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UTILIZATION OF ENVIRONMENTAL MONITORING INFORMATION IN PHARMACEUTICAL MANUFACTURING

Master's Thesis in Technology
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ABSTRACT

Samuli Sormunen: Utilization of environmental monitoring information in pharmaceutical manufacturing
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In the manufacturing industry in general, digitization has been a big trend for some time now. However, manufacturing companies do not yet know how to utilize all the data they collect about production processes and thus gain additional value. The pharmaceutical industry is very different industry compared to other manufacturing industries and requires the manufacturer to closely monitor the processes to guarantee their reliability. Pharmaceutical manufacturers also have to follow exact requirements and laws, which are monitored by external parties. The purpose of this thesis was to focus on pharmaceutical manufacturing and environmental monitoring data that is collected from production processes.

The company, for which this thesis was done, needed to find out how the monitoring data of their current environment is utilized and how it could be developed. The company was aware that they collect certain information in order to meet the requirements for pharmaceutical manufacturing, but there are still gaps in how they utilize this collected information. A lot of information in the pharmaceutical industry is collected only because of requirements, and companies do not always think about utilizing that information for other purposes.

The answered research question of this thesis was "How environmental monitoring data can be utilized better in a pharmaceutical production environment?". The research was conducted at one manufacturing site of a pharmaceutical company. The study was conducted as a semi-structured interview study where the participants were personnel who are involved in monitoring the manufacturing environment at the site. The thesis also explores technical solutions for the utilization of environmental monitoring data, which were developed based on the interviews.

Based on the interviews and the site's documents, it was possible to get an understanding of the current environmental monitoring programme and how the data collected from it is utilized. With the help of the key points that emerged from the interviews, it was possible to design technical solutions for better utilization of the environmental monitoring data in production. The results of the thesis are presented to the company and site, and the implementations of these technical solutions are not part of this thesis.

The thesis brought up the current state of utilization of data in one area of the manufacturing industry, where there are still not many studies to compare with. Although this study only gave a small view of the utilization of data in the pharmaceutical industry, and especially of the utilization of environmental monitoring data. It is important to create the basis for possible new research in this area, where there is clearly a lot to be developed. The utilization of manufacturing industry data is to some extent comparable to pharmaceutical manufacturing, but due to its differences, it is important to remember the details that make it different. Because of the differences, this industry has different needs for the usage of data.

Keywords: pharmaceutical manufacturing, pharmaceutical industry, manufacturing industry, production environment, data utilization, data usage, environmental monitoring, environmental data

TIIVISTELMÄ

Samuli Sormunen: Ympäristöseurantatiedon hyödyntäminen lääkkeiden valmistuksessa
Diplomityö
Tampereen yliopisto
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Teollisuudessa yleisesti digitalisaatio on ollut suuri trendi jo jonkin aikaa. Valmistavat yritykset eivät kuitenkaan vielä osaa hyödyntää kaikkea keräämäänsä tietoa tuotantoprosesseista, jolla saataisiin lisäarvoa. Lääketeollisuus on hyvin erilainen toimialana kuin muut valmistavan teollisuuden alat. Se vaatii valmistajalta prosessien tarkkaa seurantaa ja suunnittelua niiden luotettavuuden takaamiseksi. Lääkevalmistajien on myös noudatettava tarkkoja vaatimuksia ja lakeja, joita ulkopuoliset tahot valvovat. Tämän diplomityön tarkoituksena oli keskittyä tuotantoprosesseista kerättävään ympäristövalvonnan tietoon lääkevalmistuksessa.

Yritys, jolle tämä opinnäytetyö tehtiin, oli tarve saada selville, miten heidän nykyisen ympäristön seurannantietoja hyödynnetään ja miten sitä voitaisiin kehittää. Yritys tiedosti, että heidän on tiettyjä tietoja pakko kerätä vaatimuksien täyttymisen takia, mutta tämän tiedon hyödyntämisessä oli vielä aukkoja. Monia tietoja lääketeollisuudessa kerätään pelkästään vaatimusten takia ja niiden tietojen hyödyntämistä muuhunkin ei aina osata ajatella.

Diplomityön tutkimuskysymys oli "Miten ympäristön seurantatietoa voidaan hyödyntää paremmin lääketeollisuuden tuotannossa?". Tutkimus tehtiin lääkeyhtiön yhdessä tuotantolaitoksessa ja se tehtiin puoliksi rakennettuna haastattelututkimuksena, jossa osallistujina oli tuotantolaitoksen henkilöstöä. Valittu henkilöstö on työssään ollut mukana tuotantoympäristön seurannassa. Diplomityössä tarkastellaan myös haastattelujen perusteella kehitettyjä teknisiä ratkaisuja ympäristön seurantatietojen hyödyntämiseen.

Haastattelujen ja tuotantolaitoksen dokumenttien perusteella oli mahdollista saada käsitys nykyisestä ympäristön seurantaohjelmasta ja miten siitä kerättyä tietoa hyödynnetään. Haastatteluissa esiin tulleiden avainkohtien avulla pystyttiin suunnittelemaan teknisiä ratkaisuja ympäristön seurantatietojen parempaan hyödyntämiseen tuotannossa. Diplomityön tulokset esitellään yritykselle ja tuotantolaitokselle. Tämä opinnäytetyön teknisten ratkaisujen toteuttaminen eivät ole osa tätä diplomityötä.

Opinnäytetyö toi esille datan hyödyntämisen tilannetta valmistavan teollisuuden yhdessä osa-alueessa, josta ei vielä löydy paljon tutkimuksia. Vaikka tämä tutkimus antoi vain pienen näkymän lääketeollisuuden datan hyödyntämisestä ja erityisesti ympäristöseuranta tietojen hyödyntämisestä. On tärkeää luoda pohjaa mahdollisille uusille tutkimuksille tällä alueella, jossa selkeästi olisi paljon kehitettävään. Valmistavan teollisuuden datan hyödyntäminen on jossain määrin verrattavissa lääkevalmistukseen, mutta sen erilaisuuden takia on tärkeää muistaa ne yksityiskohdat, jotka tekevät siitä erilaisen. Näitten takia tällä toimialalla on erilaisia tarpeita datan käytölle.

Avainsanat: lääkevalmistus, lääketeollisuus, tuotantoteollisuus, tuotantoympäristö, tiedon hyödyntäminen, tiedon käyttö, ympäristön seuranta, ympäristödata

PREFACE

I would like to thank the company, for which I did this thesis, for making this possible. I also want to thank all the people who were part of this process, either as participants or otherwise supporting the thesis process. Although I cannot mention the company or people by their names. I would also like to thank the thesis advisors at Tampere University for their help with the thesis. Without everyone's input and support, I would not have been able to complete this thesis.

When I decided to start studying for a master's degree alongside work life, I knew that there could be difficult moments ahead. Fortunately, the journey was overall very rewarding and there were not any insurmountable obstacles. I survived the headaches. This thesis is part of a good decision I made when I decided to start my studies and almost an end to my studies, for now.

Tampere, 19 December 2022

Samuli Sormunen

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LIST OF SYMBOLS AND ABBREVIATIONS

IoT	Internet of Things
IIoT	Inudstrial Internet of Things
R&D	Research and development
FFDCA	The Federal Food, Drug, and Cosmetic Act
EMA	European Medicines Agency
Fimea	The Finnish Medicines Agency
FDA	U.S. Food and Drug Administration
GMP	Good Manufacturing Practice
GxP	Collection of Good Practices
cGMP	Current Good Manufacturing Practice
CAPA	Corrective and preventative action
QA	Quality Assurance
QC	Quality Control
VMP	Validation Master Plan
CSV	Computerized systems validation
CFU	Colony forming units
EMS	Environmental Monitoring System
MES	Manufacturing Execution System
HSE	Health, Safety, and Environment
IT	Information technology
ISA	International Society of Automation
RTLS	Real-Time Location Systems
RFID	Radio Frequency Identification
UHF	Ultra High Frequency
OPC UA	OPC Unified Architecture

1. INTRODUCTION

The pharmaceutical industry is among the most rapidly growing industries in the world [28]. This industry formed from the development, research, manufacture, and marketing of biologicals and medicines for both veterinary and human use. In 2020 this industry had over $1228.45 billion in sales, and it has had an annual growth rate of 5.8% since 2017. In 2021 the global revenue was $1454.66 billion, and it is estimated to grow in 2022 to $1587.05 billion with an annual growth rate of 9.1% [40].

The pharmaceutical industry has started to change shape in recent years and the most significant reason for this is Industry 4.0, Big Data, and smart manufacturing trends. These trends have started a vast transformation in all industries that is been driven by automation, digitalization, and data. Data is collected from the manufacturing processes in huge amounts and more than ever before. This ongoing transformation of industries has allowed companies to evolve their manufacturing processes to be more data-driven. Manufacturing going to full digital maturity enables the processes to gain knowledge from the digitalized data and this fully digital and integrated ecosystem helps companies to transform to more proactive and predictive operations instead of a reactive approach. In 2017 it was estimated that companies use only 5.5% of acquired data to optimize the manufacturing processes with data analytics [23]. The importance of data and how we can get value out of it has increased and manufacturing companies need to adapt to this. Digitalization of manufacturing industries has enabled the new potential for companies to optimize their manufacturing processes in new ways. This digitalization can be seen in all sections of manufacturing. Large amounts of data are generated and collected by the increasing number of sensors that are implemented in manufacturing systems. Therefore, manufacturing companies collect more data than ever before from their manufacturing processes. Information gathered from the production environment is an essential view of production processes and the correct utilization of this information and data-supported business decisions making can lead to an increase in companies' competitiveness. Digitalization and Industry 4.0 have changed manufacturing systems to make more use of the Internet of Things (IoT) or Industrial Internet of Things (IIoT). Sensors that are embedded into gadgets and machines gather a big part of data from manufacturing processes. Gathered data can be used to indicate the quality of processes and products through the machine parameters or product

features. [23] In digitalized smart manufacturing the data is a key enabler, but the data cannot be used in its raw state. Data can be transformed in several steps and with different methods. These include data storage, collections, visualization, and analysis, and these stages can be called the “data life cycle”. [12]

Currently, companies do not utilize this gathered data effectively and usage of the data is a future goal for many companies to exploit it better for profit. Manufacturing data analytics is needed to establish the context of data and what is the meaning of data. This data can then be converted to knowledge when the data is related to expert knowledge, experiences, and value judgments. Stored data is still often insufficiently used for knowledge acquisition and production process optimization [49]. The importance of data analytics in manufacturing has already been noticed by companies but companies have struggled the adaptation to these circumstances regarding the changes that Industry 4.0 and data analytics have brought to the industry. Changed circumstances, such as increased connectivity and communication between machines, will lead to automated data analytics and storage, and an overall better understanding of the application of data analytics in the industry in the near future. With the current manufacturing processes and challenges in them, interdisciplinary studies are needed to map the statistical methods to challenges in manufacturing to derive use cases. [23]

Environmental monitoring in pharmaceutical manufacturing is a critical part of the production. It is used to monitor clean room areas in the production environment. Environmental monitoring of cleanroom areas is mandatory according to the regulations in the pharmaceutical industry, regulations that are set by regulatory authorities. Regulations also set the bounds for the conditions in the clean rooms. The environmental monitoring programme generates data from the production process, and it can be a valuable asset for the company. The monitoring programme collects particle, temperature, pressure, and humidity data and it can be collected in different ways.

This master’s thesis study was conducted for a pharmaceutical manufacturing company and its purpose was to answer the question “How environmental monitoring data can be utilized better in a pharmaceutical production environment?”. By answering this question, this study found use cases where the company can get value from the existing data and technical solutions for these use cases. This study brought use cases and concepts to the company, that they can start implementing into their systems and processes to bring more value from the data. No similar studies were found where the usage of environmental monitoring data in pharmaceutical production was studied.

Semi-structured interviews were conducted in this study to get an understanding of the company's current environmental monitoring programme. Interviewees were selected from different departments of the company. The interviewees knew about the existing programme, and how environmental data is collected and used currently in production. The interviews were conducted via Teams and were recorded. Key points were collected and recorded in a journal from the interviews. This process was done after the interviews by re-watching the Teams recordings. With the collected key points, it was possible to find similar subjects and the most relevant points from the key points. After this process, it was possible to find and construct use cases where the usage of data could be improved.

The rest of the thesis is constructed as follows. In Chapter 2 the pharmaceutical industry is covered and what things are relevant to this research. Chapter 3 focuses on environmental monitoring and what is monitored there. Both Chapter 2 and 3 focuses on the theory part of the thesis. In Chapter 4, the research methodology is opened and discussed in more detail. Chapter 5 goes through how the interviews went, what was discovered, and what use cases were created. In Chapter 6, possible technical implementation methods for the found use cases are presented. This also includes some theoretical background for the technical solutions. Chapter 7 discusses the thesis and research processes and how they went, as well as what thoughts have developed during this thesis. Chapter 8 contains the conclusions and results of the thesis.

2. PHARMACEUTICAL INDUSTRY

The pharmaceutical industry is the world's main manufacturer of drugs and represents a growing and significant share of healthcare and development spending in the world. This industry is mainly a research-based industry in which research and development laboratories have historically been successful providers of important new medical treatments for different diseases and increased our basic understanding of those diseases. The success of the pharmaceutical industry has been a significant part of our day-to-day life and it has enabled us to live healthier and longer lives. The pharmaceutical industry is quite a unique one and it has some characteristics that differentiate it from other industries. Firstly, as earlier mentioned, is that this industry is highly research-oriented and therefore there is a lot of interaction with research facilities and universities. Research and development (R&D) processes in the pharmaceutical industry are expensive and R&D for a new product can be time-consuming and take years. Secondly, because R&D is not cheap, manufacturers aim to always focus their products worldwide to get compensation for high R&D costs. Thirdly, this industry has a lot of regulations that are controlled by different organizations and countries. Finally, in many countries, there are complex interactions between insurance groups, governments, and medical professionals that often pay most of the expenses from the pharmaceutical products in their country.[36]

Understanding this industry and the requirements set for it is an essential part of this thesis. In the pharmaceutical industry, information about processes is not only collected from a business or process point of view, but also because of requirements. This is an essential part of the data collected from the production environment. The pharmaceutical industry also sets certain requirements for data integrity and the technical systems used to collect and process data.

2.1 Regulations

In the pharmaceutical industry, there are a lot of regulatory authorities and regulations that they manage, and these regulations must be followed in the pharmaceutical industry. All around the world in almost all countries manufacturing, development, and marketing of pharmaceutical products is under governmental approval and regulations.

