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SEINÄJOKI UNIVERSITY OF APPLIED SCIENCES

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Gun Wirtanen, Leila Kakko,
Minna Karvonen & Silja Saarikoski (eds.)

Proceedings of the 51st Symposium on Cleanroom Technology and Contamination Control

Publications of Seinäjoki University of
Applied Sciences B. Reports 174

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INTRODUCTION

Food Safety and Food Technology is one of the strategic focus areas at Seinäjoki University of Applied Sciences. This combined with expertise in Professional Cleaning and Hygiene research at Tampere University of Applied Sciences forms activities in good and vivid cleanroom studies. The Research, Development, and Innovation (RDI) activities at these both Universities of Applied Sciences as well as at Turku University of Applied Sciences will enable the stakeholders to enjoy improved services in the area. The knowledge presented in the sessions by the speakers, at the exhibition by the represented companies and in panel discussions by all attendees will improve the outcome of the event.

The R^3Nordic association, which is a NGO is arranging the event, wants to inspire cooperation in cleanroom and contamination control.

The Proceedings of the 51st Symposium on Cleanroom Technology and Contamination Control provides useful insights in the event's focus areas. Besides speakers from the four Nordic counties (Denmark, Finland, Norway, and Sweden) there are knowledgeable speakers from Belgium, France, Germany, Ireland, Luxembourg, the Netherlands, Spain, Switzerland, and United Kingdom.

In the exhibition, there are in total twenty-four exhibitors. The exhibition allows the participants to discuss practical solutions needed in updated process schemes either publicly or in privacy during the breaks. This publication seeks to disseminate RDI knowledge and expand the dialogue on sustainable solutions in cleanroom technology and contamination control.

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PREFACE: RDI ACTIVITIES IN CLEANROOM TECHNOLOGY AND CONTAMINATION CONTROL AT THE 51ST R3NORDIC SYMPOSIUM 2022

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The sessions in this cleanroom and contamination control symposium deal with cleanroom technology in the pharmaceutical environment, hospital wards and health care as well as food processing and hospitality management. Each of these themes are approached based on RDI activities and new sustainable solutions in the areas covered. The aim is to generate RDI activities, which can generate innovations promoting both well-being for stakeholders and cooperation between the university and industrial actors. These articles provide insights in RDI activities carried out mainly in the Nordic countries with enlarged influence from European colleagues and in a global cooperation environment.

Hospitality Management in contamination control is mainly considered as surface hygiene and cleaning. The importance of cleaning has been more obvious during COVID-19 pandemic disease. All countries have updated cleaning instructions and they are mainly based on WHO instructions. In Finland, the Finnish Institute of Occupational Health (FIOH) has published guidelines regarding cleaning for preventing COVID-19 infections and they can be applied in general cleaning to prevent the spread of communicable diseases and protect cleaning staff from infections. The guidelines of the FIOH are drawn up together with the Ministry of Social Affairs and Health (Sosiaali- ja terveysministeriö = STM) and the Finnish Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos = THL). We also follow the publications of the European Centre for Disease Prevention and Control (ECDC) and the

World Health Organization (WHO). In Europe Germany and England has developed National guidelines. For Germany it is a new guideline published as a standard (DIN 13063), for England it is an update of the previous guideline. Both recommendations were published in 2021 and describe i.a. the requirements for hospital cleaning, how compliance with the requirements can be demonstrated and the distribution of responsibilities between cleaning and nursing staff. Finnish standard SFS 5967 determines cleanroom cleaning as a cleaning carried out in a room with a standardized level of cleanliness and cleaning as cleaning, protection, and care of surfaces, as well as various arrangement work in which cleanliness is produced professionally indoors. Cleaning is dealt with this Symposium on Wednesday afternoon programme.

In food manufacturing the process hygiene is important. This task is dealt with through risk management in which both external and internal risks are included. This issue is regulated through the European food safety laws, e.g., EC regulations no. 178/2002 on food safety matters, no. 852/2004 on the hygiene of foodstuffs and 2021/382 on food allergen management, as well national food laws e.g., the Finnish food act 297/2021 and food safety decree 318/2021. The risk analysis is based on risk assessment, risk management, and risk communication. In the programme, the focus is on hygienic design, on surfaces used in food and biotech including pharma environments. The growth of microbes as biofilms can be counteracted through proper cleaning procedures, hygienic design of equipment and motivated workers, who know what to do and who work according to good production rules. In the 1-day food & biotech session, the focus is on sustainability in designing, and building processes, on hygienic quality of food contact surfaces in RDI and in practice, on surface hygiene in small hospitality entities as well as waste-minimizing cleaning techniques in cleanrooms. Proper hand and clothing hygiene is of utmost importance in the food processing and services, e.g., cleaning and maintenance, in the food industry.

The importance of hygiene is obvious in hospital areas. The biggest Cleaning Fair, which is held in Amsterdam every second year, has a side programme The Healthcare Cleaning Forum. This spring the forum focused on the importance of cleaning in the fight against healthcare-associated infections. According to current estimates, 50–70% of

healthcare-associated infections originate from contaminated hands. There is no exact information about what causes the remaining 30-50%, but the proportion of surfaces is estimated at 20 –40%. The conclusion of the forum was expected: more high-quality research is needed. But in the meantime, a lot can be done, such as careful cleaning of surfaces, measuring the quality of result obtained and, if necessary, changing working methods. Thus, one part is the high-quality research presented at this Symposium.

Assadian et al. (2021) compiled a review focusing on routine environmental cleaning and disinfection including areas with a moderate risk of contamination, such as general wards. The review provides expert guidance for healthcare workers in their daily practice. There are some studies about different wipes and wiping techniques one example of that is Boyce (2021). S. J. Dancer has published several articles concerning hospital hygiene and one example is Dancer and Kramer (2018). This topic is dealt with in the 2-day hospital session with eleven presentations, some presentations is in news as well as the keynote presentations of Associate Professor Veli Jukka Anttila from HUS and Industry Professor Piia Sormunen from University of Tampere. And at last, but not at least the 2-day pharma session, which is dealing with many aspects good manufacturing practice (GMP) given in the draft documents on manufacture of sterile medicinal products (Annex 1 Draft 2020). In this session there are also presentations focusing on facility design and contamination control strategies.

The expert editors, Gun Wirtanen and Leila Kakko, are senior actors in hygienic design, cleanroom technology and contamination control in both food safety and hospitality management. The authors of the articles are cleanroom technology experts, who are working with RDI activities in both universities and industry. Leila Kakko has been part of research and development projects mainly in Finland in a focus area of indoor environment and surface hygiene. The latest project was "The development of surface hygiene in a changing epidemic situation" In hospital hygiene one project to combine indoor environment and hygiene was "the hospital wards surface cleanliness while cleaning of the ventilation systems". Gun Wirtanen has in her RDI studies focused on surface hygiene, i.e., biofilm formation and its elimination

in food processing. This includes aspects of cleaning, disinfection, and hygienic design. Gun Wirtanen has also been involved in hospital hygiene studies. We, all editors would like to extend our warm thanks to all the authors for their valuable contribution to this publication. The R^3Nordic symposium is an annually occurring Nordic event, which has been on hold for two years due to the COVID-19 pandemic. With this event's Proceedings based on presentations given at Naantali Spa on 30th–31st of August 2022 we seek to inspire and challenge the Nordic cleanroom society to continue to work with sustainable RDI solutions. We hope you will enjoy the reading of the articles in this publication.

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I

KEYNOTE

OPERATION ROOM VENTILATION AND RISK OF POSTOPERATIVE INFECTIONS

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1 INTRODUCTION

Postoperative infections, especially wound infections are major problems after surgery. There are several factors, which can affect to the risk of wound infections. Some of these factors are related to patient itself, like diabetes, smoking or weight. Some factors associated wound infections are preoperative, i.e., related to the situation what happens in operation room during operation. Many of these risk factors depends on preventive measures performed by operation room personnel, some are dependent on the environmental circumstance of the operation room. The knowledge about operation room ventilation and the risk of wound infections is scarce.

2 VENTILATION SYSTEM: LAMINAR OR NOT

There are very few controlled studies which have focused to operation room air and the risk of wound infections. One older study showed that laminar air ventilation of the operation room was associated with the lower risk of wound infections after total hip or knee replacement when compared to the conventional ventilation system. However, register studies published in this century could not confirm these previous findings. Some years ago (2016), WHO expert panel published a conditional recommendation about this question: Laminar airflow ventilation systems should not be used

for patients undergoing total arthroplasty surgery. In fact, the benefit of laminar air flow ventilation in the operation room after prosthetic joint surgery is still open. In other types of surgery, there are no studies focused on this question.

3 PROBLEMS OF THE OPERATION ROOM VENTILATION: WHAT IS KNOWN

There are several patient series and case reports, which have indicated that problems in the operation room ventilation system can lead to postoperative infection problems of patients. Usually in such cases the microbe detected was atypical for the wound infections. Some recently noticed mycobacterial infection problems after open heart surgery have indirect consequences to the operation room air environment.

4 COVID-19 AND OPERATION ROOM VENTILATION

COVID-19 pandemic has increased our knowledge how some respiratory infections can spread from one patient to another, or from patient to health care personnel or from personnel to patient. SARS-CoV-2 virus is transmissible by air, either by droplets or by aerosols. Because many procedures in the operation room can be classified as an aerosol generating procedures, it is obvious, that preventive measures against airborne infections are needed, when COVID-19 patient will be operated. Ventilation system of the operating room should act adequately. The personnel in the operation room should wear adequate personnel protective equipment (PPE) against airborne infections. The open question is that should the operation room be under negative pressure.

5 HOW TO FOLLOW AIR QUALITY IN THE OPERATION ROOM

Some physical measures can be used to detect that the operation room ventilation does work as planned. These can be air pressure, temperature, and humidity monitoring. It is easy to monitor carbon dioxide and air particles. Monitoring of these parameters are not used routinely. Microbe monitoring of operation room air is possible to do periodically. Monitoring of the microbes in the air of operation room is problematic because the microbial methods are time consuming and the result from the sampling will normally last some days to weeks. Better and more rapid systems to follow microbes in the air are needed. International standards focusing on the follow up of operation room air and ventilation system are crucial.

In future, there are need to follow the air quality and ventilation system function continuously or at least periodically. The is also a need to study more the operation room air quality and it's consequences to the risk of postoperative infections. However, it is clear, that operation room air should be clean and dust free.

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PANDEMIC CONTROL STRATEGIES IN SMART BUILDINGS – INDIVIDUAL AND SHARED RESPONSIBILITY

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1 INTRODUCTION

COVID-19 pandemic challenged the world in the understanding of how respiratory infections spread. Social distancing, face masking, and vaccination have all been essential in controlling the pandemic (Chu et al., 2020). At the same time, many studies revealed that airborne transmission plays a significant role in spreading corona pandemics. Since the virus spreads most effectively in confined, densely occupied and inadequately ventilated spaces, the importance of adequate ventilation and air purification has considerably increased. Furthermore, government, corporate tenants and building owners need to plan to prevent infections in buildings. However, indoor air conditions have had too little role in pandemic response discussion and future prevention actions of pandemics. The smart building is one of the critical building service technologies that could anticipate, respond to and improve people's safety and ensure indoor environmental health.

The framework employed in occupational safety and health is needed to understand the relative effectiveness of different risk reduction strategies and help determine how to implement feasible and practical

solutions. For example, the hierarchy of controllers of ventilation solutions to reduce indoor infection risk has been developed in REHVA guidelines (REHVA, 2022) as an upside-down pyramid with four categories represented in descending order of effectiveness: elimination, engineering controls, administrative controls, and personal protective equipment. However, a systematic model is needed to represent the group occupational risk control measures for COVID-19 at the governmental, industry and supervisory levels, as well as interventions targeting individuals. James Reason's Swiss cheese model (Emmentaler cheese model) of accident causation (Reason, 2000) applied to COVID-19 transmission recognizes the additive success of using multiple preventive interventions to reduce the risk of SARS-CoV-2 infection. The Swiss Cheese Model of Pandemic defense states that one single intervention is not perfect for preventing the spread of the disease. It is visualized as multiple stacked cheese slices, each with holes in different locations, and the critical risk happens only when the holes of all the layers line up. Thus, the key to preventing a covid transmission risk is to ensure that multiple failures do not coincide.

Parkkila et al. (2021) presented the model of virus infection risk and factors of virus and epidemic spread in pandemics. In this model the factors were divided in four categories: microbes, host, environment, aerosol, and human behavior. Each of these factors has a significant role in infection risk for respiratory diseases (Parkkila et al. 2021).

This paper presents an adapted Swiss cheese model taking account WHO 3C's and Parkkila et al. model for individual and shared responsibilities in smart buildings to improve the health and safety of building users.

2 INFECTION RISK MANAGEMENT IN SMART BUILDINGS

Using smart building technology, the improved Swiss cheese model (Figure 1) illustrates the layered and multi-dimensional hazard control strategy needed to prevent COVID-19 transmission. The model includes the societal impact on the epidemical situation, where vaccination and testing have a significant role.

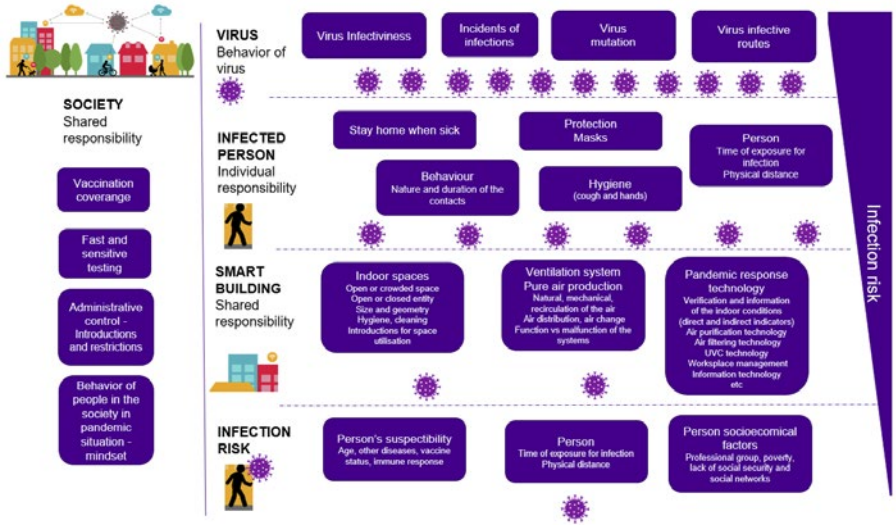

Figure1. Infection risk management in smart buildings.

The nature and behavior of virus transmission are undoubtedly taken of high importance. Then, the individual responsibility of the possibly infected person and the behavioral requirements is essential to prevent the virus spread between individuals. As people return to the office, smart technologies can be applied to ensure a safe indoor environment, for instance, sensors applied to measure workplace occupancy, reservation systems to relocate meetings to larger team spaces as needed, etc. Furthermore, data from indoor measurement sensors can be applied to measure CO_2 level, analyze occupancy, adjust ventilation strategies, and reveal the spaces where air cleaning is required. The pandemic response technologies and pure air production play important role in smart buildings to eliminate viruses in indoor environment. Finally, the factors related to the individual infection risk, such as person susceptibility, time of exposure and in-direct socioeconomic factors which effect on individual infection risk in indoor environment.

3 DISCUSSION AND CONCLUSIONS

Since airborne transmission plays a significant role in the spreading of coronavirus spread, smart buildings will have a significant role in indoor health safety and the mitigation of future pandemics. The further

developed risk management model describes different factors which influence on infection risk in smart buildings. However, more research needs to be done to develop pandemic response technologies and create scientific background to understand different factors' influence on the infection risk. As it can be seen the influence of different factors to infection risk form very difficult multidimensional problem.

The current COVID-19 pandemic has shown the importance of resilience in society and global economics. WHO presented the three Cs model which is an excellent recommendation for improving individual health safety in built environment. The well-known Swiss cheese model in respiratory virus pandemic defense has been presented for individual and shared responsibilities in pandemics. However, smart buildings and indoor air conditions have had too little role in pandemic response discussion and future prevention actions of pandemics. During the COVID-19 more evidence has accumulated confirming that airborne transmission of viruses plays a very important role in the spreading of respiratory diseases. Smart buildings will have a big role in indoor health safety and the mitigation of future pandemics. Here, an infection risk management model in smart buildings adapted from Swiss cheese model for individual and shared responsibilities is presented to accommodate the technique, which has shown that the health and safety of building users can be improved.

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II

PHARMA

CONTAMINATION CONTROL STRATEGY ACCORDING TO THE REVISED EU GMP ANNEX 1 REQUIREMENT

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1 INTRODUCTION

There is a paradigm shift in Good Manufacturing Practices' (GMP) regulations towards more risk based, holistic and proactive methodologies. The revisions of EU GMP Annex 1 and ICHQ9 covering Quality Risk Management (QRM) and introduction of ICH Q12 covering product Life cycle strategies set the scene for this new paradigm. The principles of QRM are fundamental to GMP compliance of the complete (revised) EU GMP Annex 1. Complementary to those principles is Quality by Design (QbD) encouraging designing in contamination controls (technical control measures) with less reliance on human interactions, environmental monitoring data and end-point testing of sterility.

Principles are further extended into practice within Annex 1 with the specific requirement of a Contamination Control Strategy (CCS) required to document the approach taken in contamination control when manufacturing sterile medicinal products, considering organisational, technical, and procedural control measures that together provide collective effectiveness (in other words a holistic perspective). Although there is a specific (part 4) GMP for Advanced Therapeutic Medicinal Products (ATMPs) most regulators consider the scope not adequate and

compliance to EU GMP Annex 1 is also required as a complementary regulatory compliance requirement.

The preparation of a CCS is a major challenge to all stakeholders in sterile product manufacturing as Annex 1 only sets out the requirements at a principal level and informs less on scope, content, and documentation structure. Further the CCS has a new narrative to document the approach taken as a 'complete story' and is not expected just to be a list of existing documents that may lack connection or continuity of the approach to contamination control. One of the challenges are how much detail is required to provide this CCS 'story'. To close this gap and provide guidance on CCS preparation including scope, contents, documentation structure and positioning relative to other key site and regulatory documents the Not-for-Profit organisations/ societies, PHSS-A3P, PDA, ECA that bring together industry subject matter experts, key opinion leaders and GMP ex-regulators have prepared or have guidance in preparation.

The Pharmaceutical and Healthcare Sciences Society (PHSS) in UK and A3P in France have joined forces on CCS preparation guidance. Both were appointed as one of the (12) Annex 1 revision (v12) commenting platforms in the final Targeted Consultation process. Harmonisation was considered essential within the targeted consultation process and group meetings were facilitated as comments were collated. Specific to CCS guidance extended discussions between PHSS-A3P, ECA and PDA followed the intent of harmonisation and ensuring there was no mixed messages.

The presentation at the 51st Annual R^3 Nordic Symposium in Finland, Naantali 2022 focuses on the PHSS-A3P CCS guidance initiative and current thinking. All CCS guidance's provide information on points to consider for preparing a CCS with PHSS-A3P and CCS going a step further by providing a starting point with Templates for CCS structure and contents.

