly or opening the ampoule. In bottles, deformations of the neck thread can affect the correct twisting of the cap. In addition to these, the plastic may contain, for example, impurities. Taking into account that the ampoules of the BFS 4 and 5 filling line undergo a 100 percent visual inspection, it would be justified to set the AQL level at 1.0. On line 3, bottles are visually inspected only during the process controls. Although visual deviations are rare, a single deviation can render the product unusable. Therefore, it is recommended to choose a stricter AQL level compared to ampoules that are inspected 100 percent. In this case, the AQL level is set to 0.40, which ensures that potential anomalies are detected and handled effectively, even if they are rare.

The choice of the AQL level was influenced by the principle of maximum risk, and in this case the level 0.4 was chosen to ensure that the inspections are sufficiently frequent and comprehensive in relation to the quality requirements. This decision enables effective quality assurance and reduces the risk of defective products ending up at the customer's disposal.

7.2 Inspection level

When choosing the inspection level, it is necessary to take into account the risks of different parameters, and when making a decision, it is necessary to orientate according to the highest risk. This approach enables a comprehensive risk assessment, which is an essential part of the selection of the inspection level, especially when it comes to medicines for which high quality and safety are of paramount importance. It should be emphasized that if the products show a high risk of quality problems, it may be justified to consider raising the inspection level. However, this decision must be made based on a careful risk analysis to ensure that the level of inspection chosen is consistent with the risk profile of the product. Considering the current risks, inspection level II is sufficient, considering its thick sampling frequency. The selection of inspection level II assumes that it provides sufficient accuracy to ensure the quality and safety of medicines, while avoiding unnecessary increases in costs.

The choice of inspection level II, which is the most used level, can be justified from several points of view, the most significant of which are related to the sensitivity of medicines and business efficiency. Cost efficiency emerges as a business decision, as choosing level II enables a cost-effective inspection process without unnecessary cost increases in the production chain. This is particularly relevant in the pharmaceutical industry, where the increase in costs can be reflected directly in the end-user's price, which in turn affects the product's competitiveness in the competitive pricing market.

7.3 Normal inspection level

It is necessary to start process controls at a normal inspection level. If permitted, a transition to a reduced inspection level can be considered. If the compliance with the process and quality has not been in accordance with the requirements, it is necessary to consider moving to a tightened inspection level.

The results have been obtained using the AQL letter code table and a single sampling plan. The single sampling plan was chosen because its sampling cost is low and the scope of sampling is high, thus the accuracy of the data is also high.

With the BFS 3 machine, the number of samples obtained using AQL tables is 500 (Table 6). Divided evenly by the time required for filling, the result is 18 bottles per hour, which means three machine cycles. In order to ensure efficient sampling, process controls should therefore be taken every 20 minutes in order to collect a sufficient number of samples. A maximum of five defects are allowed during the batch, with the AQL level being 0.40 percent. If there were more defects, it would be necessary to consider rejecting the lot.

Table 6. Sample size for BFS 3 by using normal inspection level

Product name	Theoretical yield	Filling time (h)	Sample size	pcs/h	Ac Re
A	48077	29	500	18	5 6

From the AQL tables, with the products of the BFS 4 filling line, a sample size of 500 pieces per batch has been obtained (Table 7). This, divided evenly by the time taken to fill, process controls should be taken every 15 minutes to ensure the desired quality level is maintained. A maximum of five defects should occur during batches, when the AQL level is 0.40 percent. If the maximum number of defects is exceeded, it is necessary to consider rejecting the batch.

Table 7. Sample size for BFS 4 by using normal inspection level

Product name	Theoretical yield	Filling time (h)	Sample size	pcs/15 min	Ac	Re
B	49180	142	500	1	5	6
C	39216	112	500	1	5	6

Filling line 5 produces several different products. Table 8 shows that the recommended sample quantity for products D-G is 500 pieces per batch. For products H and I, the sample size should be around 315 pieces per batch. Despite the differences in sample sizes, process controls should be taken every 15 minutes for each batch produced. The frequent taking of samples reflects the need to constantly monitor the quality of the process and thus detect possible defects quickly.

Table 8. Sample size for BFS 5 by using normal inspection level

Product name	Theoretical yield	Filling time (h)	Sample size	pcs/15 min	Ac	Re
D	39216	110	500	1	5	6
E	39216	110	500	1	5	6
F	39216	112	500	1	5	6
G	39216	112	500	1	5	6
H	33333	102	315	1	3	4
I	30000	97	315	1	3	4

For product batches D-G, the acceptable number of defects is five pieces per batch, and this is based on the AQL level, which is set at 0.40 percent. If this number of defects is exceeded, the batch must be rejected. On the other hand, in product batches H and I, the number of defects should not exceed three pieces. These differences in acceptable defect rates can be explained by the special yields and expected defect levels of the lots. Limit quantities offer flexibility in

quality control and take into account possible random defects that do not auto-matically lead to batch rejection.

7.4 Reduced inspection level

From the normal inspection level to the reducing inspection level can switch when the switching score value is at least 30. From the accepted batch, three points are added to the switching score. Therefore, there should be at least ten ap-proved batches per filling machine before can move on to reduced sampling. This means that the results of process control must be of uniform quality and the pro-cess itself must function reliably.