Pharmaceutical products are potentially dangerous for public health and because of that national legal frameworks exist to remove risks of connections to the manufacture, development, marketing, distribution, and use of medicines. [1] Governments and other regulatory organizations have developed regulatory systems to make sure that the pharmaceutical industry will produce products that are safe for markets and that way products do not compromise public health [36]. Regulations in the pharmaceutical industry are developed together with the sciences that R&D new drugs and with health delivery systems that have been in the role of health service delivery, who are interested in effective and safe treatments that are affordable and cost-effective. There probably are not many industries that are more harmonized on regulatory requirements and work sharing on international, national, regional, and sub-regional levels between different regulatory authorities. Pharmaceutical regulations incorporate multiple mutually reinforced activities that all focus on protecting and promoting public health. [43] Manufacturers require regulatory approval for manufacturing, development, marketing, and, in most countries, pricing of pharmaceutical products [36].

Pharmaceutical products are unique to consumer products. Consumers in many instances are not capable to understand when to use these products, what products they should use, and how to use these products. The average consumer cannot compare the risks and benefits of pharmaceutical products, no drug is truly risk-free. Risk for exacerbation of the disease, resistance to drugs, therapeutic failure, and ultimately death can be a result of the use of poor quality, harmful and ineffective products. This also reduces public confidence in the health professionals, health systems, manufacturers, pharmaceuticals, and distributions of these products. The responsibility to protect public health is on governments because the public is not capable to ensure drug safety themselves. For that reason, strong regulatory authorities need to be established by governments to ensure the public health and to establish control throughout the R&D, manufacturing, and marketing of pharmaceutical products. [43]

2.1.1 Regulatory authorities

To make sure which regulations need to be followed, manufacturers of pharmaceutical products must understand where their products are manufactured and sold to know which regulatory authorities have the authority over regulations. These regulatory authorities also have the legal right to do audit inspections to ensure that regulations are met.[10] The site, which is part of this research, manufactures products in Finland and therefore is accountable to the regulatory authority of the European Union and Finland’s national authority.

European union's regulatory authority is European Medicines Agency (EMA) and in Finland, it is The Finnish Medicines Agency (Fimea). EMA which protects animal and public health in the EU was founded in 1995 and its responsibilities are the safety monitoring, supervision, and scientific evaluation of pharmaceutical products [9]. Fimea operates under the Ministry of Social Affairs and Health and its task is to promote public health and safety with biobanks, developing the pharmaceuticals sector and regulatory measures in Finland. Fimea was founded in 2009 when the previous agency the National Agency for Medicines was shut down [18]. Fimea regulates medical devices, medicinal, tissue, and blood products. EMA and Fimea have a strong collaboration together and close cooperation with relevant parties and stakeholders regarding the regulations.[17] The site is also supplying products to the United States and therefore needs to be also accountable to the regulatory authority of the United States, which is the U.S. Food and Drug Administration (FDA) and is a part of the Department of Health and Human Services. In 1906 FDA started its operations with the passage of the Pure Food and Drugs Act prohibited interstate trading in misbranded and adulterated foods and drugs.[14] FDA is responsible for ensuring public health and regulates the pharmaceutical products that are manufactured, marketed, or distributed in the U.S. FDA also regulates, cosmetics, radioactive products, and food supply [15].

2.1.2 Good Manufacturing Practice

Good Manufacturing Practice (GMP) means the right way to manufacture pharmaceutical products. It is a commonly used term that refers to pharmaceutical manufacturing international regulations. Every legal drug manufacturer in the world must produce their drugs in accordance with GMP. GMP is part of the quality assurance of medicines and its purpose is to ensure that the products are manufactured and managed according to the quality standards set by the authorities. All activities directly or indirectly related to the product fall under GMP. GMP was introduced by FDA and is a part of general good practice collection (GxP) that contains regulations and guidelines. The variable in the middle can be replaced with any word to make it represent a different area of GxP, for example, the acronym for Good Automated Manufacturing Practice is GAMP. Good Manufacturing Practice applies to both production and quality practices. [25]

GMPs describe the minimum standard and regulations for the pharmaceutical manufacturing industry and it ensures the quality and the safety of the product for use by the general population. GMP regulations are forced by law and manufacturers that do not meet these requirements can have their products removed, fined, production shut down, or jail time. [8] Different countries and regions together with institutes and inter-

national organizations manage their own set of GMP guidelines and directives to guarantee a high standard for manufacturing [22]. GMP is also sometimes referred to as the current Good Manufacturing Practice (cGMP) and it was introduced to make sure that manufacturers employ up-to-date technical systems and technologies to comply with the regulations. Innovative solutions from 20 years ago can be less than adequate by current standards and can cause an increased risk of quality [30].

The basic requirements for good manufacturing practices that govern medicinal products in the European Union [11] state that the holder of Manufacturing Authorization should have:

- A quality programme that ensures reliable manufacturing quality objectives throughout the whole lifecycle of the product. It must be comprehensively designed, correctly implemented, fully documented and its effectiveness monitored. For all the quality deviations a quality risk management principle should be applied to assess the effects of each deviation and establish corrective and preventative actions (CAPA) to reduce the risk of that deviation.
- Personnel working for the manufacturer should have adequate training and a clear understanding of their task's requirements and how GMP affects them. Continuous training of personnel needs to be tracked and relevant training needs to be kept up to date for each person. An organization chart needs to be implemented to see the relationships between the personnel and personnel with responsible positions and need to have written job descriptions and appropriate authority.
- Location, design, construction, adaptation, and maintenance of the premises and equipment need to suit the manufacturing operations. To ensure the quality of products the layout and design must ensure effective cleaning, and maintenance and minimize risks to avoid any effects on the quality of the products. Proper manufacturing conditions need to be maintained during production in every area.
- All the processes that are under the GMP should be documented, understood, validated, and adequately controlled. Control of documentation is needed to ensure the accuracy, integrity, availability, and legibility of documents. Design, preparation, review, and distribution of documents need to handle with proper care to ensure the compliance of the documentation.
- Procedures in production must be consistent, compliant, and guided. Procedures need to be supervised and performed by qualified people. If a manufac-

turer produces different products, only one product can be handled in one room. For security and safety reasons measures for restricting access to production premises needs to be in place.

- Quality control (QC) for products includes testing, sampling, specifications, organization, release procedures, and documentation. Quality control's purpose is to make sure that all relevant and necessary tests are carried out. Until product quality has been judged satisfactory through quality control, products cannot be released for sale, use, or supply.
- Appropriate procedures and programmes should be implemented. This ensures and protects public health. Complaints regarding products need to be recorded, assessed, investigated, and reviewed for potential quality defects. If products can harm public health, they need to be recalled effectively and promptly.
- Holders of Manufacturing Authorization can use outsourced services. If outsourcing is used in activities that are under GMP, the holder should define, agree, and control the outsourcing to ensure the quality of operations. Between the holder and contractor, there must be a written contract that examples the duties of each party. The holder is always responsible to manage the quality programme and needs to state the way that each batch is certified.
- All the areas of GMP should be examined at intervals, for example, all the previously mentioned basic requirements for GMP, to verify their conformity regarding quality assurance (QA). Manufacturers can use external experts for independent audits to monitor quality assurance. The manufacturer is responsible for doing corrective measures, if applicable, for each observation made during the audit.

GMP requires robust processes and technical systems from the manufacturer to ensure quality. These processes and technical systems, when fully developed and effectively managed, will lead to predictable and consistent production, which ensures the quality of the product. GMP regulations are the key element in pharmaceutical manufacturing and also influence this thesis. [48]

2.2 Validation

The quality of the product is not something that can only be assured with inspections and testing during the production process. To ensure the quality of products, validation is needed to ensure that every step in manufacturing is controlled, monitored, docu-

mented, and tested. Validation is documented evidence that the GMP activities can be done within established parameters, effectively, and reproducible so that the manufacturer can produce a medicinal product meeting its predetermined specifications and quality standards. Validation is the process of gathering documented evidence of consistency, collection, and evaluation of data from any process or system linked to the manufacturing of a pharmaceutical product. Validation implements the understanding of quality, safety, and efficacy. The basic principle of validation is to control and monitor a wide range of activities in the pharmaceutical industry, which directly links to the QC and QA of pharmaceutical products. For these reasons, the validation concept has become one of the most important elements of QA in the pharmaceutical industry. [41][48]

The scope of validation is difficult to define because it needs to cover all the aspects of pharmaceutical manufacturing processes. A systematic review of pharmaceutical activities points out at least the following validation areas in the pharmaceutical industry, analytical, instrument calibration, process utility services, raw materials, packaging materials, equipment, facilities, manufacturing operations, product design, cleaning, and operators.[37]

Validation is a GMP requirement [11] that ensures the manufacturers' control of the critical aspects of their operations. It also includes control over the life cycle of production. Manufactures' must take the following things into account in the validation:

- All validation must be planned and take into consideration the life cycle of facilities, equipment, utilities, processes, and products.
- Validation should only be conducted by appropriately trained personnel who follow approved procedures.
- Personnel conducting validation activities should report as defined in the pharmaceutical quality programme. There should always be appropriate quality oversight of the validation life cycle.
- The site's validation master plan (VMP) should be clearly defined and documented in the site's validation programme.
- The VMP needs to define the validation system used, policies, organizational structure, roles, deviation management, change control for validation, guidance for developing acceptance criteria, references to existing documentation, and the validation strategy. VMP also needs to include a summary of the systems, facilities, processes, and the validation status of these.

- For validation activities, a quality risk management approach should be used.
- To sure the integrity of obtained data, appropriate checks should be incorporated into validation activities.

The validation concept is an evolving and continuous process. The concept of validation extends from simple things to very complex methodical and theoretical investigations of how different systems and processes work. Validation is an important part of pharmaceutical manufacturing to ensure compliance with cGMP. [47]

2.2.1 Computerized systems

Organizations operating under GxP areas have been changing over from paper-based systems to software solutions for the management of data and this has been an ongoing trend for the past 20 years. The focus for effective and controlled validated computerized systems is to improve the traceability, integrity, and robustness of systems that assure quality for data management in the product's life cycle. [45] Computerized systems validation (CSV) originated from military usage where independent verification and validation of software processes was developed. It was used to ensure that software functions worked accordingly, and software design fit the purpose of use. Validation of software functions lowers the risk of user error or software error. [1] Software errors are something that can cause minor to catastrophic failures in production or public health [35]. Software failures are something that can happen and will happen, they are inevitable and often costly. The purpose of CSV is to prevent these failures and minimize the impacts they may have. [1]

Regulated processes in the biological, healthcare, and pharmaceutical industry can be supported with computerized systems and should comply with the regulatory expectations of the authorities that oversee development, manufacture, and supply. Regulations depend on which area of the GxP environment the computerized system is implemented. Regulated computerized system scope includes all the systems that manage data, support processes or are used as supporting information for decision-making. Some individual regulatory bodies have made suggestions that all computerized systems used in manufacturing should comply with regulations, regardless of the application use, because of the diversity of the scope.

The scope of computerized systems can cover product data management from the discovery, clinical trials, registration, manufacturing, quality assurance, distribution, and marketing of the product. The product can also have multiple kinds of computerized systems that affect the data management of the product in each phase of the product's

life cycle. The scope of this thesis is the Manufacturing and QA phases of the product's life cycle. These separate phases of the product's life cycle and computer systems in each phase can be seen in Figure 1. [54]

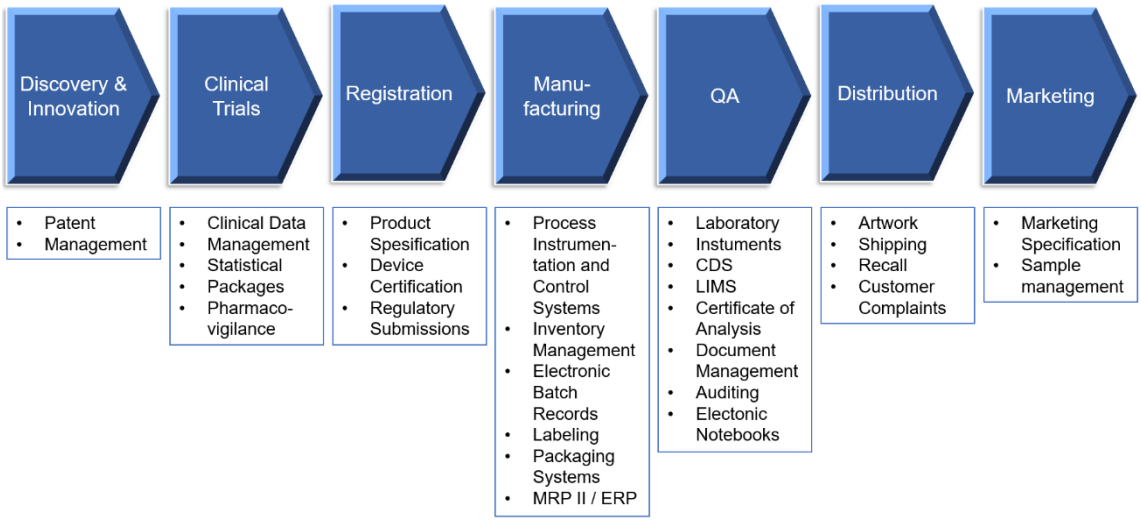

Figure 1 Regulated computer system applications. [54]

Guideline documents have been released by regulatory bodies that have anticipated the growing usage of computerized systems to help manufacturers to implement these solutions. Validated off-the-shelf software solutions can be provided by software manufacturers, but the designed software may not be appropriate for a given specific use because it is designed for a more general purpose [45]. It is recommended to systems that are used for data management be customized to fit the specific purpose from a regulatory and business perspective. When implementing computer systems regulatory perspective is mandatory and should be considered, but the operational perspective is not and these benefits should be explored.[54]

2.2.2 Data integrity

Data integrity refers to the consistency, accuracy, and completeness of data. The point of data integrity is to ensure the efficacy, quality, and safety of drugs. The cGMP sets the minimum requirements regarding data integrity in pharmaceutical manufacturing. Minimum cGMP data integrity requirements demand that:

- Digital data must be in a human-understandable form, traceable to its origin, also timely, and complete.
- Handwritten data must be verifiable, that the result is correct, recorded at the right time, from which device or process the result originates, and that nothing is missing from it.
- Backups of data are complete and exact. They need to be secure from, inadvertent erasures, loss, or alteration.
- Data must be stored to prevent loss or deterioration.
- Activities regarding data integrity should be documented at the time of performance.
- Saved records of data should be either original records, true copies of the original records, or accurate reproductions of the original records.
- There must be a complete description of all the data and complete data derived from all the tests performed.

Data integrity should be an important component for all industries working under a GxP environment and it needs to receive more attention from the industry. In recent years during cGMP inspections, FDA has increasingly found observations regarding cGMP data integrity violations and this trend is alarming. These cGMP violations regarding

data integrity have led to several regulatory actions, including import alerts, consent decrees, and warning letters. [13] Data integrity issues must therefore be taken into account when processing production data in the pharmaceutical industry, which is why this is an important part of this thesis.