2 EU GMP ANNEX 1 GLOSSARY: DEFINITIONS

''Contamination Control Strategy (CCS)'' – A planned set of controls for microorganisms, pyrogens and particulates, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications, and the associated methods and frequency of monitoring and control''.

Contamination – The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogen), or of foreign particle matter, into or onto a raw material, intermediate, active substance or drug product during production, sampling, packaging or repackaging, storage or transport with the potential to adversely impact product quality.

3 SUMMARY OF PHSS-A3P CCS GUIDANCE: SCOPE AND CONTENT – THE INTENT AND OBJECTIVES OF THE PHSS-A3P CCS GUIDANCE

A Contamination Control Strategy is based on key foundational principles, as described in EU GMP Annex 1 and supported by the other GMP chapters and annexes when applied to manufacture of sterile medicinal products, associated components and advanced therapeutic medical products (ATMPs – complementary to EU GMP for ATMPs – part 4), including;

- Need for a Quality Culture
- Following principles of Quality Risk Management (QRM)
- Having scientific understanding and thorough technical and process knowledge

The Contamination Control Strategy should also include a Governance process that should include the following elements:

- Periodic Review
- Quality Oversight
- Appropriate escalation
- Continuous improvement

The intent of this PHSS-A3P guidance is to provide a structured and practical approach to CCS preparation based on a clear understanding of what a CCS is expected to cover and be documented and why. Guidance is set out as principles to follow supported by CCS document Templates that provide a starting point for CCS preparation. Also, to support translation of guidance into practical preparation CCS case study examples are prepared as appendices with points to consider detailed for each section of the template based on a specific application. These templates and case studies are shared as a resource and reference in preparation of a CCS for specific processes, based on the proviso each process will include specific contamination risks, risk mitigations, and control requirements.

The CCS, in variance to other control strategies, is specific to EU GMP Annex 1 with a focus on documenting the strategy taken in control of contamination in the manufacture of sterile medicinal products and drug products, particularly but not limited to contaminants such as; particulate (e.g., glass and other visible and sub-visible particles) and microbiological contamination including pyrogens and endotoxins and those of and biological origin (prions, mycoplasma, etc.). As stated in EU GMP Annex 1 the CCS should also be considered to document contamination control measures and strategy applied in manufacture of non-sterile products and API/ingredients/ substances that form part of sterile products when bioburden control is required.

Considering this wider scope further consideration may also be given to devices and combination products where sterility or bioburden control may also be required. Although there is a specific EU GMP for ATMPs it is expected requirements of Annex 1 may compliment and provide a more comprehensive Quality Risk Management (QRM) approach, a key principle reinforced in Annex 1.

4 CCS DOCUMENTATION STRUCTURE

The PHSS-A3P do not consider the CCS to be necessarily a single document. Although a single site with limited Areas covering unit operations may be the subject of a CCS in the main a Site Master CCS (single document) is expected together with Area-Unit CCS's (possible multiple CCS's based on different products, unit operations and manufacturing technologies that reference product specific specifications) combine to become the CCS (Figure 1).

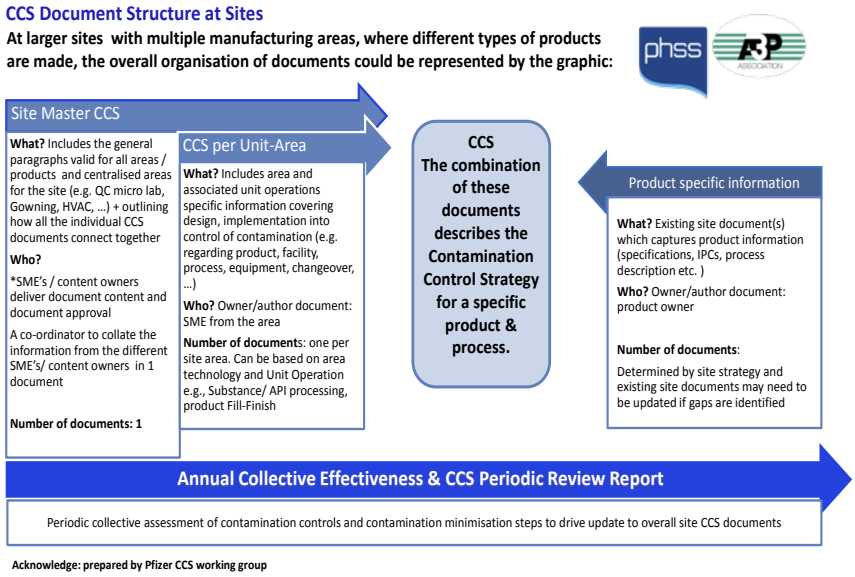

Figure 1. Contamination Control Strategy (CCS) document structure.

4.1 Contents of the CCS

To prepare a content listing for the CCS Templates a review was made to all references in the CCS in Annex 1 version 12 and contents developed based on these references.

4.2 Site Master CCS

As a single document for a site this CCS introduces the products manufactured at the site and manufacturing technologies used. Also, this Master CCS is the main document that links different Area-Unit operations CCS's on the site.

Different Area-Unit CCS's may be supported by centralised services/ facilities e.g., QC microbiological laboratory and although a specific Area-Unit CCS is not expected for such facilities the approach to contamination control in these areas does need to be documented with the Site Master CCS providing that opportunity.

4.2.1 Area-Unit CCS's

Area-Unit CCS's are prepared to a specific manufacturing area and unit operations typically with applied manufacturing technologies so product groups can be processed. Manufacturing technologies may include automation, robots, Isolators, RABS for processing products in different dose forms and/or and Blow fill seal (BFS) systems.

Each process has different and specific contamination control approaches, and these methods and practice needs to be covered in the CCS. The Area-Unit operation will be sited within a facility with contamination controls applied at each material transfer; from warehouse-supply to point of use and each operator gowning change at GMP area grade changes. The methods and practices applied at contamination control for personnel and materials should be covered in the CCS. Each area and unit operation may be supported by utilities that have measures of contamination control, applied and these measures should also be documented in the CCS.

4.2.2 Product specific information

It is not necessary to detail all the product specific specifications in the CCS but the product group and main characteristics that could impact contamination control measures should be included in the CCS e.g., Pharmaceutical, biological or ATMP product profiles.

4.2.3 Quality oversight

Together with the Technical and procedural control measures the CCS should cover the Quality oversight, connection to Pharmaceutical Quality System (PQS) and monitoring of performance together with a collective efficacy check of control measures.

5 IN CONCLUSION

The requirement for a Contamination Control Strategy (CSS) is clear in Annex 1 (included in every draft revision) and preparation should begin before Annex 1 is published as the expectation is it will be one of the early required documents by GMP inspectors and auditors as it sets out a firms/ companies approach to contamination control with control measures that are (and should be) justified. The preparation of a CCS by default will initiate a requirement for a GAP analysis and that will be the initial challenge to all stakeholders.

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Editors' comment:
The final version of Annex 1 in Manufacture of Sterile Medicinal Products (https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf) has been published in week 34 (2022). This document provides technical guidance on the principles and guidelines of good manufacturing practice (GMP) for medicinal products. The deadline for Annex 1 coming into operation is August 25, 2023, except for point 8.123, which is dealing with the frequency of lyophilizers' sterilisation and which deadline is August 25, 2024.

MAIN DELIVERABLES AND TOOLS IN SUCCESSFUL COMMUNICATION WITHIN FACILITY PROJECTS

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1 INTRODUCTION

Engineering is largely communication. Pharmaceutical facility investment projects from concepting, planning, detailed design, construction phases all the way to start-up can be complex and challenging task. The success of the project is dependent on several factors, but the key to success is in information exchange. The role of the communication has been emphasized during the global pandemic. Efficient communication process combined with relevant deliverables, communication tools, engineering and quality reviews safeguards facilities through their lifecycle and ensures proactive compliance with GMP, health authority expectations and industry best practices.

The presentation is based on the customers experience and perspective in the large pharmaceutical CAPEX project. This project execution model is based on the engineering service contract with the external engineering contractor. The presentation shares first-hand experiences of good practices, deliverables as well as lessons learned from helpful project tools like software platform for information exchange.

2 PROJECT REQUIREMENTS

Risk-based approach to facility design, commissioning and qualification starts from properly executed risk assessments:

- Preliminary project level risk assessments: Good Manufacturing Practices (GMP) & Health and Safety Executive (HSE)
- Detailed risk assessments
- Environmental monitoring locations etc.
- Process / product risks assessment leading to system specific risk assessments that finally serve the C&Q testing scope of the project; e.g., traceability from requirements to risks and all the way to verification testing.

Similarly, user requirements of the project can be roughly categorized to three categories:

- Project Requirement Specification (PRS) – What?
- Project Requirement Specification (PFS) – How?
- System Specific User Requirements (URSs) – What exactly?

Fundamental part of any investment project after approved business case is to start developing Project level Requirements Specification (PRS). It should provide the answer to a question: "What we want?", what is the purpose, target, key performance indicators of the project - How we measure the success of the project? By defining these project level requirements customer is able communicate to selected contractor the basic information needed for successful conceptual design. This basic information must be communicated through the project organization so that it is understood same way from managerial level to the individual project team member and designer level. Project Requirement Specification is not only a document; it is single source of basic information and collection of fundamental definitions like scope, battery limits, responsibilities, HSE and GMP requirements including most important reference documents and engineering standards. It provides the description of technical environment of the project and collects design relevant information of process and product.

Pitfall of any user requirement is that it is only considered to be a "paper" that just needs to exist. Far more important is to communicate the requirements and help contractor to understand the requirements before the actual design work is even started. Numerous of engineering

hours can be wasted to wrong things if there is not common understanding of design basis. Contractors and designers have a natural tendency to design a same facility again and again, because it is safe, easy, and standardized way of working. But as a customer, take your responsibility to communicate your specific requirements clearly. Do not expect that everybody reads your "paper", listen to your contractor, and let them bring their expertise to the table. As a customer you are the one who knows the product and the process, help contractor to understand the process by providing detailed process mappings and flowcharts. Well written process mapping is effective basis for the facility layout.

Based on approved and communicated requirements, conceptual design and basic design can be started by contractor. In this phase effective well organized communication route and platform between customer project team and contractor cannot be highlighted enough. Avoid sharing / commenting design information by email. Try to organize common design sharing and commenting through software platforms like Autodesk BIM 360, or similar contractor document systems to avoid ineffective email "ping pong" and to keep track of all comments and issues. By common software platform designers can offer up to date design models for customer review. Using 2D & 3D views and Virtual Reality (VR) Headset review meetings customer can independently oversight design progress and provide quick feedback. Site team can organize common virtual walkthroughs even from home office. When all design issues can be addressed and pinpointed directly to the BIM model and be seen by all users, it improves the communication to whole new level. From customers side engineering lead can easily assign observed issues to contractor's project manager or to different design disciplines. Common software platform is also excellent tool to organize engineering, quality and HSE related milestone reviews. Large amounts of review information can be packed to review sets containing only review relevant information, emails and folder structures without proper version control simply would not work as efficiently.

3 PROJECT DESIGN PHASES

After conceptual and basic design phases it is important to go deeper in the user requirements and technical specification and gradually go to system specific level. Project requirement specification can now be evolved to Project Functional Specification (PFS) which is answer to the question: "How" the project will be executed. The document is the technical basis for specifying the project in system level. Based on the information customer will have a clear picture what to expect. Facility layout, mechanical systems (HVAC, Utilities, equipment) technical requirements and technology selection are in the level that contractor can start technical specification, technical bidding and tendering process with future vendors and vendor candidates. In this phase one of the biggest pitfalls is, if contractor's designers or discipline leads or even project manager does not fully understand what customer wants. This can easily happen, if there is not sufficient communication in place or if too much is assumed and based on previous projects or standard approaches of the contractor. Good quality System Specific User Requirements (URS) communication is the key to success. First designer must understand you that he can technically specify the system that meets process and product requirements. Insufficient communication can lead to overkill in specification with significant cost impact. At the other end is under specification that can lead later to severe compliance issues.

In Detailed Design phase the future vendors will join the project, so it is important to ensure that they have received sufficient understanding of fundamental GMP / HSE requirements. Because in some project execution models engineering contractor holds all the contracts with vendors, there is a risk that contractor, if not fully understanding process requirements, can even mislead vendor by accident. Thus, it is strongly recommended to have sufficient and direct customer involvement in key direct GMP systems and HSE critical systems to ensure that there is common understanding where the project is going. The customer must have full focus on design reviews and design qualification steps to ensure the compliance with the URS requirements. Do not assume, do not trust your key SuccessFactors

in design to simple URS responses like "Yes, complies, everything ok". Expect to see evidence, ask designers and vendors to present you the solutions. Expect to have good review documentation and DQ reports with all relevant evidence referenced. Expect to see punch lists and deviations to be documented and tracked through the project. Finally witness the verification of your requirements in commissioning and qualification execution phases. Common software platform for commissioning and qualification documentation and electronical signature / execution workflows can be useful when working with external partners and during pandemic. Construction management and mechanical completion are the areas where you as a customer must have expert to support and oversight the activities. Poor construction execution can lead to significant cost and delays. It is advisable to use modern tools to handle this part of the communication like Co-console/ Autodesk BIM Field. These tools can help to work transparently, monitor and lead construction projects to evidence-based turnover and inform different stakeholders of readiness.

4 IN CONCLUSION

Again, engineering is largely communication. Be prepared to continue the communication, be prepared to repeat yourself and be prepared to several changes. Project teams change, suddenly you have a new discipline lead that do not know the background and all the decisions made in the three years of the project, good requirements and review documents are the key in onboarding of new persons. SOP lists and onboarding matrixes for all key project positions can also be helpful. Ensure your contractor stays trained throughout the project. The design will chance and most probably also the project scope can have changes, it is very important to have proper project change and engineering change workflows in place together with your contractor. Be prepared to handle enormous amounts of documentation in the project, it is advisable to have nominated document controllers in customers and contractors project organization to have good oversight on this. And remember, a document is just a document if nobody reads it, understands, or communicates it – communication is the key.

RISK-BASED APPROACH TO GMP – FOCUS YOUR EFFORTS WHERE IT MATTERS

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1 INTRODUCTION

In the early 2000s, the FDA published a report titled "Pharmaceutical cGMP for the 21st Century - a Risk-Based Approach". Since then, quality impact assessment and quality risk assessment have been basic ways to clarify risks before starting the commissioning or qualification process. Now, this theme is again topical, because a new version of EU GMP Annex 1 Manufacture of Sterile Medicinal Products will be published this year. Based on the published draft, it can be concluded that the new version is focusing on, for example, Quality Risk Management (QRM) and Contamination Control Strategy (CCS). The revised version of Annex 1 is not yet published and the applicable transition period for implementation is still unknown. However, companies should be proactive and start preparing.

In the past few years, the European Medicines Agency has also revised most of its GMP guidelines to emphasise the importance of conducting risk analyses, so that the manufacturers to understand where they should focus their quality-safeguarding efforts. In this presentation, we discuss how the risk-based approach to qualification and validation in pharmaceutical design projects is implemented, present practical

examples, and discuss the impact of approach to commissioning and qualification phases and possible time and cost savings.

2 RISK-BASED QUALIFICATION AND VALIDATION – KNOWING WHAT AND HOW TO QUALIFY/VALIDATE

During the times of increased competitiveness and new regulatory requirements/directives and norms, pharmaceutical companies must continuously optimize their operations to reduce operating costs and increase efficiency. By applying an effective risk-based qualification and validation approach, the overall time and effort spent on qualification/validation can be reduced and thus increasing productivity and profitability within the company.

The FDA defines qualification/validation as "establishing documented evidence that provides a high degree of assurance that a specific process or system will consistently produce a product, meeting its predefined specifications and quality aspects". The phrase "high degree of assurance" enables companies themselves to determine the appropriate level of inspection for the system being implement-ed. The traditional approach to qualification/validation involves the assessment of each system requirement in the same comprehensive manner without considering how much risk a failure of the function would add to the patients, products, machines, and operators. The approach assures that every requirement is thoroughly verified, but experience has shown that it causes unnecessary delays in the qualification/validation process of the system, producing lots of documents to review, which further delay the release of critical systems. This can be avoided by implementing a risk-based qualification/validation solution.

3 QUALITY RISK MANAGEMENT

The safety and efficacy of a medicinal product are in the core of qualification and validation. Quality Impact Assessment and Quality

Risk Assessment (QRA) are intended for securing the product quality by supporting to set the focus of the qualification effort to those systems that have a direct impact on product quality.

Once the specifications for individual systems have been defined, the impact of non-compliance with a requirement on system performance, functionality or other quality aspects will be assessed alongside the technical design. The most important factors to be identified are issues/deviations that may affect the quality of the medicinal product, operator safety or patient safety. At this stage, it is essential to recognize the system "vulnerabilities" and have a careful consideration on all aspects when more information about the system is available. Probabilities and consequences of functional failures can be minimized in advance by supplementing and/or modifying the design and by defining the management tools e.g., testing and inspections. The information on which requirements are of interest to the authorities is obtained – the requirements are those that may affect the quality of the medicinal product.

4 STEPS IN THE BASIC RISK ASSESSMENT

A risk assessment exercise essentially consists of the following steps (Figure 1):

1. What might go wrong?

   a. Risk identification: Which components/functions might fail within the system

   b. Risk analysis: Components of the risk associated with failure can be commercial, technical, or regulatory.

2. What is the probability that it will fail?

   Risk evaluation: Calculated based on the severity of impact, probability, or occurrence and detectability associated with the risk

3. How severe are the consequences?

   Risk prioritization: Based on the evaluation, the various risk elements can be prioritized as High, Medium, Low or No Risk

4. How to minimize consequences?

   Risk mitigation tactics: Decide the precautions to counter risk. The risk assessment exercise output may be a quantitative estimate of risk (Risk Score), depending on the risk evaluation methodology, or a qualitative description of a risk range (using qualitative descriptors High, Medium, Low or No Risk)

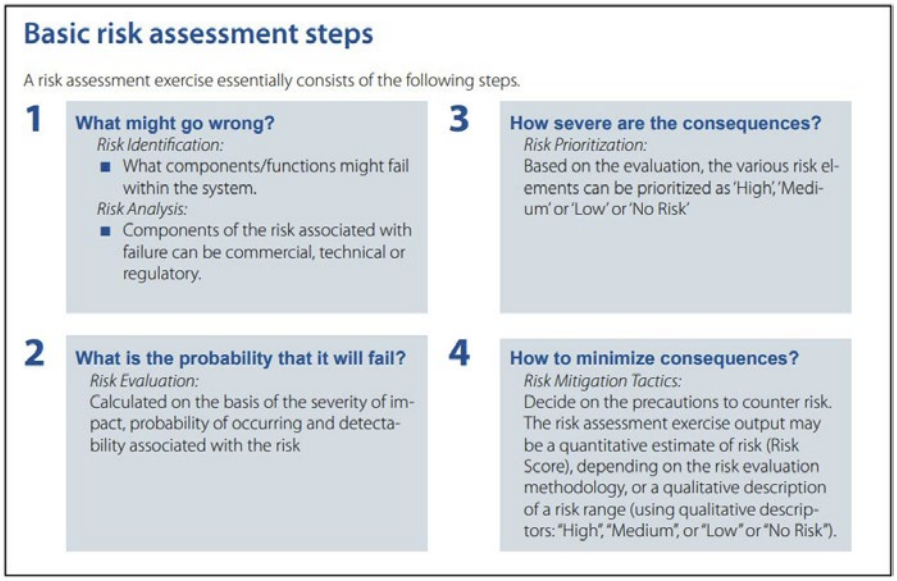

Figure 1. Steps in basic risk assessment.