When using the reduced inspection level, 200 samples should be taken on the BFS 3 filling line. This, divided equally with the time spent on filling, would mean that one cycle, i.e., six bottles, should be checked in process control every hour. During the batch, the number of defects should not exceed three on the BFS 3 line.

When reducing inspections, the average sampling frequency according to the re-duced AQL table, would be one process control every half hour on BFS 4 lines. Therefore, approximately 200 samples should be taken. A maximum of three de-fects would be allowed.

According to the reduced AQL inspection level, for product batches D-I process controls should be performed every 30 minutes. This means that on average 200 samples are collected for each product batch. If the fourth defect occurs during the batch, should consider rejecting the batch and moving back to the normal inspection level.

7.5 Tightened inspection level

If two of the five batches are rejected at the normal inspection level, must move on to a tightened inspection. This practice sets a higher standard for acceptable quality and ensures that potential quality problems are detected and corrected in a timely manner.

As a result of the tightened inspection, the batches that are accepted and rejected directly affect the continuation of production. To return to normal inspection, five consecutive batches must be approved at the tightened inspection level. This emphasizes the commitment to continuous quality improvement and ensures that any deviations are detected and thoroughly corrected before returning to normal inspection.

In a tightened inspection, the sample size and the frequency remain the same as in a normal inspection, which ensures consistency in monitoring. On the BFS 4 and BFS 5 filling lines, around 500 samples are taken for products D-G and 315 samples for products H and I, every 15 minutes. With the BFS 3 machine, the number of samples is 500 pieces and process controls should be done every 20 minutes. Keeping the sample size and frequency constant enables comparability between different batches and ensures systematic quality control.

However, differences between normal and tightened inspection appear in terms of accepted and rejected values. In a tightened inspection, with an AQL level of 0.4, the number of allowed defects during the batch is three, and the fourth defect causes the batch to be rejected. This places a higher standard on defect-freeness and ensures that batches with significant quality problems do not progress through the production chain.

8   DISCUSSION

In the thesis, the theory related to quality assurance and sampling was introduced. In addition, the thesis introduces the client, NextPharma Oy, their processes, and the operating principles of BFS-lines. The goal was to find suitable sample sizes for the products made on BFS lines and to justify the choice computationally and taking into account the risks of the parameters to be measured.

Quality assurance's main purpose is to ensure the quality and safety of products, while also minimizing production costs. Thus, when deciding on a sampling method, it is critical to find a suitable balance between the two aims. Making the right decision on AQL level and sample size is paramount. A high AQL may cause production costs to rise, but an AQL that is too low increases the danger of quality deterioration and can be detrimental to consumer safety. Risk management is a key part of quality assurance. Companies must reflect on the amount of risk they are willing to accept, and this should be taken into account when selecting an AQL level. If the risk is high, a stricter AQL and more thorough inspection may be required, while lower risk products may allow for a higher AQL and less intensive inspection.

It is also important to consider the frequency and severity of different risks. If the risk occurs frequently, increasing the sample size does not alter the chance of failures. Due to the high severity risks, it makes sense to increase the sample size. For very serious risks, it is more sensible to prevent them from happening altogether, rather than just trying to minimize their impact. A small cosmetic defect is not a problem, but when it occurs frequently, it may become a problem.

The sample sizes for the process controls of the filling lines were defined by mapping the risks and choosing the right AQL level. It would be sufficient for BFS 4- and 5-line systems to perform process control using the normal inspection level every 15 minutes. Instead, with the BFS 3 machine, six bottles were inspected every 20 minutes. It is possible to move from the normal inspection level of process controls to a reduced inspection level, if the results are good and the process itself is stable. This meant half as many samples, which would also be reflected

in the costs. If quality problems occur during the reduced inspection, it would be easy to return to the normal inspection level.

Rejecting a manufactured batch is a complex decision that requires careful consideration and balancing of various factors. In the case of NextPharma, rejections are mainly the result of abnormalities in microbiological and chemical samples, indicating a potential risk of contamination. In this situation, it is necessary to assess how significant these anomalies are for the quality and safety of the product. On the other hand, if bad products are detected in the process controls, NextPharma aims to react quickly and adjust the filling machine as soon as possible. This approach emphasizes the company's commitment to quality assurance and the effort to minimize the number of defective items. Instead of a rejection decision, proactive action and corrective measures are emphasized, which can significantly reduce potential quality problems and contamination risks.

Instead of samples ending up in medical waste after process controls, other more cost-effective methods could be considered. At the moment, on the BFS 3 line, the filling quantities of the bottles are monitored by emptying the bottles into a separate tank. Instead, filling amounts could be monitored with the help of empty bottle tare. This method is already used in culture medium filling, so it could also be applied to actual batches. In the tare method, the filling amount is determined by weight, and this can be an effective way to monitor the production process without all products ending up in waste. This method could offer a more cost-effective alternative, as it would enable the necessary changes to be made to the current process. In this way, all bottles produced on the BFS 3 line would be forwarded to customers, and no additional medical waste would be generated.

Quality assurance and sampling processes are dynamic and require continual evaluation and enhancement. It is imperative to regularly review and assess measures associated with both process controls and quality controls. If deemed necessary, these measures should be adjusted to align with emerging requirements and updated risk assessments. This ongoing evaluation and adaptability are crucial components in ensuring that quality assurance practices remain effective and responsive to the evolving landscape of standards, regulations, and inherent risks within the industry.

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