3. ENVIRONMENTAL MONITORING

This Chapter is important for research in order to understand the data sources and why data is collected from the pharmaceutical industry's production environment. First, we discuss what the production environment in the pharmaceutical industry is like and what kind of different areas there are, from which data must be collected. After this, we move on to monitoring methods and how the target site does its own monitoring of the environment.

Environmental monitoring and environmental control are two different subjects. Environmental control is more about the design of the necessary processes and parameters to maintain the environment and monitoring is the confirmation of environmental circumstances. Regular monitoring should be performed where sterile operations are performed, and the monitoring instruments and record charts should usually be separate from control instruments [11]. There are always some limitations with the monitoring methods, and these should be considered when designing the monitoring. [44]

There are a variety of monitoring methods and systems that are used to verify sterile clean room environments example for viable or nonviable particles. There are personnel, air, and surface monitoring of microorganisms and other particles. The temperature, humidity, and pressure of the clean room are also monitored. These monitoring methods are covered later in this chapter. Environmental monitoring processes and methods are usually developed and validated in the validation process of a new facility. When the products proceed through production, the concerns about cleanliness, and the intensity and frequency of monitoring increase. For example, the product preparation steps are done in the clean room classification area which is typically Grade C or D and after that, it goes to the more critical processes, like nonsterile compounding, which is done in grade B. Finally in the grade A clean rooms the sterile core part activities, like sterile compounding and filling. When designing the monitoring processes, the time and site of sampling should be designed with consideration that there is no imbalance between avoiding sampling procedures, that may inadvertently or adversely affect the quality of the product and the collection of important data. [20]

Different methods of monitoring provide a ‘snapshot’ of the moment of the production process when sampling is done, and this doesn’t always reflect the conditions in the

whole production. Individual sampling results of environmental monitoring are not often significant representations of conditions in clean rooms. Continual monitoring of sterile environments and sampling of specific activities of production provide data trends that are more valuable to the production and these trends can be examined over time. [44]

Regulations in the EudraLex [11] state that the clean rooms in operation should be routinely monitored. Personnel and surface sampling should be done after critical operations. Particle monitoring in Grade A zones should be done during the full duration of critical operations, including during the assembly of equipment, Exceptions can be made if there is a risk of contaminations to damage the particle counter or it could present a hazard, for example, radiological and live organisms' hazards. In these circumstances, the operations needed for the monitoring should be done before the equipment is set up. Monitoring should be performed also during the simulated operations. Monitoring in Grade A zones should be done with a suitable sample size and frequency so that all system deterioration, interventions, and transient events can be recorded and should trigger an alarm if an alert limit is exceeded. With automated sampling systems, the sample size is usually a function of the sampling rate used in the system. It may not be possible to show low particle levels of ≥5.0 µm during the fill activities, because the product itself can generate particles or droplets. For the Grade B zone, a similar system for monitoring is recommended but the sampling frequency can be decreased. The effectiveness of the separation between adjacent A and B Grade zones determines the importance of the particle monitoring system. A monitoring system for airborne particles can consist of a network of sampling points connected by manifolds to a particle counter, independent particle counters, or a combination of these. An appropriate system needs to be selected for the considered particle size. Any risks present by the manufacturing materials and processes, for example, risks of radiopharmaceuticals or live organisms, should be considered when selecting the monitoring system. In a sterile environment where sanitation of clean areas is important and different disinfectants are used, the development of resistant strains needs to be detected and requires regular monitoring. Monitoring results should be reviewed during the batch documentation review for finished products. Monitoring of particles is required also in non-production activities, for example after cleaning, sanitization, and validation of systems. If automated monitoring systems are used, they should be validated so the process requirements are ensured in critical processes.

3.1 Production environment

The production environment has multiple variables that can affect the production environment, but this theory part stays in the relevant areas of context. This helps us to understand the production and what kind of environmental aspects are important in the manufacturing of sterile pharmaceutical products. Universally the most challenging task in the manufacturing of pharmaceutical products is the manufacturing of sterile products.

The manufacturing of sterile products requires a good design of operations, production environment, and maintenance of equipment and facilities. If sterile products are manufactured in poorly designed and controlled processes and environments, products can have unacceptable contamination that can expose the patient to unpredictable risks. For example, these contaminations can cause microbial infections in patients. Facilities must be designed so that they provide control over pyrogens, particles, and microbials in the production environment.[20]

Sterile product manufacturing requires special requirements so that the risk of pyrogen, particulate, and microbiological contamination can be minimized. A lot also depends on the training, attitudes, and skills of the process's personnel. QA is crucial in this type of manufacturing and strict carefully established validated methods of procedure and preparation must be followed. [11] Production environment has been progressively greater subject to regulatory inspections by the regulatory authorities, because of its importance in the manufacturing of sterile pharmaceutical products.

When products need to be manufactured in a specific environmental condition, the building layout and structure need to include separate areas for product manufacturing and storage. The difference in these premises' environment can be an unusual temperature, humidity, pressure, increased cleanliness, or they can provide higher separations from the other areas. For example for the manufacturing of injectable products aseptic conditions are needed and that demands higher standards of air filtering on ventilation and surface cleaning.[3]

3.2 Clean rooms

By the modern standard definition of a clean room [27], the clean room is a room that is used and constructed to minimize the retention, introduction, and generation of particles within the clean room, relevant parameters are controlled, for example, pressure, temperature, and humidity, and the concentration of particles is controlled. Clean rooms are not only essential to the pharmaceutical industry but all high-tech manufacturing. Close tolerances, strict production, product specifications, and control over in-

puts like personnel, different materials, and chemicals are key elements in clean rooms and high-tech manufacturing. Tight control over materials and processes ensures control over contaminants like dust, dirt, compounds, and moisture. With clean rooms, manufacturers can limit the contaminations in the products and production processes.[27]

Regulations are an important aspect of clean rooms and there are specific clean room regulations made by regulatory agencies that ensure the quality and cleanliness of clean rooms. Regulations according to EudraLex [11] the manufacture of sterile products must be carried out in clean areas, where access to personnel and/or equipment and materials must take place through airlocks. Clean areas must comply with the cleanliness standard and the air supplied to the areas must have passed through appropriate efficiency filters. Clean areas used in the manufacture of sterile products must be classified according to the required attributes of the environment. An appropriate level of environmental cleanliness is required in the operating areas of every manufacturing process to minimize the risks of microbial or particle contamination of the materials or products that are being processed and handled.[11]

Clean rooms can be validated to different classifications and initial qualification includes an assessment of air quality under as-built static conditions. Clean rooms should be maintained with parameters obtained by microbiological and particle data qualification and according to their classification. In the qualification and classification of clean rooms, it is important to emphasize information produced with dynamic conditions. Dynamic conditions mean a state of as-designed active production in the clean room, this includes all the performed operations, equipment, and personnel. Clean room classification is defined by the maximum permitted amount of particles in the air and the microbial contamination maximum active levels with colony forming units (CFU). An appropriate sterile facility monitoring program should assess compliance with designated clean area classifications under dynamic conditions. [51]

The target site has two regulatory guidelines to follow, European Medicines Agency's EudraLex, Volume 4, Appendix 1, and FDA's 2004 Environmental Cleanliness Requirements for Sterile Product Manufacturing. In the EU clean air devices and clean rooms should be classified according to the EudraLex. EudraLex also follows classifications that are stated in the standard EN ISO 14644-1. EudraLex's maximum concentration of the airborne particles for each grade is stated in Figure 2 and the recommended limits for microbial contamination are in Figure 3. These maximum values and limits are defined for at-rest and in-operation states and these states should be defined for each clean room. [11]

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		In operation	
Grade	**0.5 µm**	**5.0µm**	**0.5 µm**	**5.0µm**
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

Figure 2 EudraLex classification Grade maximum particles [11]

	Recommended limits for microbial contamination (a)			
Grade	air sample cfu/m^3	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Figure 3 EudraLex classification Grade microbial contamination levels [11]

In the USA FDA also follows EN ISO 14644-1 standard to classify clean rooms. FDA's maximum particles and microbial contamination limits are in Figure 4. FDA doesn't require rest and in-operation values.

Clean Area Classification (0.5 um particles/ft^3)	ISO Designation[b]	≥ 0.5 µm particles/m^3	Microbiological Active Air Action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; cfu/4 hours)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

a- All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity.
b- ISO 14644-1 designations provide uniform particle concentration values for cleanrooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A.
c- Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
d- The additional use of settling plates is optional.
e- Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

Figure 4 USA FDA classification Grade [51]

Although EU EudraLex and USA FDA requirements follow the EN ISO 14644-1 standard, their approaches to achieving this standard are slightly different. In addition to these differences in particle sizes and operating modes, there is much consistency between the EU and USA classification systems. A summary of these similarities and differences is shown in Figure 5. [29]

FDA		In-operation particles per m³	Active air action	EU	In-operation particles per m³		At-rest particles per m³		Active air action
ISO	USP	0.5 µm	Limits	Grade	0.5 µm	0.5 µm	0.5 µm	0.5 µm	Limits
ISO 5	100	3 520	1	A	3 520	20	3 520	20	< 1
ISO 6	1 000	35 200	7	N/A					
ISO 7	10 000	352 000	10	B	352 000	2 900	3 520	29	10
ISO 8	100 000	3 520 000	100	C	3 520 000	29 000	352 000	2 900	100
N/A	N/A	N/A	N/A	D	N/A	N/A	3 520 000	29 000	200

Figure 5 Comparison of regulatory requirements [29]

The areas filled in yellow in the table show the differences between the EU and USA classification systems. Although these systems have four identified classes each, they are not identical, because USA and EU each have a classification category that the other does not have. [29] There are also differences in the microbial contamination requirements. The difference between EU and USA requirements for microbial contamination in Operation can be seen in Figure 6.

ISO Class/ EU Annex 1 Grade	FDA		EU	
	Active air sampling, CFU/m3	Settle plates 90 mm/ 4 hours	Active air sampling, CFU/m3	Settle plates 90 mm/ 4 hours
5/A	1	1	< 1	< 1
6/-	7	3	-	-
7/B	10	5	10	5
8/C	100	50	100	50
-/D	-	-	200	100

Figure 6 Comparison of microbial contamination limits [16]

3.3 Airlocks

Airlocks are bidirectional points that act as separation and transition points when you change from a different clean room classification or non-clean room environment to another classification environment, for example, between Grade C and D. Airlocks in this use are designed to achieve the higher the two air quality levels in use when transitioned between environments.

Airlocks can also be used for decontamination purposes for equipment or materials that cannot be sterilized but must be transferred to a higher-classification clean room environment. Airlocks can be equipped with vapor phase hydrogen peroxide generators, spray systems, ultraviolet lights, or other devices to enable the decontamination of the material or equipment so it can be transferred. Decontamination processes are not needed when the airlock is used as an exit point. Regardless of the intended use, the process should always be validated to ensure quality. The doors at both ends can be interlocked automatically and controlled according to ensure the standard operation

process. It is good practice that processes with airlocks are monitored and the time that any person spends in the airlock is minimized. [20]

3.4 Personnel & Gowning area

Many possible sources, such as materials, personnel, or equipment, can contaminate the cleanroom environment. Contamination can occur from personal movements, gas escape, repair air, exhaust air, heat, static electricity, and friction. Still, in clean room environments personnel generate the most particles that can cause contamination.

Appropriate procedures, including gowning codes and personnel hygiene, are necessary to minimize human contamination. Gowning refers to putting on correct clothing, protective equipment, or uniforms when entering a clean room environment. Growing aseptic techniques are used to add various barriers that prevent microorganisms or other contaminations in the clean room sterile production environment. Gowning areas can be used as airlocks between different clean room classification areas and hygiene and growing codes vary for each clean room classification and for the requirements in the specific clean room depending on what is done in the clean room. [7]

3.5 Particle monitoring methods

The purpose of particle monitoring is to enumerate and detect the number of microorganisms and other particles in the cleanroom. Clean room particle samplings should always be performed by well-trained personnel following careful sterile techniques to improve data reliability by reducing the likelihood of false positives and minimizing risk to the product [20]. Particle monitoring methods can be separated into viable and non-viable monitoring. Viable particle monitoring and sampling in clean rooms detect the number of microorganisms in different locations. Non-viable particle monitoring measures the amount and size of particles in the air. This separation may not be significant in the future when more technologically advanced methods can monitor viable and non-viable particles at the same time, but for now, these classic sampling methods are still widely used and this separation is needed for these methods. Viable particle monitoring methods can be done by using different methods of air and surface sampling methods:

- Active air sampling: volumetric air sampler
- Passive air sampling: settle plates
- Surface samples: swabs and contact plates

- Personnel samples: gown and finger plates

Used sampling methods should not interfere with clean room zone protection [11]. Several practical considerations must be taken into account when using any of these methods, even though these methods are well established. It needs to be considered that too-aggressive sampling in clean rooms can have the opposite effect on sterile environment conditions. Aggressive sampling frequency can increase the risk of contamination in a clean room instead of supporting it because some of the sampling methods are conducted by personnel and personnel in the clean room environment are the biggest source of particles. When considering particle sampling frequency, there is no value to take more samples than necessary. [44]

3.5.1 Air Sampling

In the most critical environments according to Gad [20], the particles in the air are sampled with active air sampling or with passive air sampling. Active air sampling can be estimated volumetrically, and passive air sampling can be done with settle plates. Isokinetic design should be used in the active air sampler to establish undisrupted unidirectional airflow. Volumetric active air samplers gather particles that are present in each volume and the given air volume is usually one cubic meter, which gives results in CFU / m3 units [44]. The sample volume should be the same as the volume that was used for the validation of cleanroom classification [11].

Settle plates that are used in passive sampling are used in critical areas where there is intervention risk or airflow is interfered with by active air samplers and if there is limited accessibility. According to Sandle [44] settle plates are usually 9 cm or 14cm diameter agar plates. These plates are designed to gather microorganisms that are carried in the air and settle in a specific area to surfaces. If located in appropriate locations, settle plates can provide an estimation of how many and how often microorganisms have been deposited on surfaces, including exposed products.

3.5.2 Surface Sampling

Surface sampling and monitoring can be performed with a variety of methods in clean rooms. These samplings are usually performed in Grade A or B classification clean rooms after processes are completed, this minimizes the risk of contamination of materials and products during the sampling activities. All the manual environmental sampling methods have the risk to contaminate the clean room, which can make the sam-

pling data also less reliable. Studies have indicated that during the normal operation processes contamination build-up is not so likely.