5 IMPLEMENTATION OF RISK-BASED QUALIFICATION/VALIDATION

Although the risk-based qualification/validation is a widely heard expression in the pharmaceutical industry, the methods for implementation might still be unclear. Risks could also be assessed at the functional requirement level, thereby focusing qualification/validation efforts on those system functions that are at high risk with respect to data security, system security, operator safety and product and patient safety.

Risk assessments are conducted to determine the risk level of the requirements in the system, in the case of adverse events related to

the requirements. The risk levels help to determine the scale of testing that needs to be performed on that function. This requires the ability to approach the requirements at system level, to identify the broader risk and to identify the specific risks concerning that function at micro level.

It is also important to ensure individuals from various cross-functional disciplines within an organization to participate in the process. This ensures that risks are assessed from commercial, technical, regulatory, and other aspects. This is usually considered as an acceptable investment in view of the qualification/validation efforts saved thereafter.

6 GETTING STARTED WITH A RISK-BASED APPROACH

The first step Quality Impact Assessment is to assess the individual system for its impact on the product, operator safety and patient safety. The result of this assessment is either having "direct impact" or "no impact". The "direct impact" systems are considered for qualification. Further, a component criticality assessment can be made for "direct impact" systems based on the factors such as data security, system security, operator safety and product and patient safety. "Critical components" are considered for qualification and are subjected to Quality Risk Assessment. Based on the Quality Impact Assessment and Quality Risk Assessment, the qualification protocols are generated and executed. Qualification protocols are written for "direct impact" systems only. Each qualification protocol includes only the critical components of the impact system. The protocol contains the parameters on which basis it is segregated as a critical component.

7 ADVANTAGES OF ADOPTING A RISK-BASED QUALIFICATION APPROACH

Risk-based qualification enables organizations to focus more closely on the areas of the process or system that, in the event of a failure, pose the greatest threat to product quality and patient safety. As examples

Environmental Monitoring System (EMS) and Building Management System (BMS) are used. EMS and BMS are different, EMS monitors the environment of the facility and BMS controls the environment (Table 1). As there is a clear difference between the intent of the systems, their compliance levels are also different. EMS has a direct impact, which clearly fall under GMP, whereas the implementation of BMS in GxP environment has an indirect impact i.e., it is typically falling under GEP, not under GMP. BMS though needs to be commissioned, but not necessarily need qualification. As per risk-based approach to qualification, this means that the BMS has reduced documentation and qualification requirements. Further reasons – for time and cost savings during the implementation and also during life-cycle management - to have separate systems are e.g., 1) BMS sensors located also in non-GMP area – not to waste time for performing qualification for sensors in non-GMP area and 2) change management is only required for GMP systems i.e., EMS, not for BMS, thus changes in BMS system do not require a heavy change management procedure. It reduces the cost of qualification within the organization and, as a result, throughout the industry.

Table 1. Few risk examples from EMS Quality Risk Assessment.

Risk	Cause	Effect	RPN before qualification	Corrective / preventive measure	RPN before qualification
Operators are not aware of whether the production conditions are within limits.	No signalling devices have been installed in the production area.	Production activities can happen in unclassified conditions.	27	During DQ check that... During SAT check that... During IQ check that...	9
Data from EMS system is lost after a power outage.	No backup systems.	GMP relevant data is missing.	18	During DQ check that... During SAT check that... During IQ check that...	9

Another example could be ventilation system for cleanrooms and high-efficiency particulate air (HEPA) filters. The ventilation system could be classified as an indirect impact if HEPA filters will be separately

classified as a direct system. This means that the ventilation system could be taken into use with commissioning. Quality Risk Assessment will be made for HEPA filters, and it will be qualified. If HEPA filters are seen as part of the HVAC system, the ventilation system needs to be classified as a direct impact and needs to be qualified.

Table 2. Few risk examples from Quality Risk Assessment of HEPA filters.

Risk	Cause	Effect	RPN before qualification	Corrective / preventive measure	RPN after qualification
Particles inside clean-room are not within limit.	A leak in the filter.	The production environment is at risk.	24	During DQ check that... During IQ check that... During OQ check that...	8
Filter is blocked.	Too much particulate load on filter over time.	Uneven flows to various filters.	16	During DQ check that... During IQ check that...	8

An industry-wide shift towards a risk-based qualification approach would allow innovations to be introduced without adversely affecting product quality or patient safety.

8 IN CONCLUSION

It is a universal regulatory expectation that pharmaceutical manufacturing facilities, systems, utilities, and equipment must be designed, constructed, and qualified to be suitable for the intended purpose. However, it is much more difficult to decide what is essential and what needs to be done, and how to do it in a cost-effective and efficient way.

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STERILIZATION – WHY PERFORM A PRODUCT D-VALUE STUDY?

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1 INTRODUCTION

Validation of sterilization processes is a continuous challenge in the Life Science industry. The overkill method is commonly used as minimal information on bioburden characteristics is required. However, when the characteristics of the product may be degraded by the overkill method, time and/or temperature parameters must be reassessed not to affect the quality of the product. In these cases, the validation approach is based on the Biological Indicator- Bioburden method.

A precursor to both methods is the performance of product D-value studies. The D-value studies are required by the USP and the European Pharmacopoeia and are necessary to know the impact that the properties of the material to be sterilised have on the resistance/lethality of microorganisms. D-value studies are therefore necessary to ensure that the biological indicator used to validate the cycle represents an adequate challenge to ensure the required level of sterility assurance (SAL). These studies can be carried out on liquids and other materials such as stoppers, caps, and other packaging materials.

2 DEFINITIONS – WHAT IS A BIOLOGICAL INDICATOR AND D-VALUE

A biological indicator (BI) is a test system containing viable micro-organisms providing a specified resistance to a specified sterilization process. This resistance is defined as the D-value and is the time or dose required under stated conditions to achieve inactivation of 90% of a population of test microorganisms.

The BI should comply to applicable standards, such as ISO 11138 "Sterilization of health care products — Biological indicators, USP 43, and European Pharmacopeia 10. These standards define how the BI's must be manufactured, which characteristics should be respected, depending on the process it will be associated, and how it must be used for a correct sterilization validation. To achieve a successful validation of the sterilization process, it is important to understand the relationship between the D-value of the test organism in/on the product as well as the biological indicator D-value.

3 PRODUCT D-VALUE STUDIES

The liquid load sterilization must be validated using a liquid-submersible BI in contact with the liquid. For example, in the case of a vial, the BI must be placed inside the vial, in contact with the pharmaceutical product it contains. This alone does not consider the impact of the composition of the liquid on the resistance of the spores. Depending on the characteristics of the product, the resistance may be increased or decreased, which is the reason the D-value studies have to be conducted prior to the validation. Factors influencing the resistance can be composition, formulation, viscosity, pH, preservative, etc. During the study, the liquid to be evaluated will be inoculated with a calibrated spore suspension, and the D-value of the spores suspended in the product will be calculated. The result will be compared to the resistance of the initial suspension, to conclude on the impact of the pharmaceutical product.

The same process can be applied to the packaging material, like silicon tubes, stoppers, plungers, etc. When the result is known, different options must be considered. If the product D-value is lower or equal to a standard BI, then it is appropriate to use a standard BI. If the product D-value is higher than a standard BI, the BI will no longer represent the worst-case scenario and direct inoculation using a calibrated spore suspension onto the material must be considered (custom BI).

4 CUSTOM MADE BIOLOGICAL INDICATORS

Custom-made BIs are test items or products inoculated with a suitable test microbe. Just as with standard BIs, the performance of custom BIs must be evaluated if these test units are to provide meaningful results when used in the validation process.

5 OTHER RESISTANCE STUDIES TO CONSIDER

The Z-value is an important value to know when the sterilization cycle is at a non-standard temperature (for example 121°C with steam) because it permits the calculation of the D-value at other temperatures of sterilization. In case of "flash sterilization", it is also very useful to calculate the total lethality of this type of cycle.

6 CONCLUSION

The objective of D-value studies is mainly to understand the impact of the pharmaceutical product, or a porous material, on the resistance of the microbe. D-value results and characteristics of the product to be sterilized allow the user to choose the most suitable sterilization method and biological indicator challenge to guarantee acceptable SAL on the sterilized product without impacting product quality attributes.

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DESIGN CONSTRUCTION AND C&Q OF A BSL3 GAPIII FACILITY

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1 INTRODUCTION

GMP (Good Manufacturing Practices) (European Union (EU), 2008) are a well-established set of requirements for the pharmaceutical industry. BSL (WHO - Biological Safety Level) are also reasonably well known for biotech applications. GAP-III (WHO - Global Action Plan III) is less well known as it focusses on polio type 2 specific facilities.

Where the combination of GMP and BSL-3 already involve special considerations to adequately balance protecting the 'product' (GMP) and the operators and environment (BSL). This requires 'bio-containment'. GAP-III ads a specific 'layer of control' like 'quality management' over the facility, the way it is operated and maintained. This 'GAP-III' covers both the BioSafety as well as BioSecurity. The definitions of Biocontainment and GMP clarifies the different focus of both requirements:

1. Biocontainment is the combination of physical design parameters and operational practices that protect personnel, the immediate work environment, and the community from exposure to biological material (Canadian Biosafety Standard, 2015).
2. GMP is a system for ensuring that products are consistently produced and controlled according to quality standard (ISPE, 2022). According to EU GMP Annex 1 the focus is on minimizing the risks of microbial, particulate and pyrogen contamination of the product (European Union, 2008).

The facility in this case study is a combination of a GMP QC function and pilot plant with the BSL-3 GAP-III requirements. The nature of operation of QC sample processes includes working with live polio virus. For all open steps this is done in primary containments like an isolator or a biosafety cabinet class 2B. Pilot production is done in closed bioreactors but also need sampling and assessment that require material to be taken out of the enclosure and into the test environment.

Where a state-of-the-art polio vaccine production plant uses closed processes only so the surroundings are not contaminated unless there has been a spill, in this particular case the live polio material is not continuously enclosed, so the surroundings are always considered potentially contaminated.

2 RISK BASED APPROACH TO DESIGN AND QUALIFICATION

To manage the design process with a balanced approach on all the requirements, the processes that will be performed in the facility have been studied and put into a flow chart. Such a flow chart shows the basic steps with personnel-, material-, sample-, product- and waste-flows.

During the development, a set of assessments need to be performed to develop the VMP/VPP/URS. A System Impact Assessment (SIA) as used for a GMP facility can be expanded by incorporating the Bio-containment aspects. The same applies to the Critical Quality Attributes (CQA). Typical Bio-containment related CQA would be aspects would be for the various outbound flows: microbiological reduction; for the containment perimeter: maximum air leakage rate, minimal extract air filtration efficiency e.g. These can be reflected in the Critical Process Parameters (CPP's) such as: temperature / time parameters for destruction autoclave, kill-tank; 6 log reduction on BI's for the VHP airlock and pass thru, flow/pressure cascade direction and values e.g. These CQA's and CPP's will allow to define the Critical Aspects (CA's) and Critical Design Elements (CDE's) that can be fed into the URS's.

To achieve adequate assessments, the team performing the assessments should be multi-disciplinary with at minimum subject matter experts on process, biosafety/security, quality, design, CQV, QE/QC. The flow chart, with the process steps and above assessments, can be used for both the GMP Contamination Control Strategy (CCS) as well as the Bio Containment and Bio Security Strategy (BCS and BSS).

Such strategies can be set up based upon a SWIFT (Short What IF Technique) assessment along the various 'flows'. Where for the CCS the focus mainly is to ensure the cleanliness towards the (open) process steps, the BCS focusses on the possibility of release from the primary containment barrier as well as the surrounding secondary containment barrier. The normal transfer from outside to inside as well as from inside to outside requires specific air locks and destructing/ decontaminating transfer equipment. This is of particular importance to demonstrate the adherence to GAPIII.

The development of the named CCS and BCS strategies is never a static action as the design needs to be challenged at each design step. A phased approach implementing the risk-based elements is essential. The use of the above assessments during the design, construction, commissioning, and qualification process can be fully exploited when documenting the design in distinct packages along the output of the SIA. Critical systems have system coding and associated documents like P&ID, functional specifications, drawings, and component specifications that can be used during IV/OV verifications. Noncritical systems can be dealt with likewise but based upon Good Engineering Practice only.

The risk-based design can be made explicit by performing HAZOPs for all critical systems. For a typical bio-containment situation these should include e.g., HVAC, Kill tanks, Destruction Autoclave, Isolators.

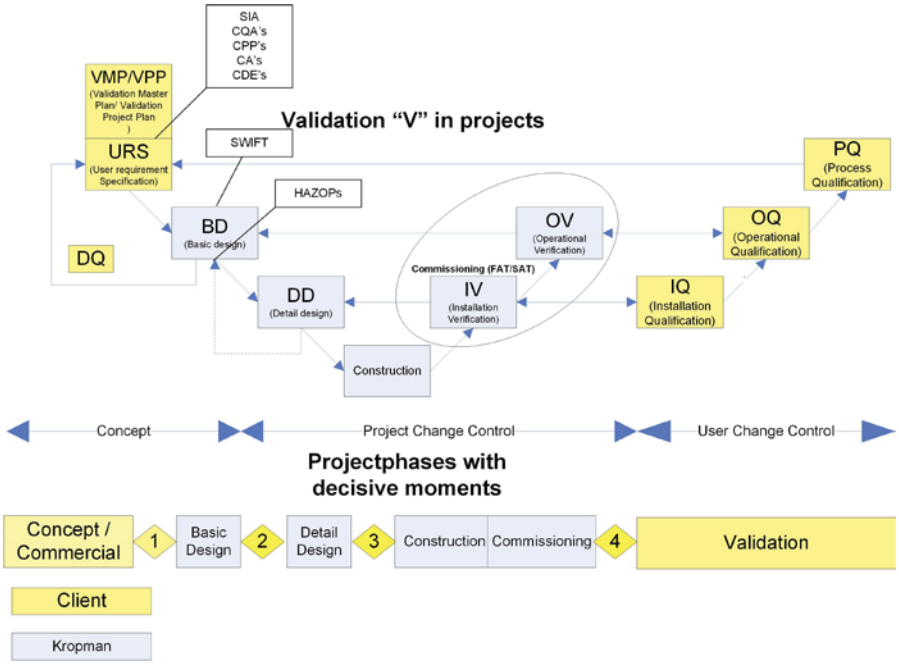

Figure 1. Project V-model indicating risk assessment steps.

The results of this design process are explained below followed by some results of the employed SWIFT and HAZOP assessments.

3 TYPICAL DESIGN ASPECTS

The design process will lead to design choices that reflect the differences between GMP and Biocontainment. For aseptic processing Personnel, utensils, materials, and product flow requires inbound contamination control, bioburden reduction or sterilisation. After the asepting processing and filling the products, materials and waste flows usually can be transferred outbound without specific restrictions.

For a facility with potential contaminated conditions both personnel as well as all materials need to be decontaminated or when possible biological destruction.

The autoclave is the main routing for outbound gowning, waste, and materials. Samples out and other flows that that cannot be autoclaved need secure enclosures that can be disinfected at the outside by e.g., VHP.

Personnel can only leave the containment zone by decontaminating showering. Figure 2 shows schematic the specific logistics for GMP or BSL-3 flows.

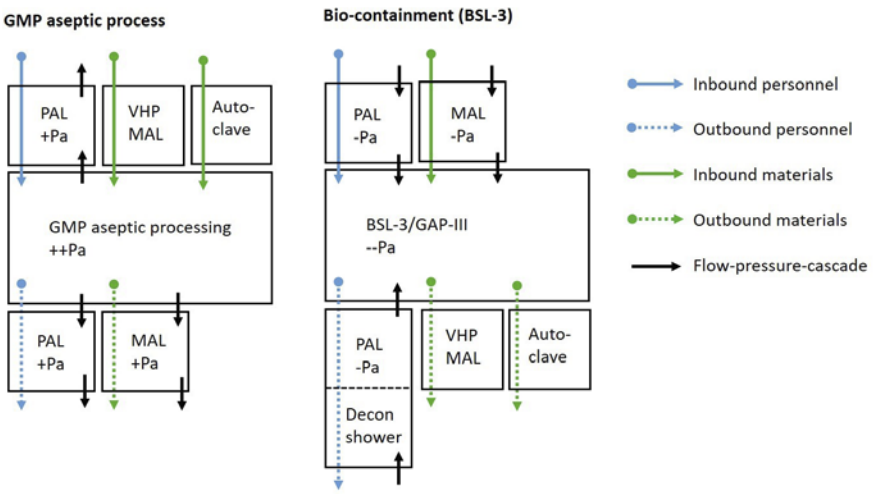

Figure 2. Lay-out configurations for GMP aseptic processing and bio-containment (BSL-3).

For the biocontainment it is essential to clearly identify the containment zone perimeter and the containment barrier. The containment zone perimeter refers to the outermost physical boundary of a containment zone where the containment barrier refers to the boundary between "clean" and "dirty" areas inside a containment zone (Canadian Biosafety Standard, 2015). The doors located at the containment barrier are so-called critical doors. At those door locations an inward directional airflow (IDA) from "clean" to "dirty" is required to create a physical barrier protecting airborne infectious materials being distributed to the outside.

In the case study the doors in between the clean and dirty gowning, and between the MAL and corridor, are projected as the critical doors. See 3. At those locations IDA is realized via discrete openings (orifices) in the doors. The flow through these openings is maintained by the offset between air supply and return. To avoid contamination from the outside being distributed into the facility the clean gowning and unloading areas are set to an overpressure acting as a "bubble" in the pressure cascade.

Within the rest of the facility the flow-pressure-cascade is based on the overflow of air from areas of lower containment to areas of higher containment resulting in a negative differential pressure. In this case study the BSL-3 / GAP-III requirements take precedence above the GMP requirements, however GMP grade-D is not compromised as the overflow of air is from the same grade.

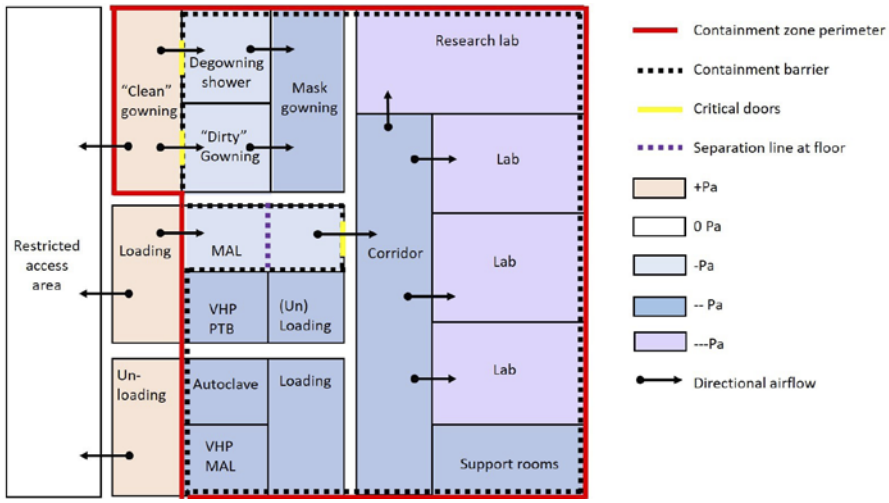

Figure 3. Containment zone and barrier vs. flow-pressure-cascade.

The design of the cleanrooms is based on the box-in-box principle, where the outer box is the building envelope, and the inner box are the cleanrooms surrounding the containment area. Wind attack and ambient pressure fluctuations are disconnected from the cleanrooms as they are fully surrounded by a common "zero" pressure (Figure 4).

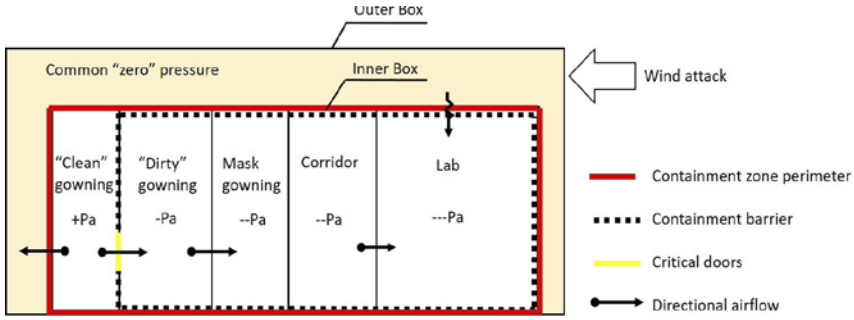

Figure 4. Box-in-box principle.

The containment zone must be airtight to be able to maintain the required inward airflow, to prevent the escape of airborne biohazards and to protect the surroundings to exposure of VHP when disinfection is performed.

The cleanrooms are designed at a maximum allowable leakage rate of 0.1l/s*m^2 at 70Pa differential pressure according to client specific requirements. This leakage rate is in the range of leakage class L2 / L3 according to VCCN guideline 10 (VCCN, 2018). The challenges with respect to the airtightness are related to the penetrations through the cleanroom envelope. At specific locations with multiple penetrations for power sockets and data outlets, airtight stainless steel connection boxes are implemented in the design. Equipment such as autoclave and VHP pass through box and the VHP MAL are provided of a biological sealing flange (bio seal) to guarantee integrity of the containment barrier. Also the return ductwork and its components until the second HEPA filter (police filter), which are potentially contaminated, should be airtight and leak tested.

4 SWIFT AND HAZOP

The SWIFT analysis led to a relevant improvement in the lay-out of the facility. The preliminary facility lay-out in combination with the inbound and outbound flows of materials, personnel, samples, equipment, and utilities have been used as the basis for the what-if scenarios. The lay-out of the facility and flows are schematically shown in Figure 5. It should be noted that this figure is only a simplified sketch. In the case study there are multiple gowning blocks (yellow box) for inbound and outbound personnel. All those gowning blocks are connected to the central mask gowning, where personnel put on a respirator mask.

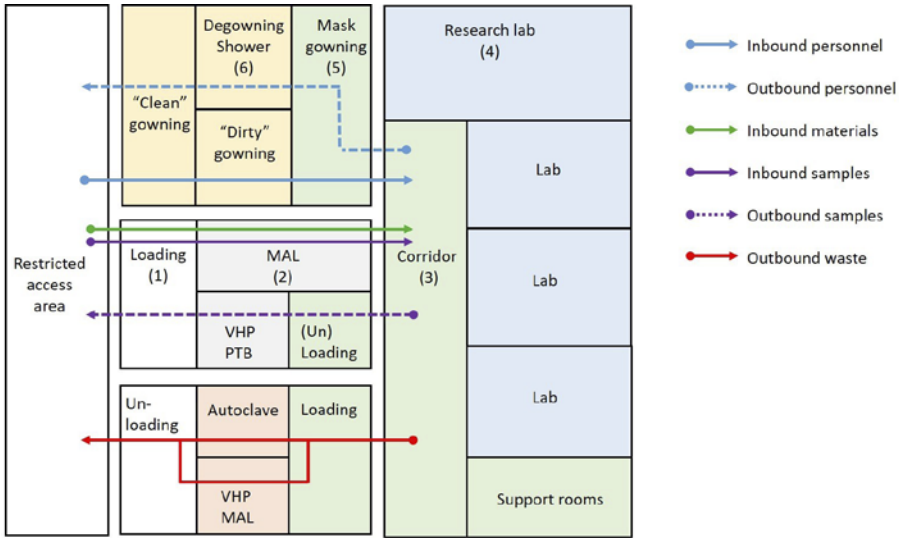

Figure 5. Simplified sketch of the facility lay-out (1st floor) with personnel, material, sample, and waste flows.

Each individual transition step has been assessed taking into account the safeguards as implemented in the preliminary design. Where the risks are not mitigated, additional safeguards are proposed. Typical examples of mitigation measures arising from the SWIFT:

1. The material airlock (MAL) (2) is entered from both the non-containment loading room (1) and the containment corridor (3). What if a person enters the MAL shortly after a contaminated object or person was inside? A potential risk for carry-over of contaminants arises! A recovery time delay in the access control/ interlock mitigates this risk as the room can be flushed properly by the HVAC system. In addition, to avoid unauthorized access to the containment area an extra access barrier (keypad) has been incorporated in the design.

2. The chance of a spill in the research lab (4) is most likely to happen. When there is a spill accident in the research lab, would the personnel be able to use a dedicated shower (6) outbound? The preliminary layout (Figure 2) does not allow for any waiting area except the research lab itself or the central mask gowning area (5). Both options are considered not safe. For this reason, an extra waiting-room for exit of the research lab in case of a

spill has been implemented in the layout. See 6. In addition, the research lab is designed for a separate VHP cycle allowing individual fumigation without impacting the rest of the facility.

3. What if a leakage occurs in the kill tank system or an emergency shower is used in the central corridor (3) without drain connection? As a safeguard civil floor barriers are implemented in the design to avoid potentially contaminated liquids causing a breach of containment or liquids flooding to higher contained areas within the facility.

4. What if a BSC failures due to HVAC failure? As a safeguard a thimble connection was chosen over hard ducted BSC connections to guarantee operator safety during tests and experiments and simplify the HVAC controls to maintain under pressure in the facility.

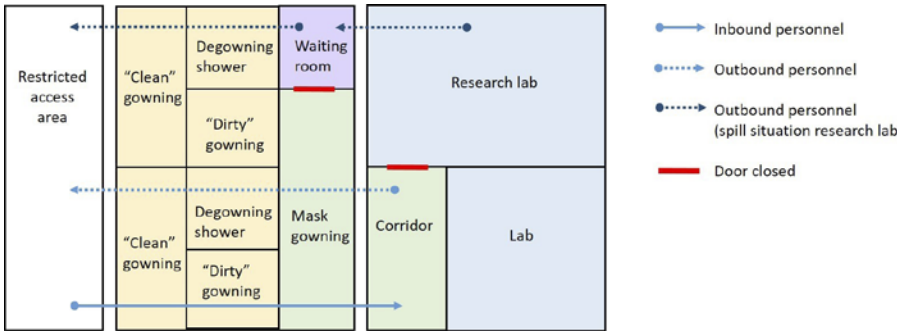

Figure 6. Outbound personnel flow in case of a spill accident in the research lab.

5 HVAC SYSTEM HAZOP

The HVAC system is designed to create a physical containment barrier to minimize the release of infectious materials to the environment. The single pass air handling system is schematically shown in Figure 6. A HAZOP analyses was performed to assess the HVAC system item-by-item. Below some of the failsafe design solutions are presented.

5.1 System failure

The supply and exhaust air handling units (AHU's and AEU's) are designed fully redundant to guarantee the supply and exhaust airflow. During normal duty both AHU's are running parallel each AHU providing 50% of the total airflow. In case of failure the remaining AHU will immediately ramp up to provide 100% of the airflow.

All cleanrooms within containment are provided of primary and secondary (police) HEPA filters to avoid loss of containment in case of single HEPA filter failure. For backflow prevention as well as GMP purposes all air supplies are provided of a terminal HEPA filter. For rooms having a single variable volume (VAV) extract damper a safeguard VAV damper was added to the design. In addition, the supply and return fire dampers connected to a single room are interlocked to avoid loss of containment in case a return fire damper accidently fails. It is of high importance that the HVAC controls are also incorporated in the redundancy strategy, having multiple controls for at least the facility exhaust system.

5.2 Power failure

All exhaust systems and their controls are connected to the uninterrupted power supply (UPS) as well as the emergency power supply (EPS). In case of power failure, the supply systems are shut-down, the inward directional airflow at the containment barrier is maintained by the exhaust system.

5.3 Fire

In the containment area the use of sprinkler and uncontrolled water jets for firefighting are considered as high risk as all the water used is potentially contaminated and needs to be contained and can be disposed of after validated disinfection only. In addition, fire fighters are not allowed to enter this area. For this reason, an inert gas extinguishing system has been implemented. Normally a gas extinguishing system is designed for overpressure, having a pressure relief valve that

opens quickly after the gas is released into the room. For the BSL-3/GAP-III rooms this is not allowed as inward flow/negative pressure at the containment barrier should be maintained even during the fire extinguishing mode. In the case study, the HVAC exhaust system is specifically designed to maintain inward directional airflow during the fire extinguishing process.

After a fire alarm the HVAC system is switched to emergency operation mode:

- All air supplies in the applicable zone are closed.
- The exhaust system is set to high under pressure (-1000Pa in the exhaust duct plenum) and all air extract VAV dampers are switched to approximately 20 ACH (nominal the facility is designed for 15 ACH) to be prepared for the incoming inert gas flow.
- After a time, delay of approximately 60 seconds the inert gas is released into the applicable zone filling the room in no time with inert gas. From this point the room pressure is controlled according to normal operation.

The high under pressure in the exhaust plenum in combination with the "zero flow" situation (note that all air supplies are closed) is a challenging situation for the cleanroom as it must withstand this -1000Pa pressure. In the design phase special attention need to be paid to cleanroom envelope construction.

Another challenge to address in the preliminary design is the maximum inert gas flow per room. In the case study the facility is nominal designed for 15 ACH, while in fire mode the exhaust needs to ramp up to 20 ACH to compensate for the inert gas flow and to maintain inflow / under pressure in the containment area. All air ducting, valves, HEPA filters and fan capacities needs to be designed for this higher airflow.

Last challenge is to maintain inert gas concentration and oxygen concentration between predefined limits (10%–12.8% O_2) during a time of at least 10 minutes. Due to the inward directional airflow of the laboratories, there is a constant supply of fresh air replacing the

inert gas. During design and engineering this requires very precise coordination.

5.4 Spill situation

Annually or in case of a spill incident the containment area, including the HVAC system through both the primary and secondary HEPA filters, is fumigated with VHP. The HVAC system set-up allows individual zones to be fumigated separately. Mobile VHP generators are installed into the applicable zone and a dedicated fan circulates the VHP through the rooms as well as the HVAC system. After the police HEPA filter a 6-log reduction in bioburden needs to be achieved.

Challenging is to maintain inflow / under pressure in the VHP zone without impacting the flow-pressure-cascade in the rest of the facility. The design does not incorporate airtight boundaries in between the zones, openings in between should be taped off. As this impacts the overflow situation, pressure controls need to be designed for. The pressure within the VHP zone is controlled via a by-pass VAV-damper parallel to the main shut-off valve.

Another challenge is the distribution of VHP through the entire zone having a complex lay-out or rooms filled with equipment. In the design low air returns are incorporated to improve VHP distribution. However additional temporary fans for distribution of VHP are necessary at specific locations.

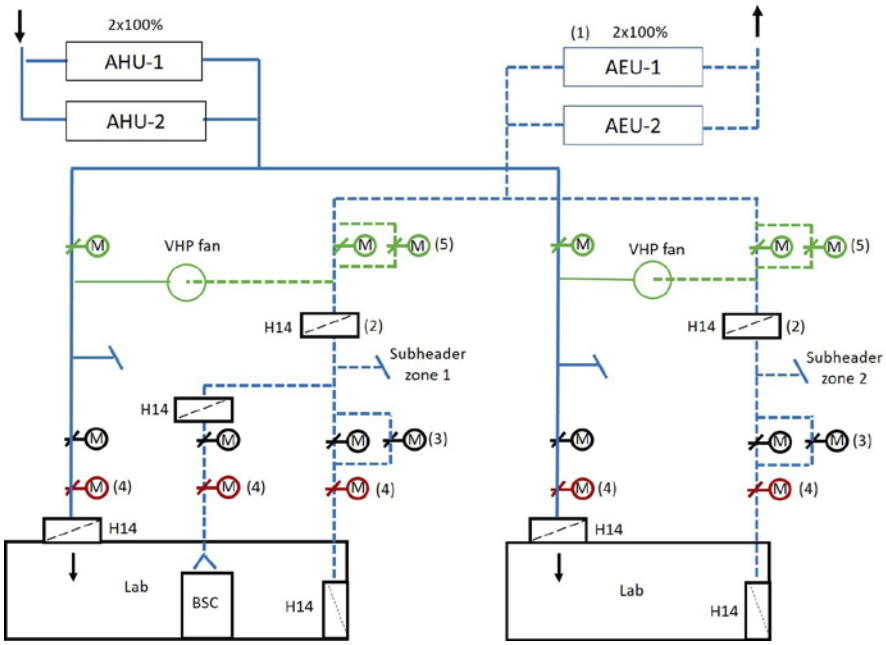

Figure 7. Schematic overview of the HVAC system.

1 = Redundant AEUs connected to UPS power, 2 = Police HEPA filter,
3 = Safeguard VAV damper, 4 = Fire dampers with interlock function,
5 = Bypass control damper for VHP.

6 COMMISSIONING, VERIFICATION AND QUALIFICATION

Having the design developed and documented incorporating all the assessment results, the right conditions for construction and forthcoming testing and qualification are set. For this case study, the commissioning did not only include individual verifications and setting to work/balancing and testing but included many additional tests. As illustrated above the various systems have quite a few operational statuses. Not only need all these statuses to be tested itself but also changing from status to status needs to be a secure process remaining always bio-contained maintaining IDO/under pressure. These status changes also require the well-coordinated functioning of associated

systems such as HVAC and VHP-units, HVAC and fire suppression, HVAC, and Isolator/Biosafety cabinet operation e.g. Not to mention decontamination showering in combination with the door-interlock/ access-control, shower water control and the contaminated waste to kill tank system.

The performance qualifications with respect to biocontainment include the decontamination VHP units, the destruction autoclave, isolator and biosafety cabinets, the total contaminated waste effluent and kill tank system as well as full room disinfection of the facility by VHP.

7 EVALUATION AND CONCLUDING REMARKS

This paper gives insight in the complexity of the integrated design process for BSL-3 / GAP-III and GMP grade D compliant facility. A risk-based design approach, using SWIFT and HAZOP, turned out to be a very helpful and effective to assess the contamination- and containment control strategies and associated safeguards during all design phases.

Systems like HVAC must be designed for multiple operational modes to ensure biocontainment is maintained under non-normal situations such as power failure, system failure, fire or during a spill accident. As a result, the systems and their controls are getting more complicated. In the case study the fire extinguishing process turned out to be the most challenging situation due to the large impact on the HVAC design, cleanroom construction and complexity of controls.

To manage this complexity and provide documented evidence the facility complies to both GMP as well as BSL-3/GAPIII requirements, the use of various assessment steps and tools showed not only to be very useful but also a 'conditio sine qua non'.

8 IN CONCLUSION

Combining contamination control with containment ads a separate approach to the design process that covers all systems involved. Risk analysis and failure mode analysis need to be incorporated and at all stages of the process the systems need to meet the system requirements as well as form part of the integrated system. Inflow/ pressure cascade, fail safe systems, fire suppression, filtration, VHP disinfection, incorporating of decontamination devices as autoclave, VHP-chambers and waste disposal/kill-tanks form a complex system. In such a facility closed systems, isolators, biosafety cabinets, need to be included. Amongst pharmaceutical projects a project combining GMP with BSL-3 and GAP-III requirements fall into the most complex category. In this case study the approach and essential challenges and solutions are demonstrated.

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ENVIRONMENTAL CLASSIFICATION AND QUALIFICATION AND A PHASED APPROACH FOLLOWING QRM PRINCIPLES

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1 INTRODUCTION

With GMP facilities that employ clean air systems for cleanrooms, barrier technologies and transfer devices a phased and step wise approach is required and typically applied for environmental Classification (particulate levels), through into Qualification (particles and microbiological levels) considering at rest and In-operation studies.

For manufacture of pharmaceutical sterile medicinal products and new advanced medicinal therapeutic products (ATMPs) reference is taken to EU GMP Annex 1 (currently in revision) with associated reference to ISO 14644 part 1 when considering environment Classification of GMP area grades. Annex 1 has a fundamental principle to follow Quality Risk Management (ICHQ9) guidance and such principles should also apply through environmental classification, environmental qualification (including APS – Media fill simulations) into routine production environmental monitoring (EM).

ISO14644-1 is a generic standard for all industries and applications where clean air systems are applied as such for GMP applications interpretation of requirements and connection of classification and

qualification need to be made. For GMP applications a phased approach is applied that considers at-rest and in-operation requirements following a holistic and risk-based methodology now encouraged through a paradigm shift in GMP regulation revisions. An overview of phased approach and steps is shown in Figure 1.

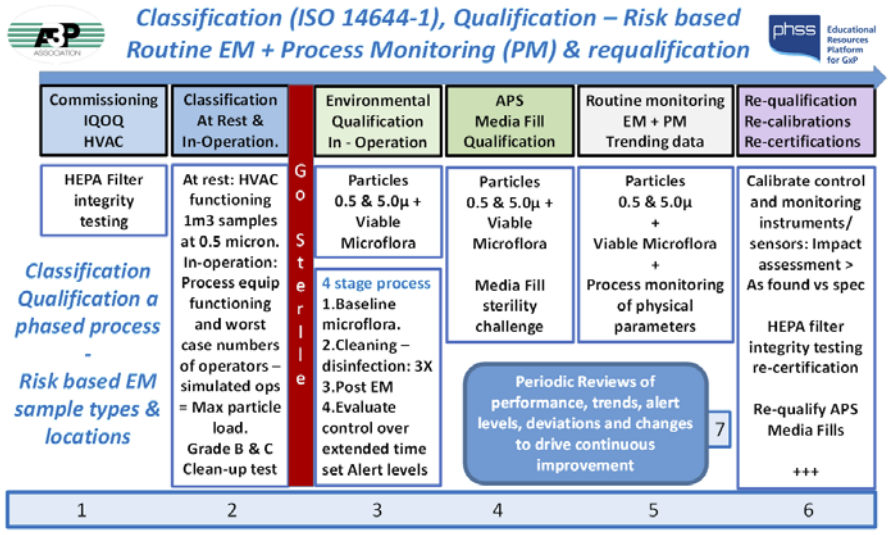

Figure 1. Represents the seven steps in the phased approach to environmental classification and qualification.