Surface sampling methods can include contact plates for smooth surfaces and swabs for more irregular surfaces. Surfaces need to be cleaned when the sampling is done because these methods can leave traces of water or particles on the surfaces that were sampled. Surfaces that are in contact with the product should also be tested only after the process is completed, for example, feeder bowls or fill needles, and these samples cannot be used to test the sterility of the product. When floors and walls of clean rooms are designed with attention to standard sterile clean room techniques the surface sampling of floors and walls is not necessary frequently. Surface sampling of floors and walls is useful when there is an assessment of microflora changes in the clean room or verification of the disinfection program. [20]

3.5.3 Personnel Sampling

A sampling of personnel and monitoring of particles this way is a part of surface sampling where samples from personnel gowns are taken. In the classification Grade A clean room, these samples can be taken from gloves and forearms, because these surfaces are most critical and can often be close to sterilized equipment or components and sterile products. As in the sampling of the surface, these personnel samples should also be taken after the completion of sterile activities. In this case, there is also the risk of contamination if the sampling is done during the processes and this should be avoided. A sampling of other surfaces of sterile gowns is usually done only when testing post-media fill or gowning is certified, in these situations extra sampling can be informative.

A sampling of gowned personnel should be done in a background environment that is not Grade A classification. After the sampling personnel should exit and re-gown if they continue their activities in the clean rooms. In the less critical areas sampling of personnel can be informative, but the meeting of requirements in these environments is usually more straightforward. [20]

3.6 Pressure, Temperature & Humidity

Pressure in the clean room is an essential part of facility design to reduce contamination. Clean rooms are normally pressurized to protect the product that is exposed to the environment because without pressurization products can be exposed to outside contamination sources. Pressure is used to keep the particles out of the clean rooms and

the pressure is higher in the more critical clean room grades. This pushes the particles toward lower clean room classification areas. This pressurization can be used in hazardous situations to generate negative pressure to keep the hazard in the operating area. [3]

Clean room temperature and humidity should be maintained at an appropriate level that allows the person to work comfortably in the gown they are wearing. Temperature and humidity should also be maintained within the specific range, that is validated to the clean room, during all operations. Temperature and humidity can vary depending on the nature of the processes and what products are processed.[11] Humidity can cause contamination risk to the product with human perspiration, absorption, and condensation. Temperature and humidity need to be at a level that is acceptable to personnel and where it minimizes risk to the products.[3]

According to EudraLex [11], the clean room should maintain positive pressure and airflow to surrounding areas with a lower Grade. It also gives a guidance value for pressure difference, clean rooms' pressure difference should be 10 – 15 pascals. These pressure differences should be documented or recorded regularly. Temperature and pressure should be utilized to monitor processes. Airlocks and gowning areas must be monitored for physical conditions so that the pressure differences remain correct and thus particles do not get into a higher cleanroom class.

3.7 Action & Alert Levels

Recorded results from environmental monitoring are either compared to alert and action levels or as incidents. These levels should not be used as a pass-or-fail decision for products, because these levels are not specifications. These levels are used as indications if the normal operating conditions are drifting from the norm and should be assessed through data with trends over time. During the validation process of monitoring programme action and alert levels should be defined. When reviewing historical data on environmental monitoring it should be considered that typically the data is positively skewed and not distributed. [44]

Appropriate action and alert levels should be set for environmental monitoring. Corrective action should be prescribed in operating procedures if these levels are exceeded.[11] For levels, there should be a rationale and documented description of how the levels were decided. When the levels for action and alert are validated, they should be reviewed periodically and for this, an annual periodic is recommended. [44]

3.8 Site's environmental monitoring programme

The clean room classes they use (A, B, C, and D) correspond to EU EudraLex Clean room categories of Appendix 1. The cleanliness classification has been supplemented for controlled facilities with classifications (E, F, F2(F1), F2, and FLab), which are not included in the classification of EU GMP Appendix 1. The production areas and operations are divided into cleanliness classes (A-F2) with class-specific equipping with which the risk of contamination is minimized to the level of use. Physical, particle concentration, and microbiological concentration of cleanroom areas environmental monitoring is carried out according to the environmental monitoring instructions and, if necessary, further department-specific ones in accordance with the operating instructions.

Classified environments (A-E) are periodically monitored for microbiological and particle contamination. The principle of microbiological environmental monitoring is that the monitoring results work as indicators of microbiological risk and control is therefore risk-preventive. The purpose of this monitoring is to detect not only the risk directly to the product but also the microbiological risk to the farm because contamination of the premises can lead to contamination of the product.

The production hygienist is responsible for production hygiene in the cleanroom departments under his responsibility for supervision, preparation of guidelines, and evaluation of results, and acts as the primary person monitoring trends at least every six months and recording the inspection in the logbook. Particles are measured from cleanrooms during the rest and production phases. The particle sampling needs to be done by trained personnel. If the clean rooms are in operation, the production department-designated sampler takes the particle samples. The minimum requirements for sampling intervals can be seen in appendix A Figure 19.

The selection of microbiological and particle monitoring sampling points takes place primarily in connection with the clean room qualification process. The selection of sampling points has also considered, among other things, the stage of the production process, open product location, space size, geometry, personnel, and material traffic. The limits of microbiological and particle contamination environmental monitoring are based on EU EudraLex Annex 1. Exceeding the particle concentration limits is allowed if the exceedance is caused by the nature of the process and the particles originate from the product itself, e.g., dusty work steps. Critical physical conditions are monitored. Critical conditions can be e.g., temperature, humidity, and pressure difference. These values are monitored in rooms if conditions may affect the product's quality or analysis results. Physical monitoring and data collection take place with a property monitoring system or

manual accounting of local meters. If conditions have been ordered to be monitored on the premises, which the monitoring system monitor, the department regularly records values from local meters. The physical environmental monitoring system (EMS) automatically prints the trends of the previous week in graph form every week with a report printer. The reports are then checked and signed to ensure the monitoring of physical conditions.

Microbiological and total particle monitoring is currently done with a paper report process. Report information from the sampling is transferred to validated Excel after inspection and signing are done. The validated Excel table is used for creating trends and for the determination of alarm limits. In addition, monthly, department-specific results are printed in Excel. Original documentation, printouts, and their copies as well as measurement protocols are original information. Original Data must be archived so that data integrity can be ensured and GMP requirements are met.

Currently, the physical conditions of environments are monitored with a validated computerized system, that collects real-time data on physical conditions. The EMS is used at the site to control and regulate the HVAC systems and to register related data from the substations. The substations control the field devices and collect measurement data from the measuring devices. The collected measurement data is transferred to the database server. The measurement data is saved on the database for later use, for example for reports. A database is an organized collection of data and information stored by a computer. Databases are collections of files compiled for a specific purpose, from which individual information or combinations of information can be obtained using search methods and which can be corrected or supplemented. A user can use workstations connected to the system to view the measured values and alarms and enter set values within the rights granted to the user group.

4. METHODOLOGY & APPROACHES

In this chapter, the thesis focuses on the methodology of the research. It goes through what are the approaches and objectives of the research so that it can answer how the site can utilize the environmental monitoring data in production. This thesis tries to find ways to utilize environmental data, that is produced in the production, to get more value out of the data. Target company produces sterile medicinal products and because of this regulations require environmental monitoring program, which ensures the right conditions are needed by collecting data from the production environment. Because this data is already collected it is beneficial to the company to utilize it for more value than just for regulatory compliance. For this, it is needed to find out how the existing environmental monitoring programme works, how the data is currently used, and what are the possible use cases for the data usage.

This research has an inductive approach to the research question. An individual opinion-based interview survey is used to gather data for inductive reasoning. Similar studies were not found, where a study tries to find ways to utilize environmental data to benefit the pharmaceutical production process. To understand how the site can utilize the environmental monitoring data in production, it is needed to find out the current state of the environmental monitoring programme in the target company. Interview surveys and documentation that the organization has been used to collect necessary information about the current state. An interview survey is a data collection method that allows a more interactive approach to surveys. The researcher can explain the intent of the interview and use explanatory comments or additional questions to clarify subjects. Documentation is used to get a better understanding of base variables that are present in the environmental monitoring solutions used in the site and to aid in the analysis of survey data. [31]

These interviews are done as semi-structured interviews. How structured an interview is varies depending on the research question and what is the interpretive orientation. This form of interview provides a sufficient structure for the interview to conversate specific topics while still leaving opportunities for more open conversation. A key advantage of the semi-structured interview is that it focuses on lived experience and specific theoretical variables. A semi-structured interview was used because these moni-

toring programs can be complex and environmental monitoring data can be acquired with different solutions. With more complex surveys a semi-structured interview is a good option where a more open conversational style is helpful. This approach helps us to keep in the specific topic, but this lets the discussion go deep into the details of how the existing environmental monitoring is done. It is possible to gather a more complete picture of existing environmental monitoring solutions by not limiting the flow of thought of the participant. This approach also allows the participant to come up with new use cases on how environmental monitoring data could be used. [21]

Interviews are done through Teams software. Teams meetings are recorded, and a transcript is made after the interview. Interviews are conducted in Finnish and all the questions asked during the interview are translated into this thesis. From the organization, the research selected ten participants that are working with environmental monitoring at the site and have the most knowledge about the current state. Interviews are conducted over the course of one month. The first interview serves as a pilot interview so that it is possible to assess the effectiveness of the questions and whether the questions need to be modified for the following interviews. Interview questions used to guide interviews, which are translated to this thesis, and the goal of each question are listed in Figure 7.

Question	The goal of the question
What's your job and how long have you been doing this work?	To understand the person's background.
What kind of work and educational background do you have?	To understand the person's background.
How does the environmental monitoring of production appear and affect your work?	Find out the person's approach to environmental monitoring and what responsibility the person has in it.
How is environmental monitoring done in your department and how is data collected from the production environment?	Find out what their department's role is in the current environmental monitoring program and what responsibility the department has in it.
In what ways do you use environmental monitoring data?	Find out how currently environmental monitoring data is used or is it used at all and how data is seen.
What is your view on the utilization of environmental monitoring data and is there anything that can be improved	Find out what the person's views are regarding the use of data. Can highlight possible use cases.
Which information in environmental monitoring is the most critical?	Clarify critical data from environmental monitoring. This helps us to see, and prioritize use cases for the data.
Do you see connections between production events and the conditions of the production environment?	Find out if there is any direct connection between production events and environmental monitoring data and if can there be use cases.

Figure 7 Initial interview questions and question goals

Teams meeting recordings are later analyzed by viewing all recordings and finding out all the key points from each interview. These key points are collected in a journal. This journal can be then analyzed to find similarities in subjects, specific aspects, or suggestions for improvement that came up during each interview. From there, this research can create use cases and start the process of finding a technical solution for them.

Participants for the interviews were selected from production departments, where there are clean rooms, microbiological QC department, QA department, and infrastructure and utilities (I&U) department. Ten interviewees were selected from these departments. Five from the production departments, two pharmacists, two production leads, and one line leader were selected. From the microbiological QC department production, a hygienist was selected. Two were selected from the QA department, a technical QA specialist and a Project Quality Lead, who have and are working with environmental monitoring. One former production lead has a lot of knowledge about the environmental monitoring programme. Lastly one from the I&U department, a technical specialist. The I&U department is responsible from the technical side to maintain and produce clean room environments.

5. FINDINGS

This chapter contains information about the existing monitoring programme, what were the interview findings, and what use cases can be created from this information. This chapter first goes through the findings of the semi-structured interviews and what main points that emerged from these interviews. Then, it represents what kind of use cases were created based on the information that was gathered from the interviews.

5.1 Interviews

The interviews were conducted over the course of one month, and an hour was reserved for each interview. The duration of the interviews varied between half an hour and an hour. The variation in the duration of the interviews was predictable because not everyone necessarily has a lot to say about the topics covered.

After the first interview the Teams recording was analyzed, and key points were written into the diary. After the first interview, it was noticed that one of the questions is irrelevant to the question and can be removed. The question was removed, and the final questions can be seen in Figure 8.

Question	The goal of the question
What's your job and how long have you been doing this work?	To understand the person's background.
What kind of work and educational background do you have?	To understand the person's background.
How does the environmental monitoring of production appear and affect your work?	Find out the person's approach to environmental monitoring and what responsibility the person has in it.
How is environmental monitoring done in your department and how is data collected from the production environment?	Find out what their department's role is in the current environmental monitoring program and what responsibility the department has in it.
In what ways do you use environmental monitoring data?	Find out how currently environmental monitoring data is used or is it used at all and how data is seen.
What is your view on the utilization of environmental monitoring data and is there anything that can be improved	Find out what the person's views are regarding the use of data. Can highlight possible use cases.
Do you see connections between production events and the conditions of the production environment?	Find out if there is any direct connection between production events and environmental monitoring data and if can there be use cases.

Figure 8 Final interview questions and question goals

The question about which information is most critical is irrelevant. All the information that is collected from the clean rooms is collected because of the regulations and at the target site they do not collect any additional information about the environment. This still does not mean that other data could not be collected in the future related to the conditions of clean rooms if a value is obtained from it.

When all the interviews were completed, each interview recording was watched, and all the key points per interview were recorded in the journal. After this process, the journal can be processed and found out if the same key points or topics were found in the interviews. Then it was possible to find use cases for environmental data.

5.2 Key points

The first topic that was immediately noticeable was that environmental information is not used proactively. All processes are based on the investigation of a deviation or failure situation, where environmental data is used to find out the root causes. For example, when there is a deviation in the environment, personnel send a query for all the information about the environmental conditions. After this, the scope of the deviation is assessed, and which production batches it may have affected. All of this is reported to the deviation investigation and this information can be used in the root cause investigation, which is a mandatory part of the deviation investigation process. Once the potential root cause is determined, CAPAs to prevent this from happening again are defined. From this, it is possible to conduct that all activities are based on reactive processes, where the reaction is made in a case of deviation or failure.

The second essential topic for this thesis is the visibility of data. The real-time data of the validated EMS is not directly visible in the production departments. There are employees in production who have no understanding or visibility into situational information, even though the departments should be responsible for their environment. Department has visibility to total particle and microbial sampling data through the archived documents in the departments or with the validated Excel document. This same problem is also present in the QC department that is responsible of release the product. QC needs to have all the information from the production batch before they can make the decision regarding the release. Right now, QC is informed about deviations in the clean room environments with an e-mail and deviation process that is at the site.

As mentioned earlier, departments should be able to ensure their own environment and be responsible for it. At the moment, however, departments do not check or verify their own physical conditions. Weekly reports of the department's data are issued by the

EMS, and these reports must be signed in order to verify the monitoring of the physical conditions. However, most of these reports are signed by the I&U department, which is also responsible for creating environmental conditions. There is a clear contradiction here, the producer of the environmental conditions also checks the correctness of the conditions. It would be good for the production departments to check and verify their own conditions so that this process can be transparent and then there is an external party that can verify the conditions. It would be good to change the paper reporting process in order to make it easier for the production departments to verify the conditions.

The current paper process and Excel document of particle and microbiological monitoring are being replaced by an electronic solution in a near future. This already facilitates information sharing. Particle and microbiological monitoring are carried out at the intervals shown the appendix A Figure 19. These intervals can be quite long and there is no real-time visibility of particles from the departments. This sampling interval does not necessarily tell the whole truth throughout the entire production. When deviations are detected this gap in environmental data can make it difficult to find root causes. Real-time monitoring of total particle count is not currently required by regulations, and it leaves room to debate the pros and cons of this information. In all manufacturing, it is good to follow LEAN thinking and principles. According to Wang [53], “Lean manufacturing is the production of goods using less of everything compared to mass production: less waste, less human effort, less manufacturing space, less investment in tools, and less engineering time to develop a new product.”. It is a management philosophy that focuses on eliminating seven different types of futility (unproductive activities). Lean is associated with concepts that are used in operational development. Lean strives to get the right amount of the right things of the right quality at the right time and in the right place and the right quality. The key to Lean is to identify and eliminate waste quickly and efficiently, reduce costs and improve quality. Waste refers to extra, unproductive activities that slow down the process or generate unnecessary costs. If there are not enough benefits from real-time total particle monitoring compared to the additional work it produces, this can be seen as futility.

In clean rooms, the biggest producer of particles is a person. The production departments still do not know the exact number of people in their clean rooms. There have even been restrictions on the maximum number of personnel for newer departments, but in monitoring this, the departments rely completely on the training of the personnel. Currently, the departments do not have any electronic tracking of personnel or materials. The only information related to the number of people is collected in connection with

particle sampling, where the number of people in the department at the time of sampling is written on the form. However, this information does not cover the entire situation during production, so it is not possible to form a complete picture of the environment at every point in time. There are no regulations on personnel tracking and here LEAN principle needs to be considered.

In a few of the interviews, there was a discussion about process siloing. When looking at previous key points, this can also be observed. The processes and the data that are there, are very siloed and the flow of information between silos requires a lot of work. Information is requested either via Teams or by email, and only when there is a problem. This slows down everyday work and better the utilization of information because the information is difficult to access.

5.3 Found use cases

From the key point findings of the interviews, there are clear things that can be observed and could be improved. The siloing of processes could be facilitated by creating the production departments' own views of the data and more control over their environment. Upper-level views of production can also be done, by integrating the data. There is also no full visibility of the state of the environment because particles and the number of people are monitored only with sampling cycles that are mentioned in Appendix A. The following use cases can therefore be created from these interview key points.

The first one is the production department EMS views. If production condition data were visible, possible connections to the behavior of materials, machines, and other events by employees could be better observed in production. This can be used to prevent and anticipate unwanted phenomena. It would be possible to notice things in everyday activities more easily and make operations more efficient in this way. Open doors that are left open can also be detected in the wards before the alarm sounds because of the dropping of pressure and they can be closed. You do not always have to improve and develop things only through a deviation process where you need to fix the root cause. Departments also have alarm systems such as lights and buzzers that could be controlled by departments. If in the EMS there would be department-specific access and views this could be achieved. Giving this view to the departments saves resources because unnecessary work to find out the conditions could be avoided.

The second one is an EMS data integration to an upper-level system. Data integration refers to using the same data in both systems. This integration does not affect the func-

tionality of either system. With the integration of data to an upper-level system, where different systems can be integrated, better visualizations of data can be done. For example, if the Manufacturing Execution System MES data and EMS data are integrated into the same upper-level data system, the site can link the production process data to environmental condition data. The QC department could benefit if from this data integration into an upper-level system. This information can be used in the batch approval process. Currently, there is no information about the conditions in the batch reports, and they do not have an easy view of the batch-specific information. It is possible to request department-specific information from EMS for the period when the batch was processed there, but this is slow and not optimal. With this data integration information regarding environmental conditions on a specific batch can be viewed in a couple of minutes. With EMS data integration, it would also be easier to get information screens for the departments that could include information about environmental conditions and alarms. If the MES data is also integrated, this info screen could add information about the batch made in the department. Data processing and analysis are also easier when the data has been transferred to a system whose main task is data processing. Particle and microbiological monitoring is moving to an electronic format. Integrating data from this system could also be considered. In this way, a very broad view of environmental conditions information from one source would be obtained.

The third one is real-time particle monitoring. Although there are no requirements for real-time particle measurement, real-time particle measurement could be used for more accurate troubleshooting and forecasting. It could be used in troubleshooting not only for particle contaminations but also, for example, equipment faults. Machine faults could be detected by an increased amount of particles. In newer departments, these real-time particle meters have been taken into account and they are already being introduced in new departments. These particle measurement devices can be connected to the current EMS system, so there is no need to create a separate system for this function.

The last use case is related to asset tracking. This could be implemented for personnel and material tracking. As far as cleanrooms are concerned, personal monitoring is the most essential information in the asset tracking system, and by monitoring this, a better understanding of the cleanroom environment could be obtained. It would be possible to monitor the maximum number of people in the rooms and get an idea of how many people are working in the departments. This information would also be useful in terms of Health, Safety, and Environment (HSE).

At the moment, the guard or the staff cannot easily find out information about which departments have production ongoing and how many staff members there are, and this can cause problems in emergency situations. The material tracking would also add value to this system because then it would not be a system created only for one purpose. This use case would also provide good information for parties interested in production processes and what is happening in real-time. Asset tracking also helps to drive production to better LEAN operating methods [24].

6. TECHNICAL SOLUTIONS OF USE CASES

This chapter discusses the technical implementation of the discovered use cases. Four use cases were selected for investigation from the technical implementation point of view. These four are real-time particle monitoring, a real-time asset tracking system, EMS views for the production departments, and the integration of EMS data into an upper-level system. In these technical implementations, they do not go into product-specific details but stick only to the general level of what technology solutions can be found for the use cases. The purpose is to create a basis for technical implementations that are easy to discuss and develop the right solution on a case-by-case basis. For each implementation, it is always necessary to consider whether the changes or new computerized and technical systems are subject to GMP and are quality-critical. Operations under GMP always require validation of changes and new systems. This chapter does not take an opinion on the GMP aspect or on the determination of activities that require validation.

When starting to implement technical solutions for the production environment, it is good to understand the enterprise-control system hierarchy. With the help of this hierarchy, it is possible to explain the impact and scale of different processes and how things are integrated between different systems in manufacturing. The International Society of Automation (ISA) has published an international standard ISA-95, which is often used as a reference when developing an automated interface between enterprise and control systems. This standard defines the basics for production management that is based on The Purdue Enterprise Reference Architecture (PERA). PERA hierarchy has 5 levels that can also be called 5 automation levels. [46] This hierarchy can be seen in Figure 9.

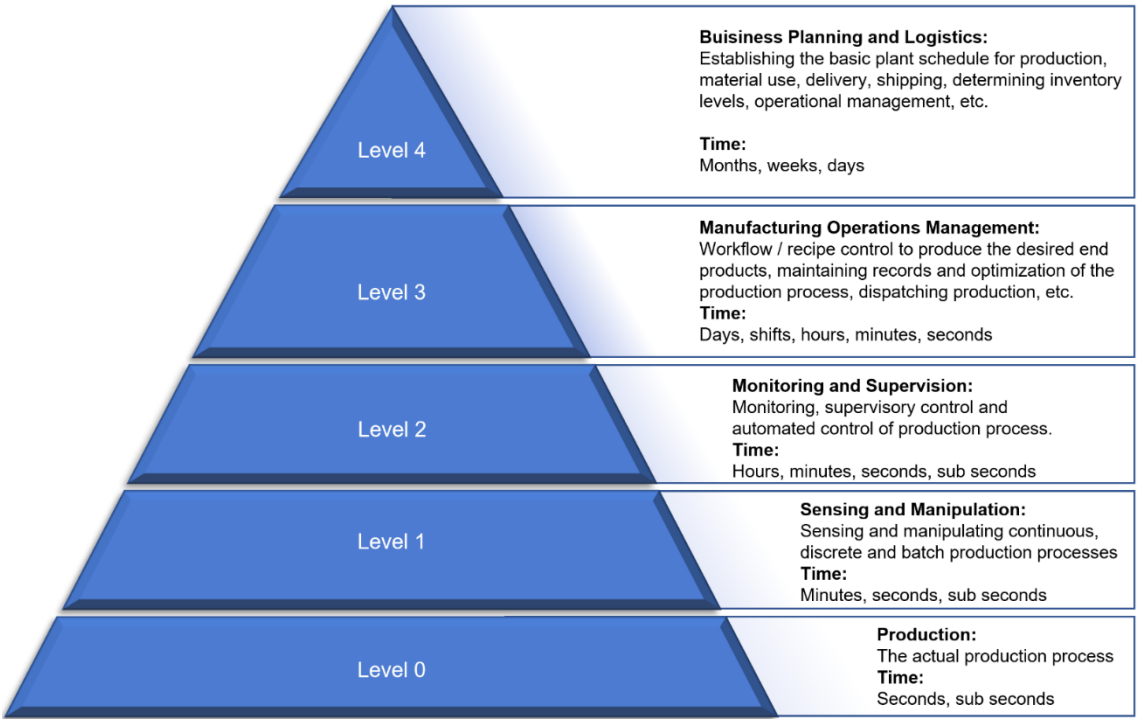

Figure 9 Functional hierarchy [46][19]

- Level 0 defines the physical processes of manufacturing
- Level 1 contains the actuators and sensors of the production equipment. The concept of time is real-time or microsecond and even down to the microsecond.
- Level 2 defines the functions of the production line. The concept of time varies from hours to microseconds and even down to less than a microsecond.
- Level 3 is the configuration and management of the production unit. At this level, the production workflow and recipe content for the company's products are determined. The level analyzes and stores production data and optimizes production processes. Time concepts can range from seconds to shifts and days.
- Level 4 controls production and the company's logistics. The top-level parameters for products and the general ones for production planning are formed at this level. Such general parameters are, for example, production quantities, materials used, and delivery times. Concepts of time at level 4 range from days to months.

Achieving optimal productivity requires a combination of functions that are implemented by an enterprise resource planning or production control system. The ISA-95 standard

helps to define functions by modeling data transfer between enterprise resource planning, production control systems, and manufacturing control systems. Understanding these levels is important when talking about system integration and data transfer between systems.

6.1 Real-time particle monitoring

The real-time particle measurement use case can be implemented with an existing EMS. Particle counter devices can be connected to the system with Fieldbus communication on hierarchy level 0, to already existing controllers on level 1. This implementation of the existing EMS can be seen in Figure 10.

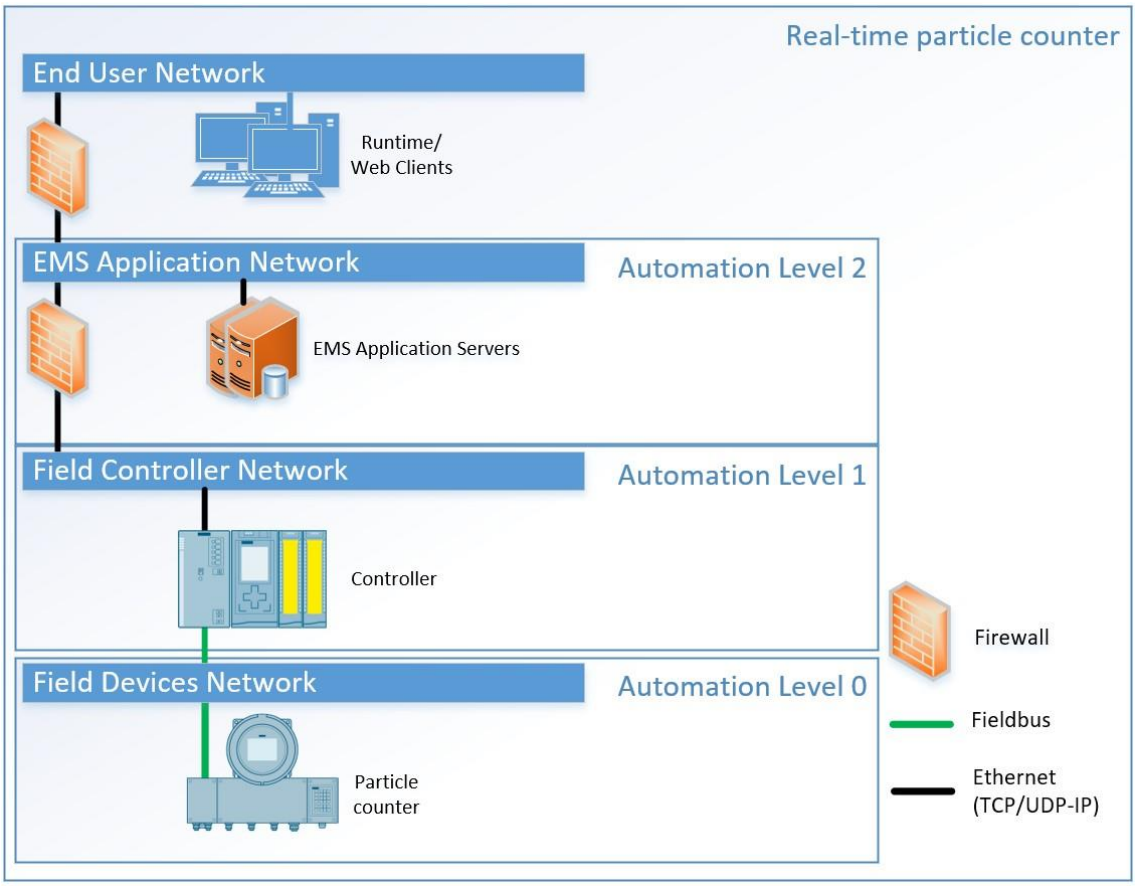

Figure 10 Real-time particle counter implementations

The controller collects data from the particle counter and transfers it to the EMS server with an ethernet connection. EMS will then store the data in a database for further usage and storage. This information that is saved in the EMS can then be accessed through the system's client interfaces. A firewall is used between the hierarchy levels to ensure the Information technology (IT) security of the system. A firewall is a system in IT that is meant to prevent unauthorized access from one network to another, especial-

ly from the Internet to a local network. In most cases, a firewall is needed to protect against attacks from an open Internet connection. Firewall devices have rules that filter out everything but the minimum necessary from incoming connections. Only the necessary communication ports can be enabled on the firewall to reduce the risk of unwanted access to the system with connections made by other devices. This communication port enabling is usually done as a point-to-point communication that ensures that only two specific devices can communicate through the firewall with the set port. This strengthens the data integrity of the system as the ways to do undocumented or unwanted changes to data are reduced. In this case, there is no need to use a firewall between level 0 and level 1. The controller and the devices in the field do not store sensitive data that could lead to possible leaks or unwanted functions in terms of data that needs to be stored as a GMP requirement. Current EMS collects data from the measurements and operators and engineers can use this data. The particle counter goes through the same data flow process as all the other measurements. The data flow of EMS with the implementation of the particle counter can be seen in Figure 11.