2 KEY POINTS TO CONSIDER AT EACH STEP OF ENVIRONMENTAL CLASSIFICATION AND QUALIFICATION

2.1 Phase 1: Commissioning, IQOQ HVAC facility and Barrier Technology environmental control systems

Separate protocols applied for commissioning and IQOQ of the Cleanroom facility and the installed barrier technology. IQOQ to include HEPA filter integrity testing and function testing of the air handling units (AHUs). Clean air system Filter integrity testing is a key requirement

before beginning environmental classification (performance testing) of air handling systems. A cleanroom in Grade C environment is shown in Figure 2.

Figure 2. Isolator barrier technology aseptic processing filling line with Grade C surrounding cleanroom.

ISO14644 part 3 2020 provides guidance on HEPA filter integrity testing. It should be noted this standard has been revised so the two principal methods can be aligned and accepted internationally. The two principal methods of filter integrity testing are the PAO 'Photometer' method and more complex 'Particle counting' LSAPC method. Most of the revision related to the particle counting method to outline and further detail the required calculations, test method and acceptance criteria. Although defined as a particle counter method like the photometer method in clean air systems a 'particle challenge is required. For the photometer method the challenge is an aerosolized synthetic oil polyalphaolefin (PAO) and for LSAPC method a di-ethyl-hexyl-cebacat (DEHS) aerosol test challenge is applied (particle count).

In Pharma applications, the LSAPC method there is a general acceptance after revision of ISO14644-3 2020 there is alignment of LSAPC with PAO based method that are now accepted as sufficiently similar to determine filter integrity of installed filters e.g., not as a filter manufacturers test. It may be a long process to get international contractors/operators to understand and test filters correctly with LSAPC method, where

photometer method has been the norm. It is more complex, requires a preprepared spreadsheet [set up correctly] to drop the data into and needs more careful thought on practical implementation (background entrainment issues etc.). LSPAC method has been popular in Germany/ Switzerland/Japan for some time. The rest of Europe and the USA has been heavily Photometer method driven, but the tide is turning a little as more LSAPC method testing is now being used for barrier technologies manufactured in Germany and Switzerland.

GMP applications applies area grades: A, B, C, D – Particle and Microbial cleanliness and not ISO Grades: ISO5, ISO7, ISO8 etc. – Total particles only. In ISO there is only one set of particle count data indicating performance requirements and it is in operation only.

The reference to cleanroom environment classification in the EU GMP Annex 1 (4.27) reads as follows: For cleanroom classification, the total of particulates equal to or greater than 0.5 and 5 µm should be measured. For Grade A and Grade B areas at rest, classification should include measurement of particles equal to or greater than 0.5 µm. This measurement should be performed both at rest and in simulated operation. The maximum permitted total particulate concentration for each grade is given in Table 1 (ISO 14644-1:2015).

According to EU GMP Annex 1 the reference to particle monitoring that applies to environmental qualification with both 5.0 micron and 0.5 micron particle size measurements is required (Table 2).

Table 1. Classes of air cleanliness by particle concentration according to ISO 14644-1:2015.

ISO Class number (*N*)	Maximum allowable concentrations (particles/m³) for particles equal to and greater than the considered sizes, shown below[a]					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
1	*10*[b]	d	d	d	d	e
2	100	*24*[b]	*10*[b]	d	d	e
3	1 000	237	102	*35*[b]	d	e
4	10 000	2 370	1 020	352	*83*[b]	e
5	100 000	23 700	10 200	3 520	832	d, e, f
6	1 000 000	237 000	102 000	35 200	8 320	293
7	c	c	c	352 000	83 200	2 930
8	c	c	c	3 520 000	832 000	29 300
9g	c	c	c	35 200 000	8 320 000	293 000

Table 2. Maximum permitted number of particles according to EU GMP Annex 1.

Grade	Maximum permitted number of particles/m³ equal to or greater than the tabulated size			
	At rest		In operation	
	0.5µm	5.0µm	0.5µm	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

2.2 Phase 2: Environmental Classification (ISO 14644-1). At rest and in operation

In operation classification of the cleanrooms considers collective samples through a period of simulated processing operations with operating equipment and personnel occupancy (maximum), but not a full APS: Aseptic processing simulation at this stage. The extent of continuous of collective samples depends on area grade.

The Barrier Technology environments e.g., Isolator Filling line Grade A environments are classified in association with (following) classification of the Grade C surrounding environments. In operation of the Grade A Isolator environments may be completed with a 'Dry run' or 'Water fill' so filling-process equipment is operational and particle generating (but not a full APS).

Classification follows the principles of ISO14644 -1 and the GMP requirements of EU GMP Annex 1. Sample locations take a risk-based approach with risk assessment to define locations and sample frequency where monitoring at the specified locations would continue through qualification into routine EM to provide a connection in trending EM data.

2.3 Phase 3: Environmental Qualification

Environmental qualification should verify not to exceed particle levels (both 0.5µ and 5.0 µ particle sizes) and microbial viable contamination levels meet requirements of EU GMP Annex 1 and specified levels in a CCS. Environmental qualification is completed at rest and in operation and follows stages of establishing environmental control including microflora baseline profiling and implementation of qualified cleaning procedures, disinfection together with personnel gowning and material transfer qualifications (surface disinfection, packaging layer removal).

In operation environmental qualification of the cleanroom requires occupancy of personnel (at maximum specified levels) simulating activities to generate a particle loading (but not a full APS). Operator training may be also applied. In operation environmental qualification of Grade A environments e.g. Filling lines are completed with a simulated process (operational equipment providing particle generation and operators following SOPs) but at this stage not a full APS – Media fill e.g. may be Dry run or Water fill run.

Environmental Qualification of a new facility/ cleanroom requires steps through stages (4) of building data of starting bioburden conditions of environmental microflora, through cleaning and disinfection as environmental control is established; firstly unmanned other than QC for sample recovery (at rest) followed by in-operation studies (with operators/ QC) that are completed over an extended period to qualify control efficacy meets specified requirements.

For reference and more detail on a case study refer to the PHSS Sterile product manufacturing conference 2021 presentation on a 'Staged approach to Environmental qualification: Presented by Suzanne Nutter AstraZeneca Group Quality manager. The case study presented included the following guidance of the four applied stages (Figure 3) of environmental qualification of microbiological levels.

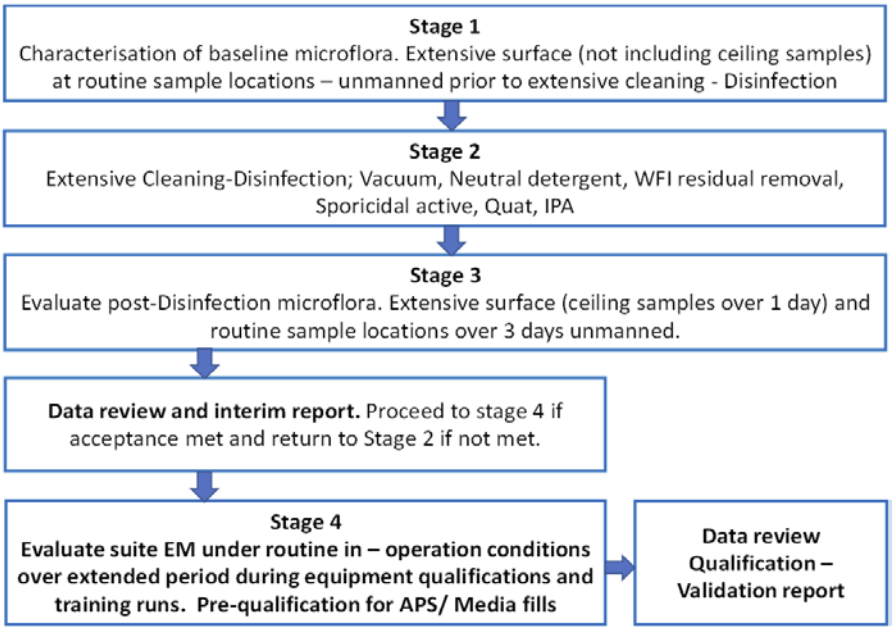

Figure 3. Four stages of establishing environmental control of viable contamination.

2.4 Phase 4. APS: Aseptic process simulation (APS) Media fill qualification. Refer to EU GMP Annex 1 for APS/ Media fill requirements

The APS must include qualification of authorised (specified) inherent and corrective interventions through routine production. Cleanroom and Isolator filling line EM is also completed through the Media fill APS (Figure 4).

PUPSIT: Pre-Use and Post-Use product sterilising Filter integrity testing is applied within the APS qualification of media transfer into the Grade A filling environment forms part of the process of product sterilisation by filtration e.g., Aseptic processing.

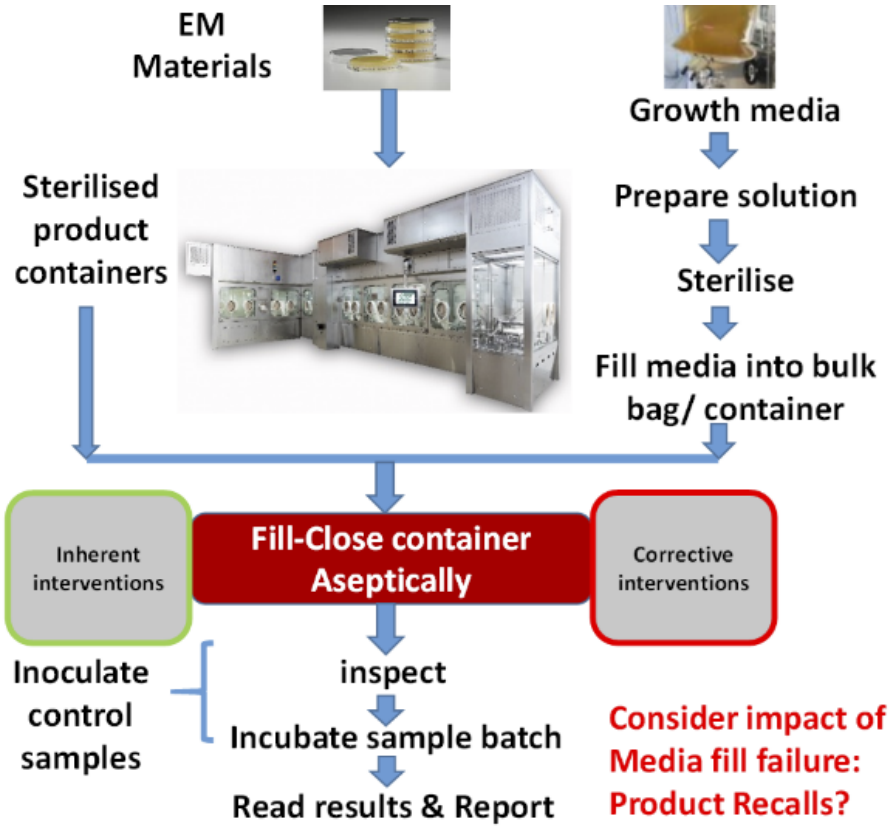

Figure 4. An overview of an aseptic process simulation.

Media fills should follow a strategy and be specified in the CCS; Where filling is batch wise three back-to-back Media Fill runs are typically completed for APS Qualification. For campaign filling 'Piggy back' APS may be considered. A strategy for repeat periodic APS Media fills should also be defined in the CCS. Environmental and Process monitoring should be undertaken in Media Fill qualifications; EU GMP Annex 1 refers (Figure 5):

9 Environmental & process monitoring

General

9.1 The site's environmental and process monitoring programme forms part of the overall CCS and is used to monitor the controls designed to minimize the risk of microbial and particle contamination. It should be noted that the reliability of each of the elements of the monitoring system (viable, non-viable and APS) when taken in isolation is limited and should not be considered individually to be an indicator of asepsis. When considered together, the results help confirm the reliability of the design, validation and operation of the system that they are monitoring.

Environmental and process monitoring

9.4 An environmental monitoring programme should be established and documented. The purpose of the environmental monitoring programme, is to:

i. Provide assurance that cleanrooms and clean air devices continue to providing an environment of an appropriate air cleanliness, in accordance with design and regulatory requirements.

ii. Effectively detect excursions from environmental limits triggering investigation and assessment of risk to product quality.

Figure 5. Environmental and process monitoring according to EU GMP Annex 1.

2.5 Phase 5: Routine Environmental Monitoring and Process Monitoring

Environmental Monitoring (EM) and Process Monitoring (PM) are linked for a holistic view of contamination control (collective effectiveness) and following application in environmental qualification should be completed through subsequent production operations. Process monitoring includes physical parameters that impact environmental control and assurance of maintained protection against compromise to product sterility e.g., detection of deviation to specified CPPs; Critical Process parameters, including pressure differentials, protective airflow velocities, critical areas (barriers) access controls. Resultant protective airflows are characterised by airflow visualisation 'smoke' studies. Collective EM and PM data from risk-based locations is trended with monitoring and alarm in deviations considered as incidences that contribute to ongoing efficacy checks of controls and compliance periodic reviews.

2.6 Phase 6: Re-qualification, re-calibrations, and re-certifications

Re-calibrations and re-certifications should be completed at a six-month frequency unless justified otherwise. Re-calibrations of measuring instruments/ devices used in control and monitoring will include an as found impact assessment relative to specification and appropriate actions taken (based on criticality). Re-certification includes HEPA filter integrity testing and re-certification of integrity. Re-qualification includes repeat of APS Media fills with full monitoring; EM + PM. Strategy required for frequency.

Re-qualification of the vH_2O_2/VHP cycles (efficacy and Aeration time) should be completed at a minimum annually with Biological indicator (BI) challenges with a minimum two cycle strategy; 1) Overkill production cycle repeated twice together with a gas concentration (ppm) profile review of comparability from PQ studies. Re-Qualification follows initial three (3) PQs for each qualified cycle and months of compliant EM data. Any deviations in EM would be subject to investigations that may (if justified) include sub lethal efficacy check of the vH_2O_2/VHP cycle. A reference to requalification is given in Annex 1 in which it is stated that the requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures.

In Table 3 the requirement for requalification of cleanroom areas is given.

Table 3. Minimum test requirements for the requalification of cleanrooms.

Grade	Total particle concentration	Integrity Test of Final Filters	Airflow volume measurement	Verification of air pressure difference between rooms	Air Velocity test
A	Yes	Yes	Yes	Yes	Yes
B	Yes	Yes	Yes	Yes	*
C	Yes	Yes	Yes	Yes	*
D	Yes	Yes	Yes	Yes	*

2.7 Quality oversight – ongoing Phase 7; Alarm Management and excursion/ incidence deviations reviews

Quality oversight of a process that includes automation and monitoring systems with electronic data capture starts with Deviation and Alarm management trend reviews including incidences of alarms and excursions from specified and regulatory limits/ CCPs. The response/ actions, impact and improvements made all form part of the Quality oversite. Periodic reviews of environmental control efficacy (efficacy check) are completed as part of a quality oversight; Reviews include periodic contamination control efficacy checks; EM + PM Trends; deviation incidences together with integrity loss incidences (barrier technology and barrier gloves) where a response/ management strategy will apply.

Trend reviews are completed alongside Product Quality Reviews (PQRs) that include impact of deviations/ excursions on product quality together with assessment of sterility test trends and incidences of sterility test failure. The outcome of deviation and excursion investigations may result in requirements for changes and improvements with such improvements considered on a continuous basis through the product Life cycle (ISO 14644-1-2 2015 & ISO 14644-3 2020).

3 IN CONCLUSION

Taking a risked based and holistic approach to contamination control the environments used in pharmaceutical product manufacturing require a connection through stages of classification and qualification. A principal connection is the environmental monitoring locations and sample types (particle or viable contamination) derived by risk assessment. The generic tables for the minimum number of sample locations per unit area do not apply to GMP applications with risk- based locations taking the priority.

Considering the phased approach recommended through classification and qualification it is essential to manage requirements of studies

at rest and in-operation and the specific not to exceed levels of total particulate and microbiological (CFU) levels defined in regulatory guidance, specifically EU GMP Annex 1.

In routine production monitoring there is now a requirement to link Environmental monitoring; EM (particles and microbiological) and Process Monitoring (PrM) i.e., physical parameters of control of e.g., airflow velocity of unidirectional protective airflow through HEPA filters.

There is a requirement of a quality oversight driven through the Pharmaceutical Quality System (PQS) that also must consider an holistic perspective following Quality Risk Management (QRM) principles, where data trends across collective areas and their analysis on controls that provide a collective effectiveness are fundamental to inform of state of control and any requirements for improvement over the product manufacturing life cycle (ECA Academy 2022).

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SINGLE-USE SYSTEMS – FLEXIBILITY AND REGULATORY COMPLIANCE IN THE LIGHT OF ANNEX 1

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1 WHY SINGLE-USE SYSTEMS?

Biopharmaceutical manufacturing capacities were exploding over the last years due to the dramatic ramp-up of COVID-19 vaccines facilities which resulted in a tremendous increase of single-use systems (SUS) demand. Almost all COVID-19 vaccines are manufactured in highly configurable suites based on single-use technology (SUT). In addition, new drug modalities such as RNA therapeutics, antibody drug conjugates, and cell and gene therapy increased the number of small production batches for clinical trials.

A SUS is "a combination of single-use components/assemblies designed to be in one continuous, and often closed, wetted flow path" (ISPE, 2018). Typically, the supplier pre-sterilizes the assemblies by irradiation, and they are shipped to the end-user ready to use. Drug manufacturers value the advantages of SUS as their benefits are high flexibility, speed to market, and quick changeover of equipment. Table 1 gives some considerations of SUS usage in aseptic processing including formulation, final filtration, and filling operations.

Table 1. Advantages of SUS due to their flexibility. Statements were collected from end-user in aseptic processing.

Process Flexibility	Time Flexibility	Cost Flexibility
+ Pre-formulated drug product pooling in a closed system + Flexible batch size + Filter membrane flexibility (dimension and material) + Peristaltic pumps for filling process + Process scalability from small to large batch sizes (less process development effort)	+ 4-6 months to design and receive sterile customized assemblies at site[1)] + Plug and play system for routine manufacturing + Less stainless-steel equipment preparation + Limited changes to the stainless-steel line to integrate SUS + No cleaning validation	+ Less CAPEX investments + Less machine set-up and activity hours + Increased line capacity Drawback: - Higher consumables direct costs compared to stainless steel equipment - Business continuity in case of worldwide pandemic

[1)]Time given is pre COVID-19 and may vary due to increased SUS demand.

2 REGULATORY EXPECTATIONS

Although SUT is well established in the biopharmaceutical industry there is limited guidance on regulatory expectations today. However, not only the industry but also regulatory guidelines acknowledge that SUS can reduce the risk of cross-contamination during manufacturing of sterile products:

- "Closed systems can be single-use systems…The use of closed systems can reduce the risk of extraneous contamination such as microbial, particulate and chemical from the adjacent environment" (2)
- "Live organisms and spores are prevented from entering non-related areas or equipment by addressing all potential routes of cross-contamination and utilizing single use components and engineering measures such as closed systems." (European Union (EU), 2018)

The upcoming Annex 1 revision on Manufacturing of Sterile Products as part of the European Good Manufacturing Practice (GMP) guidelines will include guidance specifically on the use and risk control of SUS (EU, 2020). The new Annex 1 includes a paragraph where "some specific risks associated with [single-use systems] which should be assessed as part of the CCS [contamination control strategy]" are listed: interaction with drug product and SUS surface, integrity (SUS are "fragile" and "complex"), and the risk of particulate contamination. In addition, a more general than holistic to-do list includes supplier qualification (including sterilization verification), verification of integrity throughout the process, establishment of acceptance criteria and incoming control procedure, and operator training.

The interesting part of the upcoming Annex 1 is the paragraph about closed systems which can be SUS as defined before: "The background in which closed systems are located should be based on their design and the processes undertaken. For aseptic processing and where there are any risks that system integrity may be compromised, the system should be placed in a Grade A zone. If the system can be shown to remain integral at every usage (e.g., via pressure testing and/or monitoring) then a lower classified area may be used" (EU, 2020). Closed SUS are typically designed to be used in lower classified areas such as Grade C or even Grade D. The question is now, what could be the process and design compromises on the integrity that a SUS could not be used in lower classified area than Grade A, unless a pressure testing pre-use would be performed.

3 INTEGRITY RISK ASSESSMENT

SUS used in final filtration and filling operations are typically very customized assemblies built from a set of various components such as tubes, filter, bags, junctions, and sterile connection devices. It is almost not possible to get to a common standard design of such assemblies as they vary in e.g., tube lengths and diameter, number of filling paths per assembly, connection to the isolator, components outside or inside the isolator, size of bags, additional flush and sampling bags, different kind and number of filters to be integrated – just to name a few of

variations. Suppliers produce thousands of designs, so it is not feasible to validate each design to the end user's unique operating conditions, rather a "family approach" is taken. Representative combinations of components are selected, built into an assembly and tested, to ensure they can meet predefined acceptance criteria, bracketed, based on the fact that they undergo the same manufacturing, sterilization, and transportation processes. In addition, it is essential to manufacture the assemblies with a validated process, and to implement lot release criteria and testing to assure lot to lot consistency. Figure 1 shows the main elements of the supplier's responsibility. Lot release tests include typically a non-destroying leak test (low pressure decay test) which is performed for each single assembly. Here, the American Society for Testing and Materials (ASTM) published good practice guides for different SUS test methods such as pressure decay or tracer gas (helium) integrity test and provides quality risk management principles related to the integrity assurance of SUS (ASTM International, 2020).

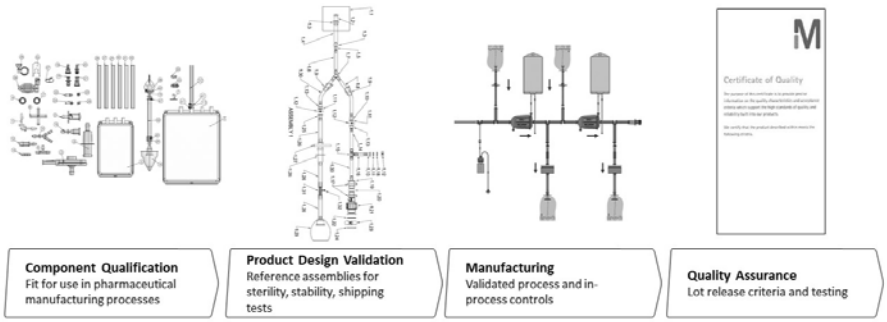

Figure 1. Single-use supplier's responsibility from component qualification to lot release.

While the supplier should have validated packaging and transport conditions it is then up to the end-user to establish incoming controls, inspection, and handling procedures at their site to complete the SUS entire life cycle transparency. With that, the use of SUS requires a strong partnership between end-user and supplier to understand the supplier's quality approach. Industry associations published useful documents and tools in the past years to describe how a good collaboration between supplier and end-user could be set-up and how critical quality information could be shared (Biophorum, 2018).

The last open question is now, if and under which circumstances should the end-user do an integrity test of the SUS at the point of use - which is technically feasible. However, new risks such as unintended bag interactions with supporting equipment or assembly damage from over-pressurization could be introduced. Furthermore, the desired test sensitivity could be limited due to the typically complex design of single-use systems used in aseptic processing.

Although the updated Annex 1 guidance will provide the first time some more details on regulatory expectations for SUS, there is still the need of an ongoing discussion between the end-user, supplier and regulatory authorities on risk acceptance, risk reduction measures, and technical feasibility. An aligned approach will help biomanufacturers to implement SUT in a timely manner to meet today's increasingly complex drug production demands. The final version of Annex 1 (https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf) was published in week 34 (2022), see the editors' comment on page 41.

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MEMBRANE HEPA FILTRATION TO LIFE SCIENCE: HISTORY, PRESENT AND THE FUTURE

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1 INTRODUCTION

Membrane HEPA filtration or ePTFE (**e**xpanded **P**oly**T**etrafluoro**E**thylene) media which is the technically description of the material used in the membrane filter media has been on the market since the mid 1980´s. ePTFE fine fibers was initially developed by Daikin as part of their chemical division.

ePTFE HEPA and especially ULPA (U15-U17) filters were quickly adopted by the semiconductors industry due to the superior mechanical stability and super low outgassing behavior and proven chemical compatibility compared to traditional micro glass HEPA/ULPA filters. Today ePTFE membrane ULPA filters is the industry standard in the most critical process steps in the semiconductor industry.

In the beginning of 2000´s the LiveScience industry started to show interest in ePTFE filters and made several test in real life environments to check if these filters were in compliance with the standards and especially in relation to the frequent HEPA integrity testing using an oil-based aerosol (photometric test methods) which is not used in the microelectronic industry (Compatible with Discrete Particle Counters (DPC) testing).

This presentation will describe the early progress of the fine fiber technology and the development process of manufacturing commercially available filters throughout the 90´s until today where modern PTFE membrane HEPA filters are replacing the traditional micro glass HEPA filters in the LiveScience industry.

2 MEMBRANE ePTFE STRUCTURE

Clear difference in structure can be seen. ePTFE membrane has much smaller pore size than glass media, in average 0,5–1 µm, i.e., about 100 million pores per cm^2. About 1.000–2.000 of such pores would fit across the tip of a ball point pen. But more important for filtration is the fiber diameter. Diameter of traditional glass fibers is in the range of 0,5–1µm, whereas PTFE fibrils diameter is in the range of 20–200 nm. These ultra-thin PTFE fibrils provide excellent filtration efficiency, particularly for very fine particles but also create an extremely low pressure drop by slip-flow effect (Figure 1).

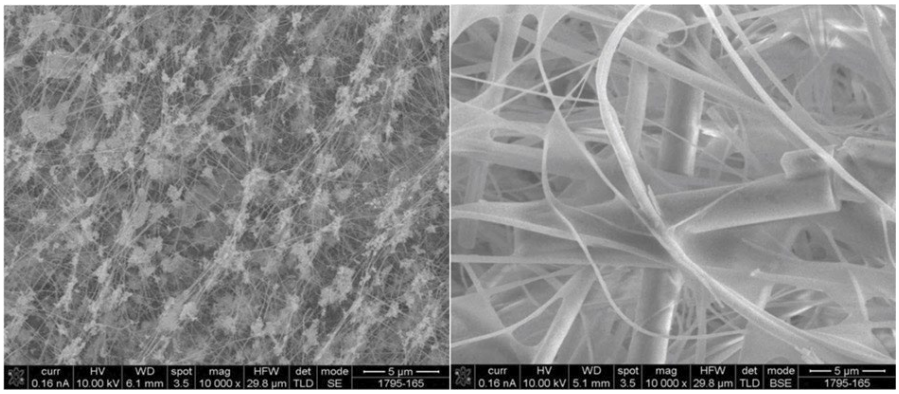

Figure 1. ePTFE membrane (left) and traditional glass fiber media (right).

3 MODERN MEMBRANE MEDIA REVOLUTION

HEPA product development, mainly in improved media performance over the traditional glass fiber media with PTFE and fluororesin media (eFRM) membrane technology has gained more attention in the last decade. Optimizing the design of the filter pack (configuration) in combination with the membrane technology offers the lowest resistance and highest efficiency at the most penetrating particle size (MPPS), therefore delivering the lowest possible total cost of ownership (TCO) over the filter's useful lifetime. End users expect that HEPA and

ULPA filters deliver a clean a product as possible. low outgassing and no particle shedding downstream during the operational lifetime.

With the dual layer eFRM membrane media filters comply to the frequent integrity testing without any significant increase of pressure drop. Using frequent PAO testing is the number one external challenge HEPA filters are exposed to during the operational lifetime.

GMP grade A and B HEPA filters are typical being tested every six months where the upstream concentration of oil aerosols represents a significant challenge effecting the lifetime and pressure drop of HEPA filters.

The dual layer membrane technology introduced 8 years ago has opened the possibility to use these filters also in the LiveScience industry utilizing the very high efficiency, extremely robust fiber structure and very low pressure drop.

4 PHOTOMETER OIL AEROSOL TEST – REAL LIFE EXPERIENCE

In the very beginning the LiveScience industry was hesitating to adopt membrane HEPA filters due to the lack of evidence during the operational lifetime in real life installations. Now with literally hundreds of installations worldwide, several long-life test and PAO challenged filters the dual layer membrane PTFE HEPA filters has proven to be very effective with zero defects and significant savings in energy due to the very low average pressure drop during the lifetime.

Especially the PAO test has been subject to several discussions. Figure 2 shows the pressure drop development of two type HEPA filters, one with ePTFE dual layer membrane (MegaCel) and one with traditional glass fiber (AstroCel). Both filters have been challenged with a PAO concentration of 20 mg/m^3.

The loading represents many on site test and the conclusion is clear. The eFRM membrane HEPA filters show similar behaviour to the

oil challenge as traditional glass HEPA filters at a lower average differential pressure drop. It clearly shows the suitability of the product in pharmaceutical applications where photometer tests with high challenge concentrations are still in practice.

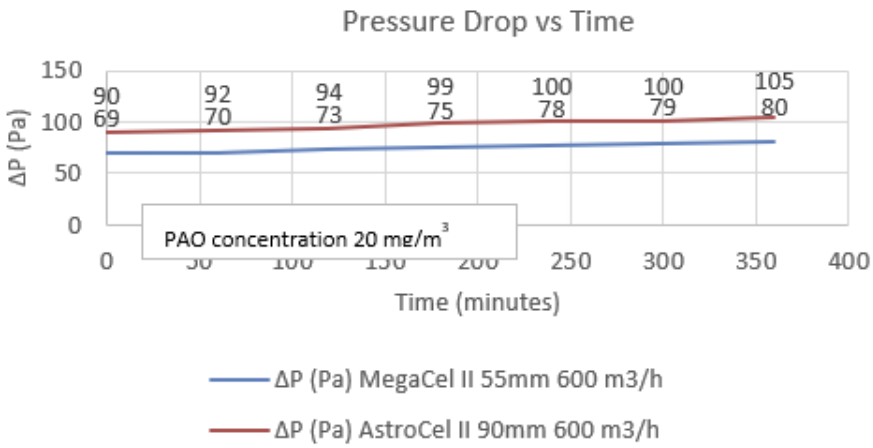

Figure 2. Field test simulation performed by NNE Copenhagen, 10-2019.

5 1000-DAYS REAL LIFE DATA TEST AND ENERGY SAVINGS

A recent 1000-day real life data test has just ended. The purpose of this test was to check how membrane HEPA filters react when exposed to ambient air under different operational conditions. The real-life test was made possible with a special designed test container using two separate test channels where both glass fiber and membrane filters was installed exposed to identical conditions. Sensors was monitoring dP, particle level, humidity and temperature making online measurement possible (Figure 3).

Figure 3. The test container with installed filters located in Latvia. Inside the container are installed two sets of HEPA H14 filters, one with membrane eFRM media and one with traditional glass fiber media. Each filter has a prefilter of class ePM1 55% (F7).

The results shows that the pressure drop correlation with relative humidity throughout the year does not affect the membrane media with increased pressure drop and lower lifetime. Certain fluctuations were observed during the test on both filters when the relative humidity increased typical during nighttime, but this went back to normal again during day time.

During the 1000 days test the average pressure drop of the filters measured was calculated. The average on the glass fiber HEPA was 428Pa and on the membrane is was 223Pa (Figure 4).

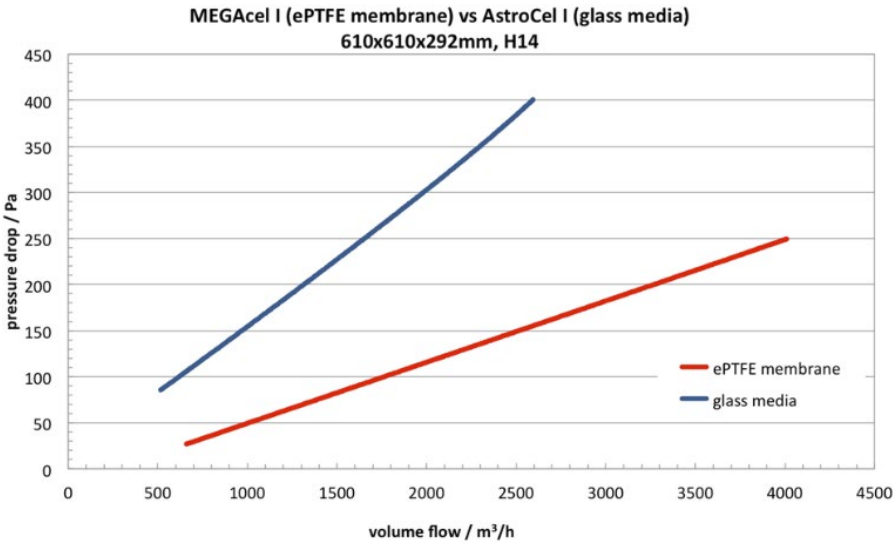

Figure 4. Showing pressure drop as function of volume flow for a H14 ePTFE membrane HEPA filter (red line) and a traditional H14 glass media HEPA filter.

6 IN CONCLUSION

With a significant average pressure drop advantage of approx. 50% over traditional glass fibre membrane HEPA filters has shown a significant energy savings. When calculating the total cost of ownership (TCO) based on total kwh consumption and the impact of the carbon footprint the significant advantages of using high efficiency membrane fibres in HEPA filters is obvious. A simple calculation based on today's energy cost shows a saving of € 1332 per filter with a constant 25-month operational condition and a reduction of the CO_2 footprint with almost 50%. Furthermore, the membrane fibres provide a high mechanical strength (84x tensile strength of glass) which reduces the risk of damaging the HEPA filters media during transportation, handling, and operation. Finally with the dual layer structure ePTFE membrane HEPA filters can handle high dust loads and oil aerosols challenges during photometer test ensuring a long operational lifetime with a low average pressure drop.

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ADVANCES OF HEPA FILTRATION IN PHARMACEUTICAL APPLICATIONS AND THEIR NEW USE IN DAY-TO-DAY POST PANDEMIC LIFE

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1 INTRODUCTION

As a result of the COVID-19 pandemic, HEPA filtration technology has become increasingly popular for treating the air and capturing the airborne SARS-Cov-2 virus. HEPA is the acronym for "High Efficiency Particulate Air" or "High Efficiency Particulate Arrestance". Until recently, this technology has predominantly used in specialised fields, such as pharmaceutical production clean rooms or hospital operating rooms where exceptional air quality is required. One of the main reasons for the increasing popularity of HEPA filters is due to their use as a consumer product when integrated on an air purifier (Figure 1).

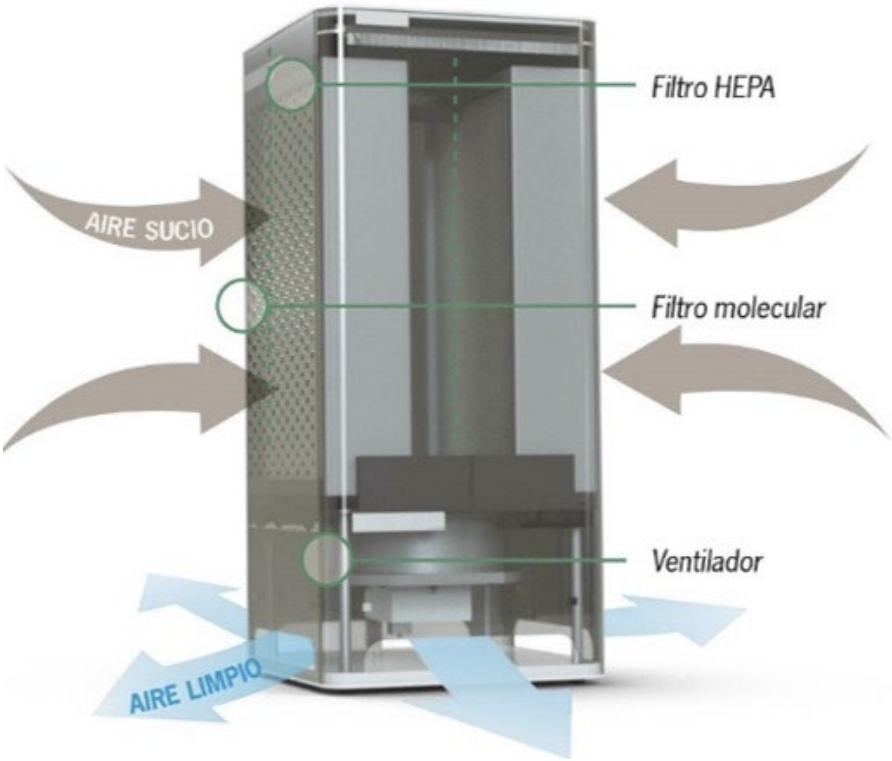

Figure 1. Diagram of an air purifier with HEPA filter.

Air filtration is a physical, biological, or chemical operation that can separate particulate and gaseous contaminants from an air flow by means of passing it through a filter media. This filter media consists of a complex structure designed specifically to provide targeted capture of contaminants of a particular size range or chemical composition.

There are a wide range of filters that serve multiple applications in industries such as nuclear, Pharma, Food & Beverage, and Microelectronics. These sectors are highly regulated, and professionals who work in these fields already have a deep technical knowledge of filtration technology. However, the concept of filtration has not been adopted so well amongst the public. There is great confusion among many people with regards to the definition of different types of filters and their performance. For example, the word "HEPA" has been historically misused by consumers of vacuum cleaners, air purifiers or even home air conditioning filters.