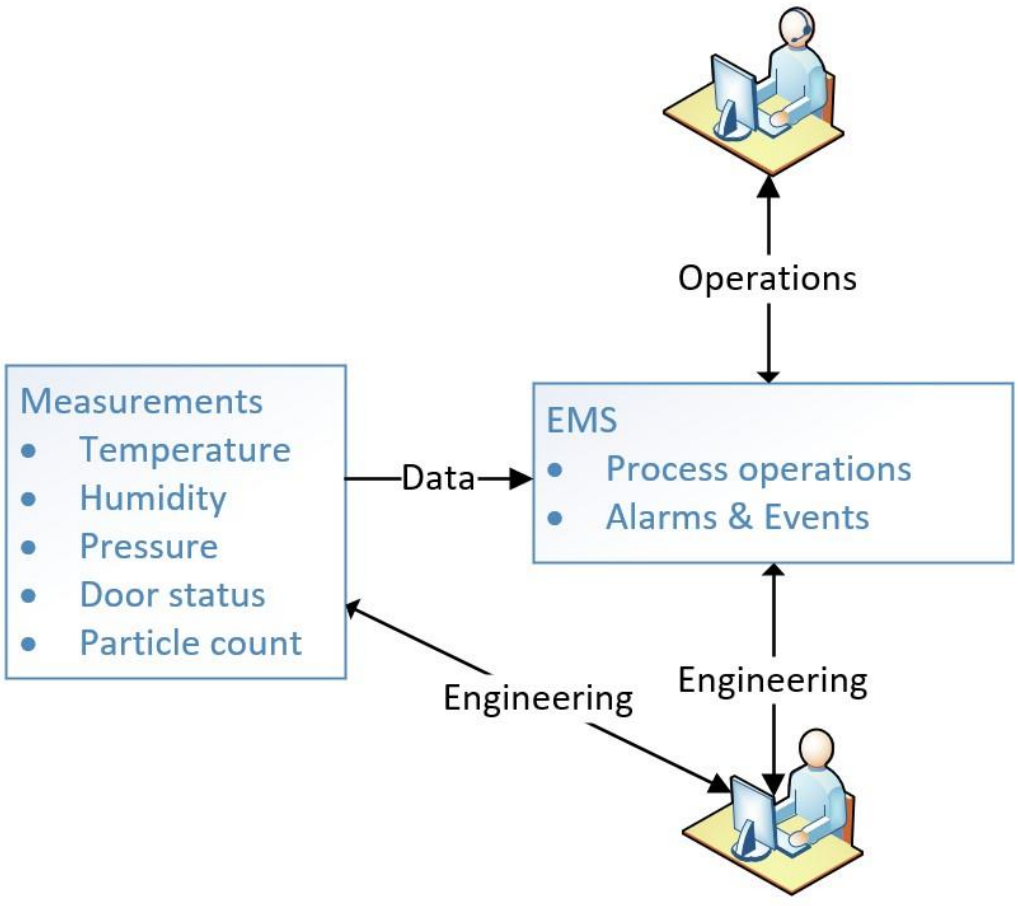

Figure 11 Real-time particle counter dataflow

With this implementation approach, it is possible to reduce the costs of collecting this information in maintenance and implementation. If the departments have their own sub-facilities, the information can be forwarded directly to the departments. Departments are able to use this information alongside existing sampling to support process operation and quality. The data flow of EMS can be seen in Figure x. The site has already planned the implementation of this feature. The benefits of this implementation come out more in the sections that deal with the integration of the EMS data into the upper-level system.

6.2 Real-time asset tracking

Real-time asset tracking or Real-Time Location Systems (RTLS) [32] are not new things in manufacturing industries. Several options for this technology already exist in the market that makes use of wireless technology, IIoT devices, and positioning algorithms to track asset positions. Typically, this system is built from three parts, tags that are tracked, anchor points that track the tags, and an engine that can locate tags with the information that anchor points provide, see Figure 12.

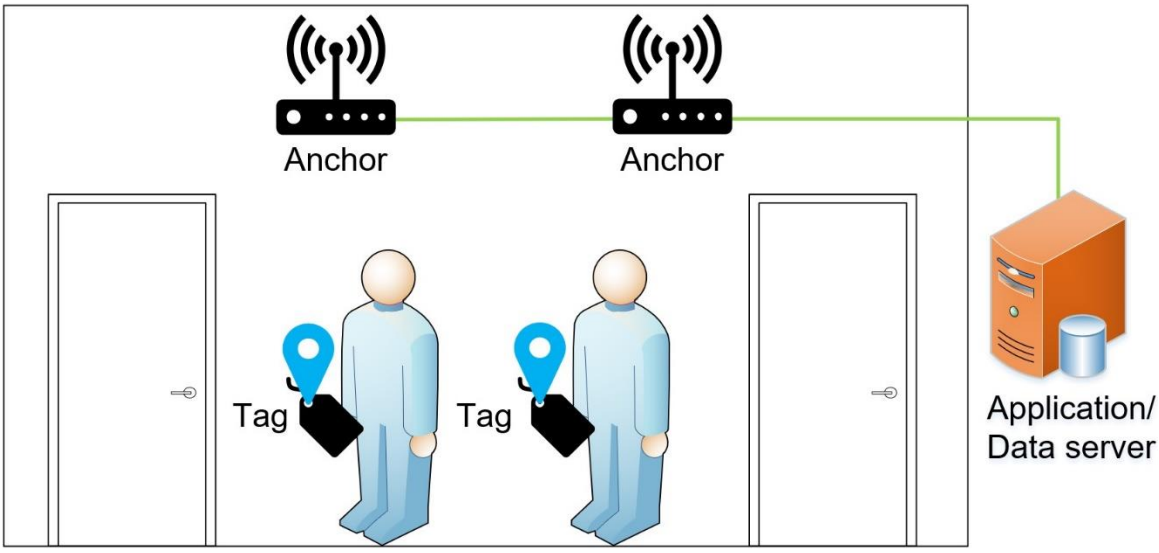

Figure 12 RTLS parts

RTLS usually uses communication methods that include radio frequency communication. RTLS solutions can include Wi-Fi, Bluetooth, and Ulta-Wideband communication. In the RTLS there is no solution that fits all. Communication methods and devices used

are heavily dependent on the environment where they are implemented. In closed rooms, there can be a lot of obstacles that can affect signals and hence fort location data. There also needs to be consideration of other signal noises that can are produced from other devices.

In this use case, Radio Frequency Identification (RFID) technology could be used, especially passive Ultra High Frequency (UHF) RFID tags could be used. These passive UHF RFID tags use frequencies between 860 and 960 MHz. With this frequency range, objects can be detected up to a distance of 10 meters. [34]

The UHF RFID tags in production can be detected with UHF RFID readers. These readers can be directly connected to the application and database server with an ethernet connection. This server then processes all the data and takes care of presenting it to the client interfaces. This process can be seen in Figure 13.

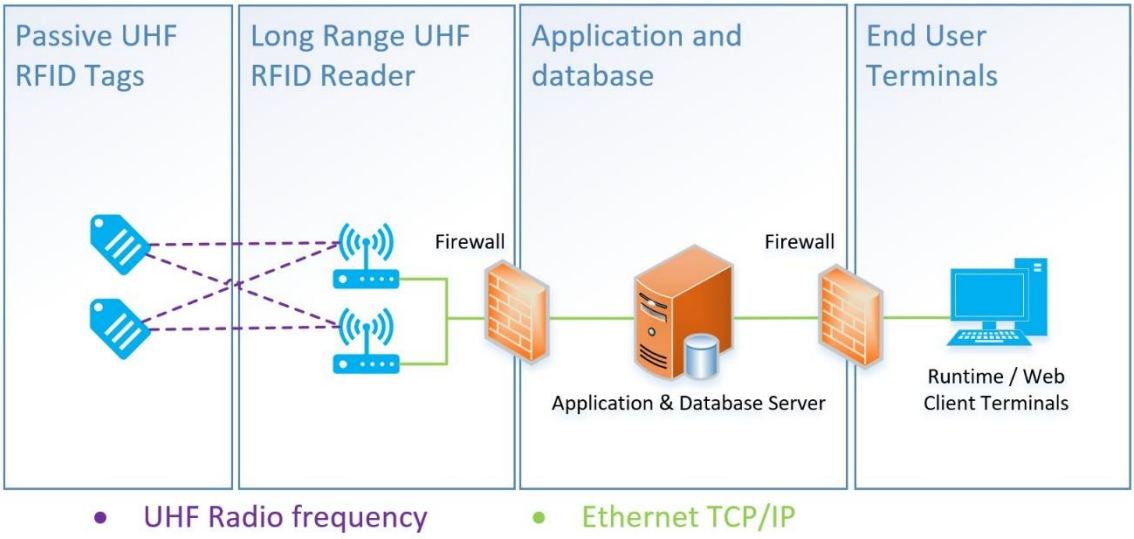

Figure 13 RTLS System architecture

IT security must also be taken into account in the RTLS architecture, and therefore the placement of firewalls between traffic must be considered. In the future, the RTLS system could also be connected to an upper-level system, where the data would be more easily visible to everyone. The main regular users of the system would probably be de-

partment supervisors and security guards. It would be good for the security guards to have visibility of people and possibly the flow of goods with HSE in mind.

RFID tags can be installed in many different places, such as pallets, cases, individual products, ID cards, wearable bands, and even clothes [33]. UHF Readers could be placed in personnel gowning areas and airlocks designed for the transfer of materials. In this way, the movement of assets into and away from the clean room could be monitored. This way it would not be necessary to install UHF Readers in the cleanroom itself and still monitor movements and asset locations. If all passageways have UHF readers, you can be sure that if something goes into the clean room, it hasn't left there without being noticed. It is always difficult to install and maintain equipment in clean rooms, so it is good to think about alternatives to avoid this.

Implementing the RTLS, which monitors all assets, the production process can bring cost savings by providing faster processes, less effort, less inventory, improved quality, and usually eliminates or reduces manual labor in processes. The RTLS investment is part of the business strategy and is therefore a strategic investment in nature. RTLS can be used in process innovation, this innovation can support the redesign of business and production processes. Cost-benefit analysis is an important part of the investment evaluation process because RTLS implementation into production processes and system deployment is not a technological decision but a business decision. Many factors have an impact on the costs and benefits of RTLS implementation. The site needs to comprehensively understand the factors related to production and business benefits to measure the value of RFID investment. Evaluating the benefits is challenging compared to evaluating the costs of implementing the system. For this reason, the management must have an estimate of the possible benefits before the final decision. It is also possible to carry out smaller-scale experiments on the functionality of the system in order to find out the benefits. However, this brings more costs and the final benefit will only be revealed in full-scale implementation. [50]

6.3 Production departments’ EMS views

One of the biggest problems at the moment was the departments' awareness of their own circumstances. The departments have visibility to the particle samples but almost not at all to the data collected by EMS. If departments need to take more responsibility for their own production conditions, access to the EMS system should be arranged for them. In the beginning, this could be simply viewing rights to the system, but in the future, the information and functionality of the EMS system could be divided into so-called sub-facilities. The sub-facilities implementation can be seen in Figure 14

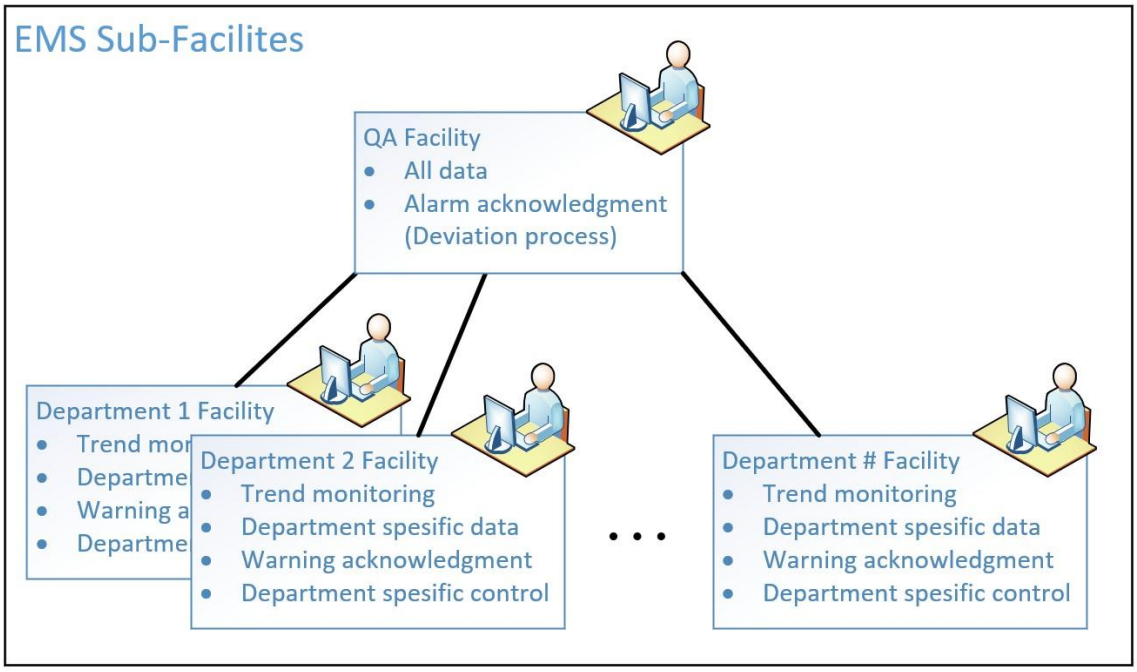

Figure 14 EMS sub-facilities

Each department could therefore have its own user interface, i.e. a separate view for department-specific data and control to some extent. With the help of these sub-facilities, responsibilities, and conditions control measures can be shared. Since the departments would have direct access to the EMS system and, in the best case, only to the department's own data, departments could react to warnings and alarms more quickly and in the right way. With the help of this implementation or just view rights to the EMS, it is also possible to remove the paper process of condition reports. The data is visible in the EMS system and when all relevant parties have access to it, it can be followed without paper trend prints.

For the sub-facilities, each department must create its own user group or groups for this implementation and these groups must then be linked to each Facility. User management and adding a facility require change management from the EMS system. The process of adding department facilities will be facilitated once the facility of one department has been implemented, and its implementation method can be duplicated.