Many filters that are currently on the market do not fully meet the industry definition, as they do not offer the minimum required filter efficiency. We even see the word "HEPA" being misused creating further confusion (HEPA-Type, HEPA-Like or True-HEPA). A true HEPA filter does not need to be given a special name. A true HEPA filter must have been tested (Figure 2) and supplied with a test certificate confirming its efficiency in accordance with EN1822 or ISO 29463. In summary, there are only two options when it comes to a HEPA filter: the filter is either a HEPA filter or it is not.

Figure 2. Leak test on a HEPA filter (above) against a so-called True-HEPA filter (below).

2 WHAT IS A HEPA FILTER?

The HEPA filter is a type of mechanical filter. It works by providing a barrier in the form of a very dense filter media which is made up of very fine fibres that trap practically all particles. HEPA filters are not a recent innovation, they were developed by the American Federal Government in the early 1950s. Their original purpose was to capture the contaminants associated with the manufacture of the atomic bomb in the Manhattan Project (Figure 3).

At that time, HEPA filters were called "Absolute" filters since the objective was to have absolute particle filtration efficiency, capturing all

particles from the air stream. Since then, the "Absolute filter" or "HEPA filter" terminology has been used interchangeably. For some time in the 1960s, the HEPA filter was not commercially viable, but applications gradually appeared with the manufacturing of audio players and in the semiconductor industry. Today's modern world would be technologically very different without the existence of HEPA filters, since it would have been very difficult to develop the sensitive electronic components that we find today in all the devices that surround us. Today, HEPA technology helps to protect advanced and sensitive manufacturing processes and protect people from microbiological contamination in research laboratories. HEPA filters are also used to eliminate infectious pollutants from the air in the health sector where the risk of infection is high such as operating theatres. They also protect the environment by eliminating polluting particles from industrial extraction systems.

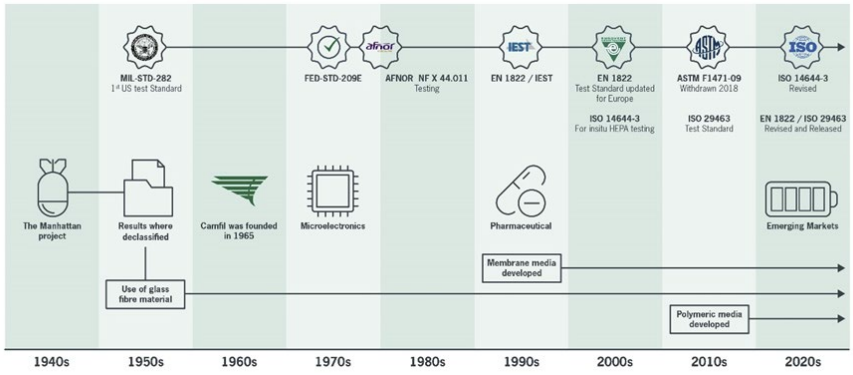

Figure 3. Historic chart of HEPA filters with their regulations and applications.

3 HOW DOES A HEPA FILTER WORK? FILTRATION MECHANISMS AND PRINCIPLES

Different types of filters use different mechanisms to capture particles. There are many theoretical and experimental studies on air filtration using fibrous media. A filter made up of fibres uses various mechanisms to trap particles, which are described in Figure 4.

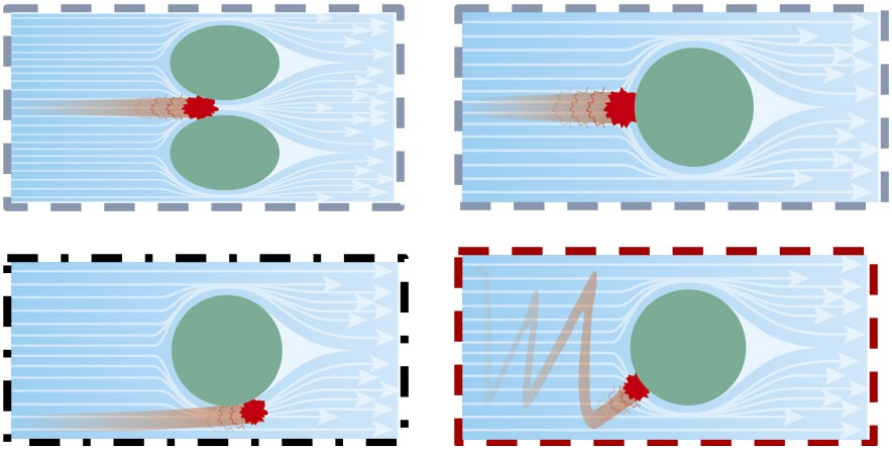

Figure 4. Various mechanisms in trapping particles: straining (upper, left), inertia (upper, right), interception (lower, left), and diffusion (lower, right) mechanisms.

The straining mechanism is the effect that intuitively comes to our minds when we talk about an air filter. When a particle is larger than the distance between the fibres, this particle cannot pass through the gap, and it gets captured by the filter. The straining mechanism is effective on particles greater than 5 µm and typically only captures 1% of the particles in the airflow.

The second filtration mechanism is known as inertia. Here, the momentum generated by the airflow causes the particle to hit the front part of the filter fibres. Large and high-density particles tend to be trapped by inertia. When the airflow passes through the filter media, it passes around the fibres. The rapid change of direction of the airflow and the principle of inertia makes the particle separate from the air stream and hit the fibre. This principle occurs when there is a large concentration of coarse particles. The inertial mechanism is effective on particles greater than 1 µm and captures 1% of the particles in the airflow.

The third filtration mechanism is called Interception. To understand this concept, one must consider how medium and small particles interact with the fibres. All particles and fibres have a small "positive or negative charge" and therefore have an inherent attraction for each

other. This principle is known as "van der Waal's law". This mechanism occurs to a greater extent in synthetic materials. The particle follows the direction of the air flow. When the particle approaches the fibre at a distance smaller than the radius of the particle, it rubs against the filter material and gets retained by it. The particles trapped by this method adhere to all parts of the fibres: the front, back and sides. The interception mechanism is effective on 0.2 to 3 µm particles and captures 30–40% of the particles in the airflow.

The smallest particles in the airflow are trapped by the diffusion effect. These tiny particles travel in irregular paths due to the impacts that happen between them and with other molecules, in a similar way to gases. This movement is known as Brownian motion. Brownian motion is a mathematical model used to describe how particles collide with each other when moving at different speeds and in different, random directions. These irregular movements increase the chances of the particle coming into contact with the fibres and becoming trapped. The diffusion mechanism is effective on submicron particles between 0.001 and 0.2 µm and captures 60–70% of the particles in the airflow.

The fifth mechanism is called "electrostatic charge or effect". The filter fibres are charged in a way that attracts the particles. This effect has a higher efficiency on smaller particles and a lower filter resistance. HEPA filters are rarely designed and manufactured to take advantage of this mechanism. Therefore, this mechanism falls outside the scope of this document.

The overall efficiency of a filter is the total result of the different filtration mechanisms. The straining, inertia and interception mechanisms can have a greater effect on large particles, whilst the diffusion effect is more relevant in smaller particles. Therefore, it is more difficult to filter out a specific particle size. Depending on the airflow speed and the filter material, this particle size tends to be between 0.1-0.2 µm, which is the most difficult particle size to capture by a filter. This particle measurement is called Most Penetrating Particulate Size (MPPS) and is shown in Figure 5.

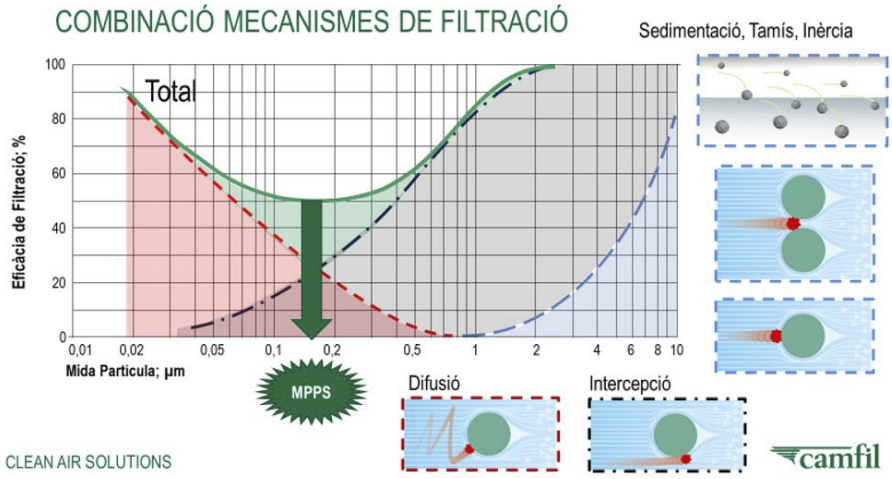

Figure 5. Global filter efficiency graph, with its minimum efficiency point Most Penetrating Particulate Size (MPPS).

In Figure 6 a real example with an H13 filter is shown. The MPPS point is between 0.1 and 0.2 µm with an efficiency of 99.982%. As we can observe in the graph, the most difficult particle size to capture is around 0.12 µm. For larger particles, the efficiency will be higher due to the interception, inertia, and sieve effects. For smaller particles, the efficiency will also be higher due to the additional diffusion effect.

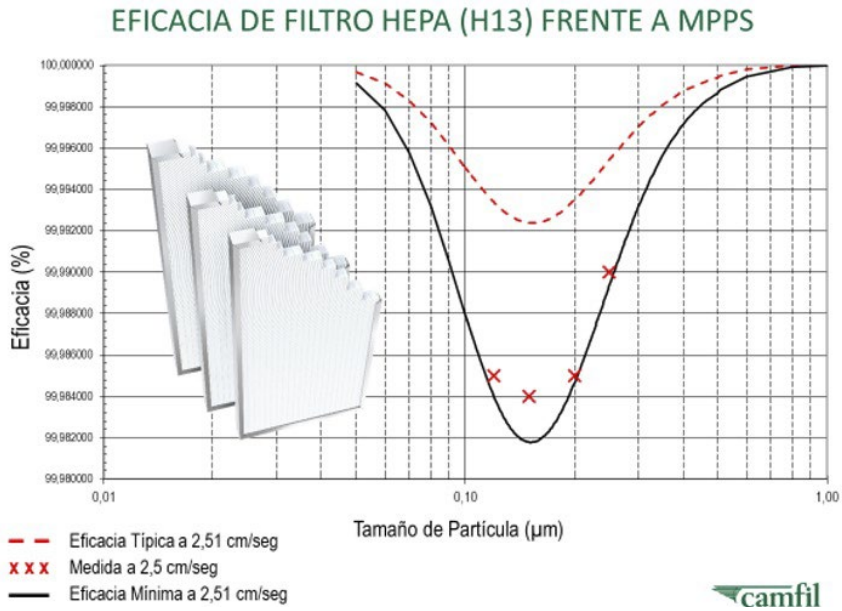

Figure 6. Real global filtration efficiency of a HEPA filter.

4 HOW HEPA FILTERS ARE CLASSIFIED AND REGULATED

We know that the most important feature of an air filter is its efficiency, which is a measurement of its ability to remove airborne pollutants, such as dust, particles, and gases. Other essential properties of a filter include pressure drop and dust holding capacity. To measure these properties, the air filtration industry needs regulations to ensure that filter testing is performed consistently and reliably. Standards based on documented knowledge allows users to classify and compare filters from different manufacturers. These regulations help us to classify HEPA filters in different classes according to the Regulations of reference: EN1822 (Europe) / IEST-PR-CC001 (USA) / ISO 29463 (International).

In Europe, the EN 1822 standard is used (Figure 7). This standard divides the EPA, HEPA and ULPA high efficiency air filter tests into five parts. High-efficiency air filters are classified based on the MPPS. Mandatory efficiency tests (leak) are required for class H13 filters and higher. In the past it was believed that the most difficult particle size to filter was 0.3µm. The appearance of electronic microscopes and optical particle counters determined that the MPPS was between 0.12 and 0.25 µm.

“ISO 29463 - High efficiency filters and filters to remove particles in the air” - is an ISO standard based on EN 1822. It is divided into five parts which are named in the same way as in EN 1822, although ISO 29463 includes additional classifications, i.e. 99.90%, which is ISO 30E (Figure 8).

EN1822 CLASSIFICATION						
Filter Class	Particle Size for Testing	Global Values		Local Leak Values		
		Collection Efficiency (%)	Penetration (%)	Collection Efficiency (%)	Penetration (%)	Multiple of Global Efficiency (%)
E10		≥ 85	≤ 15			
E11		≥ 95	≤ 5			
E12		≥ 99.5	≤ 0.5			
H13	MPPS[a]	≥ 99.95	≤ 0.05	≥ 99.75	≤ 0.25	5
H14	MPPS[a]	≥ 99.995	≤ 0.005	≥ 99.975	≤ 0.025	5
U15	MPPS[a]	≥ 99.9995	≤ 0.0005	≥ 99.9975	≤ 0.0025	5
U16	MPPS[a]	≥ 99.99995	≤ 0.00005	≥ 99.99975	≤ 0.00025	5
U17	MPPS[a]	≥ 99.999995	≤ 0.000005	≥ 99.9999	≤ 0.0001	20

[a] *MPPS - Most Penetrating Particle Size*

Figure 7. Classification table according to EN1822.

ISO 29463 CLASSIFICATIONS						
Filter Class (Group)	Particle Size for Testing	Global Values		Local/Leak Values		
		Collection Efficiency (%)	Penetration (%)	Collection Efficiency (%)	Penetration (%)	Multiple of Global Efficiency (%)
ISO 15 E	MPPS	≥95	≤5	-	-	-
ISO 20 E	MPPS	≥99	≤1	-	-	-
ISO 25 E	MPPS	≥99.5	≤0.5	-	-	-
ISO 30 E	MPPS	≥99.9	≤0.1	-	-	-
ISO 35 E	MPPS	≥99.95	≤0.05	≥99.75	≤0.25	5
ISO 40 E	MPPS	≥99.99	≤0.01	≥99.5	≤0.5	5
ISO 45 E	MPPS	≥99.995	≤0.005	≥99.975	≤0.025	5
ISO 50 E	MPPS	≥99.999	≤0.001	≥99.995	≤0.005	5
ISO 55 E	MPPS	≥99.9995	≤0.0005	≥99.9975	≤0.0025	5
ISO 60 E	MPPS	≥99.9999	≤0.0001	≥99.9995	≤0.0005	5
ISO 65 E	MPPS	≥99.99995	≤0.00005	≥99.99975	≤0.00025	5
ISO 70 E	MPPS	≥99.99999	≤0.00001	≥99.9999	≤0.0001	10
ISO 75 E	MPPS	≥≤99.999995	≤0.000005	≥99.9999	≤0.0001	20

Figure 8. Classification table according to ISO29463.

IEST, an international engineering society based in the United States, has established various test methods. IEST-RP-CC001, 007, 021 and 034 refer to high efficiency air filters (Figure 9). This standard covers different areas, such as filter media performance, classification, design, design requirements, and filter media testing requirements.

In the United States, only those filters with an efficiency greater than 99.97% on 0.3µm particles are considered HEPA. If you follow rigorously the EN1822 standard, the HEPA filter only includes two classification grades: H13 99.95% MPPS and H14 99.995% MPPS. For these filter classifications, manufacturers are obliged to provide the customer with an individual efficiency and "Leak Test" certificate. In Figure 10 a HEPA filter scanning certificate according to EN1822 is shown.

Other levels of classification are:

- On the lower end: EPA filters E10, E11, E12. These filter levels would not pass the leak test.
- On the upper end: ULPA (Ultra Low Particulate Air) filters U15, U16, U17. These are the most efficient filters available and are basically used in the microelectronics industry.

Heavily regulated industries with strict quality requirements rely on standardised HEPA filters for their air quality needs. Filters help protect against potentially devastating economic and health consequences. For example, when a food processing process becomes contaminated or when an infectious virus spreads outside of a research laboratory.

IEST-RP-CC001						
Filter Type	Particle Size for Testing	Global Values		Local Leak Values		
		Collection Efficiency (%)	Penetration (%)	Collection Efficiency (%)	Penetration (%)	Multiple of Global Efficiency (%)
A	0.3[a]	≥ 99.97	≤ 0.03			
B	0.3[a]	≥ 99.97	≤ 0.03	Two-Flow Leak Test		
E	0.3[a]	≥ 99.97	≤ 0.03	Two-Flow Leak Test		
H	0.1-0.2 or 0.2-0.3[b]	≥ 99.97	≤ 0.03			
I	0.1-0.2 or 0.2-0.3[b]	≥ 99.97	≤ 0.03	Two-Flow Leak Test		
C	0.3[a]	≥ 99.99	≤ 0.01	≥ 99.99	≤ 0.01	1
J	0.1-0.2 or 0.2-0.3[b]	≥ 99.99	≤ 0.01	≥ 99.99	≤ 0.01	1
K	0.1-0.2 or 0.2-0.3[b]	≥ 99.995	≤ 0.005	≥ 99.992	≤ 0.008	1.6
D	0.3[a]	≥ 99.999	≤ 0.001	≥ 99.99	≤ 0.005	5
F	0.1-0.2 or 0.2-0.3[b]	≥ 99.9995	≤ 0.0005	≥ 99.995	≤ 0.0025	5
G	0.1-0.2	≥ 99.9999	≤ 0.0001	≥ 99.999	≤ 0.001	10

[a] *Mass median diameter particles (or with a count median diameter typically smaller than 0.2 µm as noted above).*
[b] *Use the particle size range that yields the lowest efficiency.*

Figure 9. Classification table according to IEST-RPCC001.

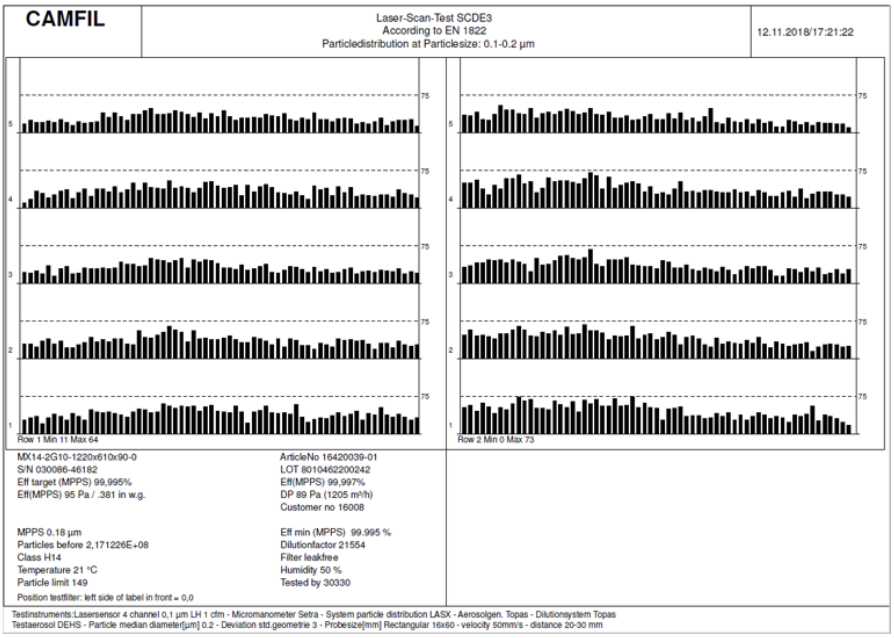

Figure 10. HEPA filter scanning certificate according to EN1822.