6.4 EMS data integration to the upper-level system

The last use case is the integration of the EMS data into an upper-level system. One example of such a system can be a Data Historian System. This Historian system can also be called a Process Information Management System. These Historian systems

can gather, store and search data in very large quantities simultaneously.[4] EMS in itself is also a Historian system, but in this case, an upper-level Historian system service is needed. This service can be utilized by integrating other systems' data into it. In this way, it is possible to create a place where data from different systems can be used together. In this case, The Historian service works as a data container, and tools can be built around it to better handle the data. Historian, therefore, works as a data processing service on the site. The environment created especially for data processing brings benefits to usability, and part of its benefits also comes from the fact that it does not directly affect the production processes themselves. Production is run by many different technical and computerized systems and when only a copy of the information they collect is transferred to the History service, it can be detached from operational activities. The Historian system platform could also be used to create tools needed for basic analytics of data or interfaces for use cases that require artificial intelligence.

One way to connect systems to this Historian service is an OPC Unified Architecture (OPC-UA) connection. OPC UA is a data transfer standard that has grown in popularity in the industry in recent years. The popularity of the OPC UA protocol in the industry is explained, among other things, by its good quality, scalability, platform independence, and data security. [26] OPC UA is a data transfer protocol intended for industry, which offers a platform-independent and secure way to transfer data between different systems. The OPC UA is developed as a successor to the OPC Classic, aiming to offer similar functionality to Classic OPC, however, expanding the protocol's capabilities to meet modern requirements. Central entities in the OPC UA protocol are data modeling and data transfer methods. In terms of data modeling, the protocol presents the general methods and rules for creating OPC UA data models. The OPC UA standard describes data transfer methods, for example, the data transfer protocols used and the data security features associated with them. [6] EMS and other systems could be connected to the Historian because this way of implementation would not be system or supplier specific but a widely used external standard. Integration of the EMS data to the Historian service can be seen in Figure 15.

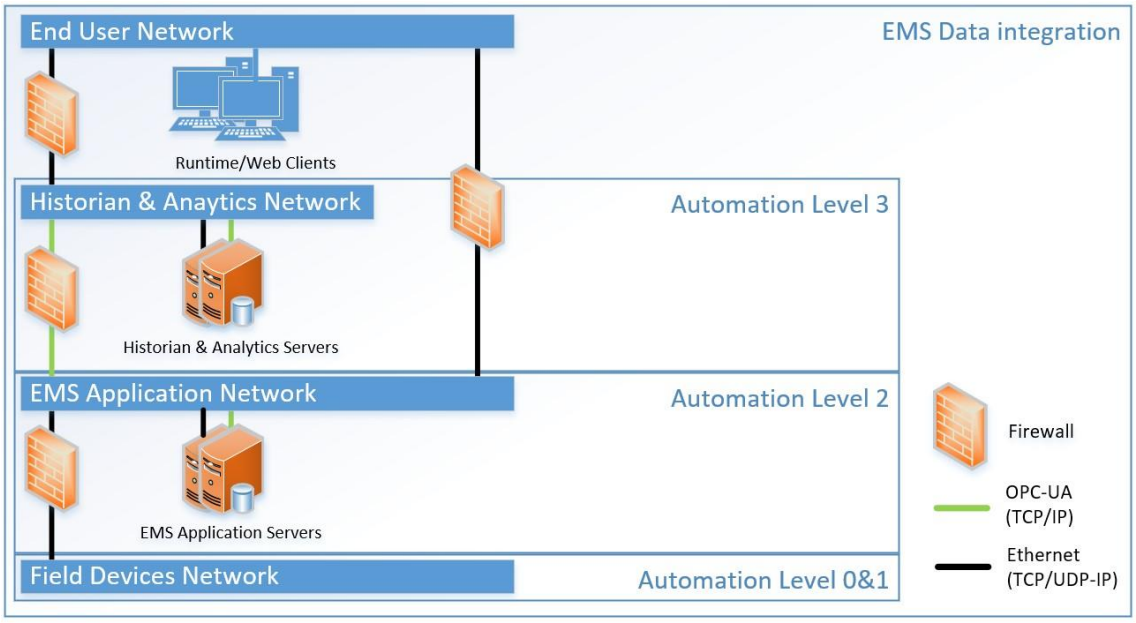

Figure 15 EMS Historian data integration hierarchy

Once the EMS data has been integrated into Historian, it can be used and shared in different departments. The data can be utilized in Management or departments by creating info views from the data. The data is, therefore, easier to view by entities that do not need to participate in EMS operational activities. The flow of data from measurement points and between the EMS and the Historian can be seen in Figure 16.

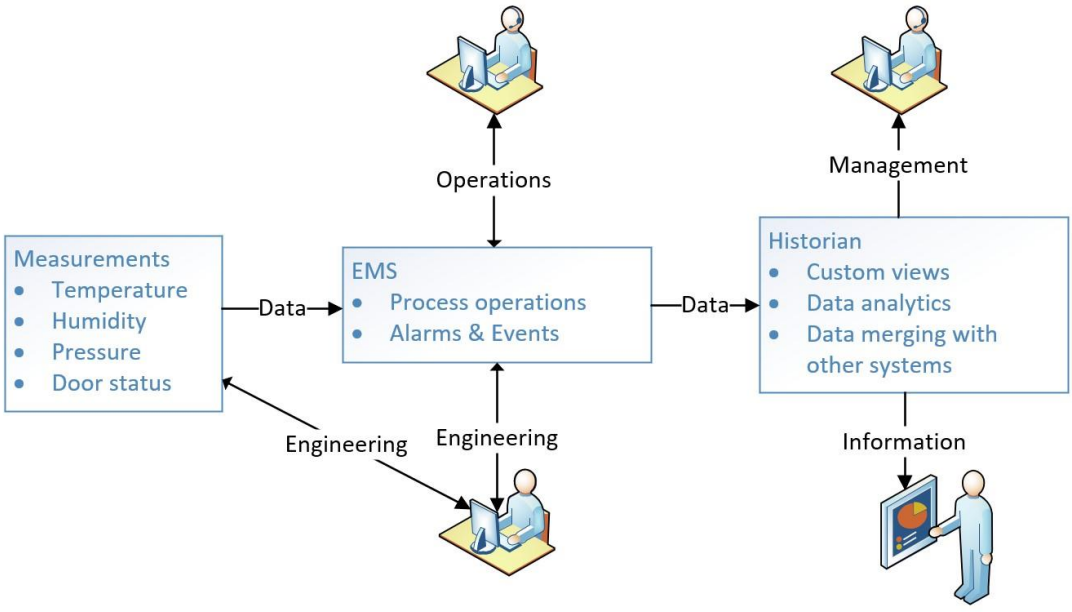

Figure 16 EMS Historian data integration dataflow

The implementation of this will also make it easier to implement different use cases in the future. Finding use cases for the data also becomes easier when departments can see and utilize EMS data in ways that were not possible before.

The utilization of The Historian system can still be expanded in relation to the subject area of this study. Since there is possible to integrate any system data into Historian, systems that are related to environmental data like RTLS data can also be integrated into it. Since environmental conditions have an effect on the quality of the product, there is also a possible need to be able to compare the environmental data with the data of the production batches. The MES system contains information about production batches. All these systems could be connected to the Historian and their data could be utilized by merging them.

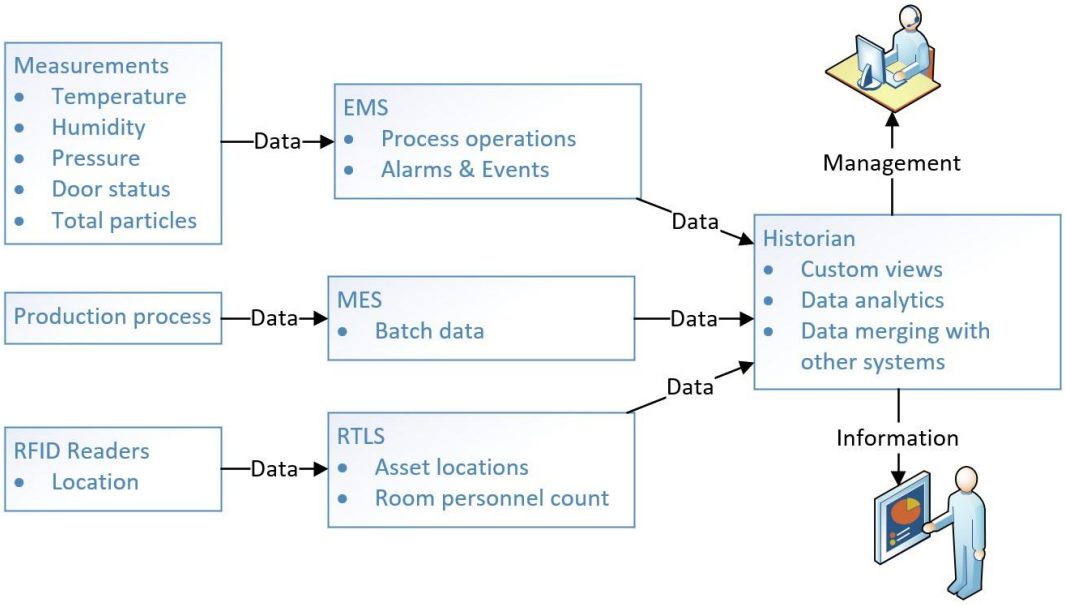

Figure 17 Historian data integrations dataflow

When all these systems are connected to the Historian service, there are immediately more use cases for utilizing the data. This also solves the key point raised in the interviews regarding batch approval of QC departments. Now QC can view condition information related to a batch. The Historian can find out where the batch has been and when from the MES batch data. EMS, on the other hand, knows the environmental conditions in the ward at every moment of time, so this information can be compared.

QC can search for a lot by lot number and the Historian can immediately display all relevant information about the lot. This makes it easier for all departments to understand production events better. The Historian can also perform this search in the other direction, i.e. the department's room information can be searched by room number and the Historian will search for all the information linked to this room. In this case, the data is pressure, humidity, temperature, particles, number of people, batch data, warnings, and alarms. For example, an information view can be created from this information, which can be published in departments on screens installed in rooms. You can see an example of this information view in Figure 18.

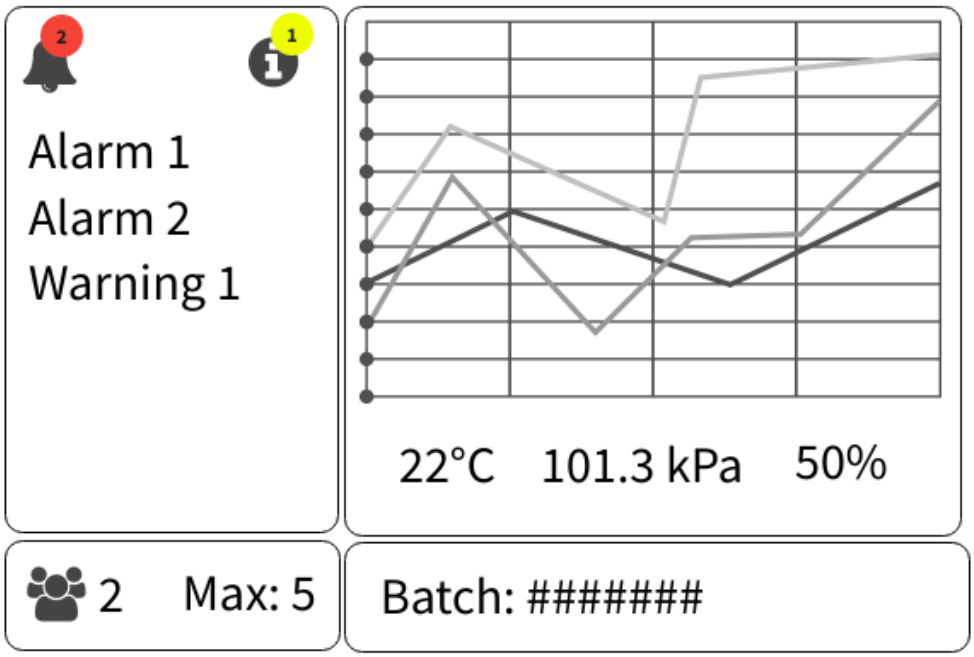

Figure 18 Historian room information screen

The information in the information view can be modified according to the needs of the departments and according to what is seen as useful.

Historian service use cases increase the value of implementing RTLS and real-time particle measurement in production processes, which are the previously presented use cases. This also solves the problem of process siloing, because rights to the Historian service can be given to all departments. There they can view all the data that is collected there. There is no need to restrict the right to view because the information being visible to everyone only makes the operation more efficient. Users could even make their own views of the data and in this way develop new use cases.

7. DISCUSSION

The utilization of data in the manufacturing industry is a very widely discussed and researched topic, but it has not been studied much in the case of the pharmaceutical industry. The pharmaceutical industry has its own differences from many other manufacturing industries, which is why the usages of data in this area are also different. The requirements of the pharmaceutical industry require manufacturers to monitor their processes closely and document everything related to the manufacture of the product. Because of this, the thesis dives deeply into the requirements of environmental monitoring. It is imperative to understand the requirements of the industry, they create an important framework and understanding of the area for the thesis. Working in the pharmaceutical industry requires a broad understanding of one's own area of work. The requirements of the industry impose certain responsibilities on us in our work.

This thesis allowed me to expand my awareness of the different aspects of environmental control and all the issues that affect the factory's operations in terms of the environment. I was also able to develop my own expertise in the development and design of technical systems. The companies in this industry are very particular about what information is available about them. Because of this, the approach to technical solutions of the research remains at a universal level in this thesis.

Before starting this thesis, I already had work experience for a year and a half in the field of the pharmaceutical industry and thereby learned a bit about this specific field. My work at the moment has revolved a lot around building automation and environmental monitoring. When planning the interviews, I decided to take the approach in this work from the point of view that I do not use the knowledge that I already had about the current situation of environmental monitoring, but wanted to find the same points that I had already noticed and new ones. It was interesting to find the same development targets and shortcomings from people that I have not talked to before about the site's environmental monitoring programme.

In my opinion, this thesis brought out a part of the current situation regarding the utilization of data in pharmaceutical manufacturing. During my working career, I have already noticed the impact of the digitization trend on companies and how companies develop ways to utilize the information they collect. Data utilization and analytics are still in the

early stages in many companies and this will be a future trend for a long time to come. Studies like this thesis are constantly developing the idea of the value of data and how much investment is required to utilize its value. It often requires a lot more resources in the beginning, but it will pay off in the long run. While researching the subject area, I did not find similar studies on the subject that I could use in my thesis to reflect on and compare the findings. This is clearly an emerging subject area that has not been studied much yet. It is therefore difficult to say based on this study whether these findings can be generalized and whether this gives the correct view of things.

8. CONCLUSIONS

In this thesis, it was found out how the data of the pharmaceutical manufacturing environment can be used better at the site that participated, and this was found out with the personnel interviews. Through the interviews, it was possible to find out the current situation of the environmental programme at the site, and with that, it was found out how environmental information could be utilized better. This included possible areas of improvement in the existing programme and whether the environmental information was missing something essential. Based on the interviews, there are points for improvement at the site regarding their environmental data collection and its utilization. There were also areas where data is not collected from the production environment which could provide more value for the site. With the help of the interviews, technical solutions were designed for the needs of the site. The research was successful in this respect.

This thesis also showed that communication and identifying the value of data are one of the challenges with manufacturing data and data analytics. it is important to recognize the value and benefits of information as well as potential users to create a data-based business. Creating value is possible by processing data and the processing requires analytics, tools, and expertise. In the production processes, it is important to measure the productivity and value of data as part of processes. The manufacturing industry ecosystem is complex and there can be multiple parties that can benefit from the value of data. [52]

This site still has to develop and search for ways to utilize the environmental data that is gathered from the production. The possible implementation of the findings of this thesis may still take some time because, in the pharmaceutical industry, the development of technical systems and different processes takes time due to precise planning and validation. During this process, things have already started to develop in the right direction, and digitalization and leadership with data have been a goal at the site for some time.

It would have brought more information for this study if the same interviews could have been conducted with several manufacturers of pharmaceutical products and sites. This would have given a broader understanding of how the pharmaceutical industry current-

ly utilizes and collects environmental information about production. Also thinking about the future, it would be good to research how the information collected from the environment could be analyzed and that way find out new use cases for the data.

REFERENCES

[1] American Chemical Society, “Emergence of Pharmaceutical Science and Industry: 1870-1930.”, (accessed July 7. 2022), pubsapp.acs.org/cen/coverstory/83/8325/8325emergence.html.

[2] Arden, N. Sarah, et al. “Industry 4.0 for Pharmaceutical Manufacturing: Preparing for the Smart Factories of the Future.” International Journal of Pharmaceutics, vol. 602, 2021, pp. 120554–120554, https://doi.org/10.1016/j.ijpharm.2021.120554.

[3] Bennett, Bill, and Graham Cole. Pharmaceutical Production: An Engineering Guide. IChemE, 2003.

[4] Cruz, Márcio Freire, et al. “Using OPC and HL7 Standards to Incorporate an Industrial Big Data Historian in a Health IT Environment.” Journal of Medical Systems, vol. 42, no. 7, 2018, pp. 122–11, https://doi.org/10.1007/s10916-018-0979-5.

[5] CSols Inc,” The Origins of Computer System Validation.”, (accessed June 25. 2022), https://www.csolsinc.com/blog/the-origins-of-computer-system-validation/.

[6] Damm, Matthias, et al. OPC Unified Architecture. 1. Aufl., Springer-Verlag, 2009, https://doi.org/10.1007/978-3-540-68899-0.

[7] Durivage, Mark Allen. The Certified Pharmaceutical GMP Professional Handbook. Edited by Mark Allen Durivage, Second edition., ASQ Quality Press, 2016.

[8] EMEA,” Good manufacturing practice.”, (accessed June 2. 2022), https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice.

[9] EMEA, “About us”, (accessed July 11. 2022), https://www.ema.europa.eu/en/about-us.

[10] EMEA, “Human regulatory - Compliance: Overview.”, (accessed July 11. 2022), https://www.ema.europa.eu/en/human-regulatory/overview/compliance-overview.

[11] European Commission, “EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines”., (accessed June 19. 2022), https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-4_en.

[12] Farooqui, Ashfaq, et al. “Towards Data-Driven Approaches in Manufacturing: An Architecture to Collect Sequences of Operations.” International Journal of Production Research, vol. 58, no. 16, 2020, pp. 4947–63, https://doi.org/10.1080/00207543.2020.1735660.

[13] FDA, “Data Integrity and Compliance With CGMP Guidance for Industry.”, (accessed June 26, 2022), https://www.fda.gov/files/drugs/published/Data-Integrity-and-Compliance-With-Current-Good-Manufacturing-Practice-Guidance-for-Industry.pdf.

[14] FDA, “FDA History.”, (accessed July 11. 2022), https://www.fda.gov/about-fda/fda-history.

[15] FDA, “What We Do.”, (accessed July 11. 2022), https://www.fda.gov/about-fda/what-we-do.

[16] Fedotov A. “FDA and EU GMP Annex 1 Differences in Cleanroom Specifications. Is it time to eliminate them?” Regulatory Focus. July 2019. Regulatory Affairs Professionals Society, (accessed October 8. 2022), https://www.raps.org/news-and-articles/news-articles/2019/7/fda-and-eu-gmp-annex-1-differences-in-cleanroom-sp.

[17] Fimea, “About us.”, (accessed July 11. 2022), https://www.fimea.fi/web/en/about_us.

[18] Fimea, “What’s new - Fimea started its operations 10 years ago.”, (accessed July 11. 2022), https://www.fimea.fi/web/en/-/fimea-started-its-operations-10-years-ago.

[19] Finnish Standards Association SFS. “Enterprise-control system integration – Part 1: Models and terminology (IEC 62264-1:2013)”. 2016.

[20] Gad, Shayne C. Pharmaceutical Manufacturing Handbook Production and Processes. Wiley-Interscience, 2008.

[21] Galletta, Anne, and William E. Cross. Mastering the Semi-Structured Interview and Beyond: From Research Design to Analysis and Publication. NYU Press, 2013.

[22] Gouveia, Bruno G., et al. “Good Manufacturing Practices for Medicinal Products for Human Use.” Journal of Pharmacy & Bioallied Science, vol. 7, no. 2, Medknow Publications and Media Pvt. Ltd, 2015, pp. 87–96, https://doi.org/10.4103/0975-7406.154424.

[23] Groggert, S., et al. “Status Quo and Future Potential of Manufacturing Data Analytics - An Empirical Study.” 2017 IEEE INTERNATIONAL CONFERENCE ON INDUSTRIAL ENGINEERING AND ENGINEERING MANAGEMENT (IEEM), vol. 2017-, IEEE, 2017, pp. 779–83, https://doi.org/10.1109/IEEM.2017.8289997.

[24] Haddud, Abubaker, et al. “Manufacturing Control, Asset Tracking, and Asset Maintenance: Assessing the Impact of RFID Technology Adoption.” Journal of International Technology and Information Management, vol. 24, no. 2, 2015, p. 35–.

[25] Hammond, John. “Four Generations of Quality—GxP Pharmaceutical Quality Assurance, an Alternative Track?” Spectroscopy Europe (2021): 29–. https://doi.org/10.1255/sew.2021.a28.

[26] Hannelius, T., et al. “Roadmap to Adopting OPC UA.” 2008 6th IEEE International Conference on Industrial Informatics, IEEE, 2008, pp. 756–61, https://doi.org/10.1109/INDIN.2008.4618203.

[27] Holbrook, Daniel. “Controlling Contamination: The Origins of Clean Room Technology.” History and Technology, vol. 25, no. 3, 2009, pp. 173–91, https://doi.org/10.1080/07341510903083203.

[28] Hole, Glenn, et al. “Digitalization in Pharmaceutical Industry: What to Focus on Under the Digital Implementation Process?” International Journal of Pharmaceutics: X, vol. 3, 2021, pp. 100095–100095, https://doi.org/10.1016/j.ijpx.2021.100095.

[29] ISPE, “Understanding Cleanliness Classifications for Life Science Facilities”, (accessed July 28. 2022). https://ispe.org/pharmaceutical-engineering/march-april-2017/understanding-cleanliness-classifications-life-science

[30] ISPE, “What is GMP?”, (accessed June 2. 2022). https://ispe.org/initiatives/regulatory-resources/gmp/what-is-gmp

[31] Jain, N. (2021). Survey versus interviews: Comparing data collection tools for exploratory research. Qualitative Report, 26(2), 541–554. https://doi.org/10.46743/2160-3715/2021.4492.

[32] Krishnan, Sivanand, and Rochelle Xenia Mendoza Santos. “Real-Time Asset Tracking for Smart Manufacturing.” Implementing Industry 4.0, vol. 202, Springer International Publishing, 2021, pp. 25–53, https://doi.org/10.1007/978-3-030-67270-6_2.

[33] Koski, Karoliina. Characterization and Design Methodologies for Wearable Passive UHF RFID Tag Antennas for Wireless Body-Centric Systems. Tampere University of Technology, 2015.

[34] Laheurte, Jean-Marc, and Jean-Marc Laheurte. UHF RFID Technologies for Identification and Traceability. 1st edition, ISTE, 2014.

[35] Leveson, N. .., and C. .. Turner. “An Investigation of the Therac-25 Accidents.” Computer (Long Beach, Calif.), vol. 26, no. 7, IEEE, 1993, pp. 18–41, https://doi.org/10.1109/MC.1993.274940.

[36] McGuire, J.L., Hasskarl, H., Bode, G., Klingmann, I. and Zahn, M. (2007). Pharmaceuticals, General Survey. In Ullmann's Encyclopedia of Industrial Chemistry, (Ed.), https://doi.org/10.1002/14356007.a19_273.pub2.

[37] Mohammad, Abdul Saleem, et al. “An Overview of Validation and Basic Concepts of Process Validation: Quality Assurance View Point.” Asian Journal of Pharmacy and Technology, vol. 6, no. 3, 2016, p. 169–, https://doi.org/10.5958/2231-5713.2016.00024.6.

[38] Nagy, Brigitta, et al. “Application of Artificial Neural Networks in the Process Analytical Technology of Pharmaceutical Manufacturing—a Review.” The AAPS Journal, vol. 24, no. 4, 2022, pp. 74–74, https://doi.org/10.1208/s12248-022-00706-0.

[39] Ongena, Y. P., & Dijkstra, W. (2021). Advances in research on survey interview interaction. International Journal of Social Research Methodology, 24(2), 177–179. https://doi.org/10.1080/13645579.2020.1824625.

[40] "Pharmaceuticals Global Market Report 2022." Financial Services Monitor Worldwide, 5 Mar. 2022, p. NA. Gale General OneFile, link.gale.com/apps/doc/A695753646/ITOF?u=tampere&sid=bookmark ITOF&xid=4d4f533a. Accessed 22 Sept. 2022.

[41] Raul, Saroj Kumar, et al. "An Overview of Concept of Pharmaceutical Validation." *Research Journal of Pharmacy and Technology*, vol. 7, no. 9, A & V Publications, 2014, pp. 1081–90.

[42] Rodríguez Pérez, José, and Josâe Rodrâiguez Pâerez. The FDA and Worldwide Current Good Manufacturing Practices and Quality System Requirements Guidebook for Finished Pharmaceuticals. ASQ Quality Press, 2014.

[43] Rägo, Lembit, and Budiono Santoso. "Drug Regulation: History, Present and Future." Drug Benefits and Risks: International Textbook of Clinical Pharmacology, 2008, pp. 65–77. https://www.researchgate.net/publication/265533479_Drug_Regulation_History_Present_and_Future_1.

[44] Sandle, Tim. "Best Practices In Environmental Monitoring.", (accessed August 2. 2022). https://www.researchgate.net/publication/342883006_Best_practices_in_environmental_monitoring.

[45] Segschneider, V., et al. "Validation of Computerized Systems– a Risk Based Modular Approach." Cytotherapy (Oxford, England), vol. 20, no. 5, 2018, pp. S71–S72, https://doi.org/10.1016/j.jcyt.2018.02.202.

[46] Semmar, Atae, et al. "Modeling Input Data of Control System of a Mining Production Unit Based on ISA-95 Approach." Communications in Computer and Information Science, vol. 1207, Springer International Publishing, 2020, pp. 47–55, https://doi.org/10.1007/978-3-030-45183-7_4.

[47] Sharma, Shalini, et al. "A Review on Pharmaceutical Validation and Its Implications." Indian Journal of Pharmaceutical and Biological Research, vol. 1, no. 3, 2013, pp. 100–04, https://doi.org/10.30750/ijpbr.1.3.14.

[48] Tripathy, Soumesh Kumar. "Pharmaceutical Validation: A Quality Maintaining Tool for Pharmaceutical Industry." Asian Journal of Pharmaceutical Research, vol. 10, no. 4, 2020, pp. 307–11, https://doi.org/10.5958/2231-5691.2020.00052.0.

[49] Ungermann, Florian, et al. "Data Analytics for Manufacturing Systems – A Data-Driven Approach for Process Optimization." 52ND CIRP CONFERENCE ON MANUFACTURING SYSTEMS (CMS), vol. 81, 2019, pp. 369–74, https://doi.org/10.1016/j.procir.2019.03.064.

[50] Ustundag, Alp. The Value of RFID Benefits Vs. Costs. Edited by Alp. Ustundag, 1st ed. 2013., Springer London, 2013, https://doi.org/10.1007/978-1-4471-4345-1.

[51] US Department of Health and Human Services, "Guidance for industry, sterile drug products produced by aseptic processing-current good manufacturing practice.", (accessed July 28. 2022) https://www.fda.gov/media/71026/download

[52] Uusitalo, Teuvo, et al. “Real Value of Data in Managing Manufacturing Assets.” 14th WCEAM Proceedings, Springer International Publishing, 2020, pp. 164–74, https://doi.org/10.1007/978-3-030-64228-0_15.

[53] Wang, John X. Lean Manufacturing : Business Bottom-Line Based. Taylor & Francis, 2011, https://doi.org/10.1201/9781420086034.

[54] Wingate, Guy. Pharmaceutical Computer Systems Validation: Quality Assurance, Risk Management and Regulatory Compliance. 2nd ed., Informa Healthcare, 2010, https://doi.org/10.3109/9781420088953.

APPENDIX A: SAMPLING INTERVALS

Test	Product	A	B (A background)	B	C	D	E
Total airborne particles	Terminally sterilized drug forms and API's when unusually at risk	Throughout the full filling operation incl. equipment assembly	Every shift	Once a week	Once a month	Every 6 months	
	Terminally sterilized drug forms and API's				Once a month	Every 6 months	
	Processing of nonsterile drug forms and APIs					Every 6 months	Only performed according to country specific provisions if required
Active air sampling	Terminally sterilized drug forms and APIs				Once a week (twice if background for A)	Once a month	Once a quarter of year
	Processing of non-sterile drug forms and APIs					Once a month	Once a quarter of year
Passive air sampling	Terminally sterilized drug forms and APIs				Once a week (twice if background for A)	Once a month	Once a quarter of year
	Processing of non-sterile drug forms and APIs					Once a month	Once a quarter of year
Surfaces	Terminally sterilized drug forms and APIs				Once a week (twice if background for A)	Once a month	Once a quarter of year
	Processing of non-sterile drug forms and APIs					Once a month	Once a quarter of year
Personnel	Terminally sterilized drug forms and APIs	Once a week					

Figure 19 Minimum requirements for sampling intervals