5 CAN A HEPA FILTER CATCH VIRUSES?

If you have been reading this document carefully, you will be able to answer this question yourself. Nevertheless, we will clarify certain concepts that have led to confusion when talking about HEPA filters. The following statement has appeared in recent publications: "A HEPA filter filters 99.97% of 0.3 µm particles. Given that a virus is a small particle, measuring 0.12 µm, then a HEPA filter will not filter coronavirus"

What is inaccurate about this statement? There are 3 fundamental errors:

1. "A HEPA filter filters 99.97% of 0.3µm particles"

   This classification only applies to one filter model according to the American regulations. However, as shown in the European and new ISO classification tables in previous chapters of this document, the efficiency is determined by the MPPS, and in the case of an H13, this efficiency would be 99.95% over the MPPS.

2. "Given that a virus is a small particle, measuring 0.12 µm"

   This implies that a virus is uniquely airborne; however, this only happens very rarely. Viruses do not travel on their own, they invade organisms by taking over their host's RNA (ribonucleic acid). They are a parasite. Current thinking is that the combination of viable viruses and the host is greater than one micron. Particles with a measurement greater than one micron will remain suspended in the air for a long period of time (several hours), but they are much easier to capture by filters than sub-micron particles.

3. "a HEPA filter will not filter coronavirus"

   Once you understand how a filter works, you will find this to be a ridiculous statement. It shows that many people only have the straining mechanism in mind when they think about air filters.

If we assume that the particle size of SARS-COV-2 is between 0.09 and 0.12 µm, then the efficiency of a HEPA H13 filter would be at least 99.95%, as we have seen in the above classification tables. This assumes that the virus travels on its own, which we have said is very unlikely. Therefore, if the virus is attached to a one-micron particle, the efficiency of a HEPA filter would be practically 100%. Currently, a more efficient air treatment technology does not exist.

To understand how difficult, it is for a virus to pass through a HEPA filter, let's do a comparison (Figure 11). Let us imagine that the virus is a football, the filter material is represented by 6 km of dense jungle and the air flow is the force of the kick. The game consists of shooting the football through the 6 km of jungle. The football, which will follow a random trajectory with changes in direction, must not hit or slightly touch any trees, branches, plants, or leaves that finds in its way. Difficult to achieve, isn't it? It is so difficult that you will not succeed 99.982% of the times. What if the football were an airplane? When the virus is attached to a larger particle, it is practically impossible that it goes through the filter media 100% of the times.

Figure 11. Microscope image of a HEPA filter fibre / Football and jungle comparison.

6 WHAT DOES A HEPA FILTER LOOK LIKE?

The components of a HEPA filter (Figure 12) are:

- Filter media, made of fibreglass, a PTFE membrane or the newly developed Multifibre polymeric material.
- Frame, made of aluminium, plastic, stainless steel, wood, galvanized steel, or others.
- Sealant. This is the material that glues the filter media to the frame. It can be made of polyurethane, silicone, ceramic, or others.
- The separating pieces that conform the filter media pleats. These can be made of aluminium, glass fibres, hot-melt, others.
- Sealing gaskets, which can be made of expanded polyurethane, neoprene, silicone, gel, others

For a HEPA filter to achieve the relevant individual effectiveness and obtain a leak test certificate, two things must happen: the filter paper must have the appropriate efficiency, and the entire filter must be designed and manufactured to a leak-free criteria.

Figure 12. HEPA filter for laminar airflow (left) and for high airflow (right).

7 WHERE DOES A HEPA FILTER GET INSTALLED?

Another important point to be aware of is the area where the filter will be installed Figure 13). This equipment must also be designed and manufactured to an appropriate leak-free criteria. The following details should be observed:

- A smooth and levelled mounting face where the filter gasket can sit properly.
- A fixing system that ensures a homogeneous tightening torque around the entire filter gasket to avoid leaks between the gasket and the mounting face.
- Leak-free equipment where the filter is installed to avoid a by-pass of unfiltered air.
- Materials resistant to cleaning and decontamination to prevent product degradation over time.

To ensure that the filter is intact and that it has not been damaged during transport or installation, it is recommended to perform a leak test on the filter at the place of use. This test is also called an "integrity", "smoke" or "DOP" test. The test consists of generating an aerosol (see table below) and passing it through the filter (Figure 14). A commonly used aerosol is PAO (hot).

Figure 13. To the left there is a terminal housing for a classified room and to the right a Safe Change housing i.e. (BIBO)BAG in bag out.

Challenge Aerosols Frequently Used for HEPA Testing	
DEHS (DOS), a liquid	Di-ethyl hexyl sebacarte
DOP, liquid	Di-octyl phthalate
Emery 3004, liquid	Product name for a type of PAO
PAO, liquid	Poly-alpha olefin
PSL	Poly-styrene latex spheres
Shell Ondina EL, liquid	Refined mineral oil
Total Finaveston A80B, liquid	Refined mineral oil

Figure 14. Aerosol table and photometer equipment.

There are different regulations set different concentration ranges for this aerosol:

IEST-RP-CC034: 10-20 mg /m^3
ISO-14644-3: 1-100 mg /m^3

After the aerosol is generated at the filter inlet port, the absence of leaks is verified by a photometer or a particle counter (DPC). To certify that the filter is "Leak Free", the penetration percentage must be below 0.01%.

The housings where HEPA filters are installed and many other equipment, such as biosafety cabinets, isolators, sterilization tunnels, aseptic fillers have many professional fields of application, for example, pharmaceutical laboratories (Figure 15).

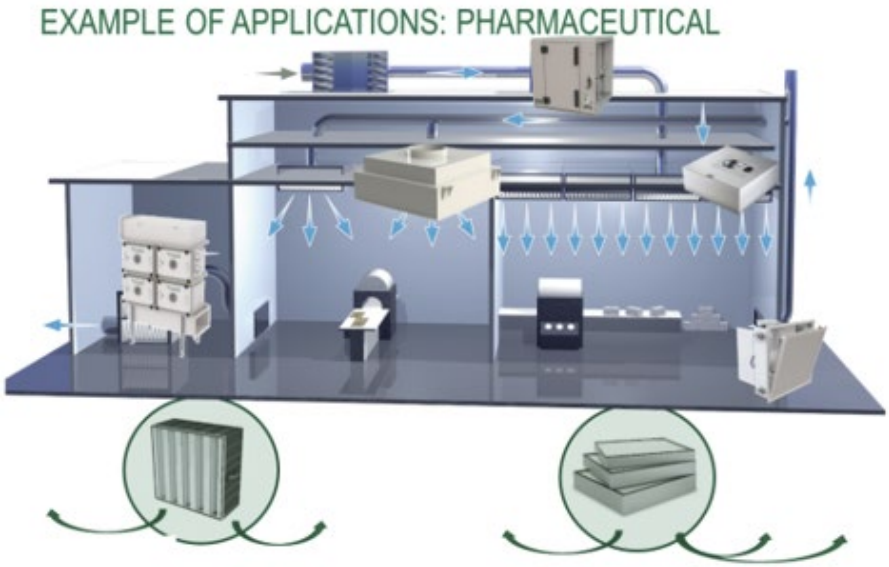

Figure 15. Example of HEPA filters being used in a pharmaceutical lab facility.

Other areas of application are hospitals, nuclear power plants, the food industry, veterinary laboratories, cosmetic industry, biosafety centres, etc. Lately, HEPA filters have become more popular due to their use in household vacuum cleaners, car cabin filters, air purifiers. HEPA filters have been around us for more than 70 years. We have most likely breathed or will breathe air filtered by HEPA filters throughout our lives. Everything suggests that HEPA filters will be around for many years to come, helping to improve the air quality of our environment. This is why I hope this document has helped you to understand a little better what HEPA filters are, how they work and their great importance now and, in the future, to protect people and processes from airborne contamination.

GMP ANNEX 1 – HOW TO VALIDATE PROTECTIVE CLEANROOM GARMENTS?

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1 INTRODUCTION

After a 2-year long consultation period, the publication of the revision of the GMP Annex 1 for the manufacturing of sterile products is finally foreseen for the 2nd semester of 2022 or latest in early 2023. Not only the lengthy consultation period, but also the expansion of the document from 16 to 50 pages herald that this revision will have repercussions on the technologies and the procedures used in pharmaceutical manufacturing and to the approach that needs to be taken when validating cleanrooms.

The following excerpt from the very first page of the 2nd draft summarizes the new approach: "*Processes, equipment, facilities, and manufacturing activities should be managed in accordance with QRM (Quality Risk Management) principles that provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality.*" It will be expected that all the activities inside the pharmaceutical manufacturing will be governed holistically by the QRM principles and documented in the contamination control strategy (CCS). It will be expected that the CCS is a living document, based on a data-driven scientific approach. It should be continuously updated and improved to control potential risks to quality. The new draft is calling for a proactive approach, simply reacting to and correcting detected contamination will no longer be enough. It will be expected from the manufacturers that they fully understand their processes and procedures, so that they identify upfront the potential risks to quality, put in place all the technical and procedural means to control these risks while aiming

for continuous improvements. Since cleanroom garment systems are a critical part of sterile and aseptic manufacturing, they obviously need to be managed under QRM principles too.

2 QUALITY RISK MANAGEMENT PRINCIPLES FOR CLEANROOM GARMENTS

Quality risk management (QRM) starts with an analysis and understanding of all the risks to quality linked with cleanroom operators wearing cleanroom garments. A complete data-based analysis will allow to design certification, qualification, validation, and monitoring procedures which have quality built into them, thus being part of a holistic contamination control strategy. A risk analysis is needed to understand the contamination risks coming from operators wearing cleanroom garments. It has been scientifically demonstrated for many years that operators represent the biggest source of contamination inside the cleanrooms and represent 75% of all contaminants (Ramstorp, 2000). This contamination is coming both from the operators themselves and from their cleanroom garments. The human contamination coming from the operators is due both to our human nature (an average person sheds 40 000 particles per minute and 10% of them carry micro-organisms) and human behaviour (Whyte & Hejab, 2007). While it is possible to mitigate the latter aspect through careful operator selection, training, slow movements or impeccable hygiene, fact is that operators will always be shedding particles, as multiple studies have proven. The only measure to prevent that the particles generated by the operators will contaminate the cleanroom are the cleanroom garments, they are the only barrier between the operator and the production environment. The 2020 draft of the annex 1 clearly points this out in the lines 830–31: *"the cleanroom garments should) retain particulates shed by the body"*.

It should not be neglected that the cleanroom garments themselves may be a source of contamination and this risk needs to be assessed too. For example, the material used for making the garments (non-woven for the single-use garments or woven for the reusables) can

shed particles depending on the nature of the fibers or filaments used, their resistance to abrasion or their construction as well as the effect of multiple wash-dry-sterilization cycles. The trims (zipper, buttons, elastics or sewing threads) too may be a source of contamination. The design of the garment plays a role too and should be evaluated. One detail which is often neglected is the packaging in which the cleanroom garments come, which could be a source of contamination too i.e., paper-back bag vs. plastic bags.

3 MAIN STAGES OF THE VALIDATION

Once the risks have been evaluated, they should be, as far as possible, removed or replaced by technical or organisational means and the residual risks mitigated as much as possible using a validated cleanroom garment system. Pavičić and Wagner (2019) have in their article "Risk & Science-Based Validation of Cleanroom Garments" described a QRM based structured approach (Table 1) to validate cleanroom garments that meets EU general guidance on validation.

The GMP Annex 1 is calling for a scientific evaluation and control of all potential risks to quality. It is therefore logical that the evaluation of the cleanroom garments must also be based on scientific test data allowing to assess the performances of the garments as well as enabling a control of these performances over the lifetime of the garments. Simply relying on experience, visual checks and recommendations from the suppliers will not be enough any longer for the authorities. In the paper by Pavičić and Wagner (2019) a series of criteria, which can be measured, scientifically tested, and documented, for validating cleanroom garments was suggested. Thus, these criteria meet the expectations of the new GMP Annex 1 (Table 2). In this article, some of these test methods will be explained with their advantages, as well as their disadvantages.

Table 1. Various qualification steps in Quality Risk Management (Pavičić & Wagner, 2019).

Table 2. Criteria for validating cleanroom garments that can be measured, scientifically tested, and documented (Pavičić & Wagner, 2019).

MATERIAL QUALIFICATION	PERFORMANCE TESTING	STABILITY TESTING	USABILITY EVALUATION
Cleanroom garments	*Cleanroom garments*	*Single-Use garments*	*User scenarios*
• Fiber and particle shedding • Sterilization compatibility • Sterility assurance level • Pyrogenicity • Particle filtration efficiency • Bacterial filtration efficiency • Porosity • Surface resisitivity • Perforation resistance • Mechanical resistance • Protection against biological agents	• Body box testing • Helmke dum test	• Properties and characteristics at the end of shelf-life *Reusable garments* • Properties and characteristics after maximum number of laundering and sterilization cycles	• Transfer to classified storage area • Readability of label • Easy opening of packaging • Aseptic unfolding of garments • Gowning • Donning additional accessories (e.g., sterile gloves, face mask, goggles) • Work situations • Safety, biosafety • De-gowning
Packaging	*Sterile packaging*	*Sterile packaging*	*Packaging*
• Fiber and particle shedding • Bioburden • Penetration of commonly used disinfectants *Sterile packaging* • ISO 11607-1	• Influence of transport on integrity/sterility (ISO 11607-1)	• Packaging integrity/sterility at the end of shelf-life (ISO 11607-1)	• Aseptic presentation of garments (multiple layers)

Source: Pavičić M. & Wagner T., *Risk and Science-based Validation of Cleanroom Garments*

4 TESTS FOR THE MATERIAL QUALIFICATION

As stated above the most important function of the cleanroom garments is to make sure to retain a maximum of the particles shed by the operators. Since the human being is constantly shedding particles and microorganisms, we must rely on the cleanroom garments to make sure that they stay inside the cleanroom garment and do not risk contaminating the cleanroom. It is therefore important to assess the filtration efficiencies of the garments, which are determined both by the structure of the material out of which the garments are made and the construction of the garments i.e., seams and design. The former will be treated in this paragraph and the latter in the section on the garment qualification.

1) The particle filtration efficiency (PFE) measures the filtration efficiency of the material used for cleanroom garments against dry particles shed by the operators e.g., skin flakes, even when stationary, people generate approximately 100,000 particles of 0.3 µm or greater). The dry particle filtration of the materials depends on the pore size of the fabric, the smaller the pore size, the higher the filtration efficiency. It may be assessed with the test method EN 143, which measures the filtration efficiency using salt particles having a diameter of 0.3µm. Since this is the smallest size of particles shed by humans and since the smallest size of particles used for the pharmaceutical cleanroom classification is 0.5 micron, this test is well suited for assessing the PFE of the materials, but since it assesses the fabrics only it cannot be used alone.

2) The bacterial filtration efficiency (BFE) measures the filtration efficiency of the material used for cleanroom garments against bacteria shed by the operators. Humans release microorganisms through skin flakes (microbe-carrying particles) or sweat. The microbe-carrying particle filtration efficiency is again determined by the pore size and may be assessed by the EN 143 test as well or by the ISO 22612 which measures the resistance to penetration by biologically contaminated solid particles. The liquid filtration efficiency is determined by the absorbency of the fabrics, the more

liquid repellent a fabric is the higher its filtration efficiency. The ASTM F2101-19 standardized test method evaluates the bacterial filtration efficiency using a biological aerosol (*Staphylococcus aureus*) with a droplet size of 3 micron (ASTM, 2019). While this test was originally developed for medical face masks, it can also be used for assessing other materials and is relevant for cleanroom garments as well since Staphylococci represent one of the highest sources of human contamination inside the cleanroom. While yielding pertinent results, this is also a material test only and therefore it should not be used as a sole assessment point.

5 TESTS FOR THE GARMENT QUALIFICATION

The particle retention performance is not only determined by the materials used, but also by the construction and the design of the cleanroom garments themselves. The Institute of Environmental Sciences and Technology (IEST) has developed two standards for assessing the particle shedding and particle retention performances of cleanroom garments which would be very useful for the qualification of cleanroom garment systems.

The Helmke Drum test method as per IEST-RP – C003.4: it is a rotating drum, with a rotating speed of 10 turns per minute, in which the cleanroom garments are being tumbled while a particle counter inside the drum is measuring the concentration of particles per minute for the sizes 0.3 micron and 0.5 micron. The results are then classified into 3 categories based on the number per size of particles released (Table 3).

Table 3. Helmke Drum test result in classification for coveralls.

Category	Particle concentration	
	Particles ≤ 0.3 µm/minute	Particles ≤ 0.5 µm/minute
I	< 2 000	< 1 200
II	2 000 – 20 000	1 200 – 12 000
III	20 000 – 200 000	12 000 – 120 000

1) This non-destructive test method is only measuring the particle release of cleanroom garments and is therefore quite widely by cleanroom laundries to control the efficiency of their washing processes, but it has also been used by scientific studies to assess the particle release over time for cleanroom garments that are washed multiple times (Ljungqvist & Reinmüller, 2005; Romano et al., 2016). Since these studies have demonstrated that the particle release is increasing with each wash-dry-sterilisation cycle, the Helmke Drum test method may also be used for assessing the particle shedding over time in order to define the moment when the cleanroom garments need to be replaced. A visual inspection of the garments after the washing is not enough to detect the degradation of the particle release of the cleanroom garments. However, the Helmke Drum test method is no able to assess the particle filtration efficiency of cleanroom garments, so should not be used as the unique qualification criteria.

2) The Body box test (IEST-RP-CC003.4) is done inside a small cleanroom cabin in which an operator wearing a cleanroom garment system is performing a series of predefined movements during which the particles inside the body box are being measured and counted. For the time being, this is the test closest to real wear conditions inside cleanrooms. It is measuring both the particle release of the cleanroom garments while they are being worn and the particle filtration efficiency of the garments. The lesser particles the garments shed and the better the particle filtration efficiency of the garments is, the lower the measured particles will be. Here some examples:

Since this is a non-destructive test, it may also be used for assessing the performance of cleanroom garments which are washed multiple times to assess the moment when they need to be replaced. Various studies e.g., by Ljungqvist and Reinmüller (2005) show that the performance of reusable cleanroom garments is going down over time. As close to real work conditions the body box may be, it does have the drawback that the test is also measuring the particle release of the test persons without being able to distinguish which particles stem from the operator and which are released by the garment itself. As the study by Whyte and Hejab (2007) shows, humans have a highly variable rate of particle

shedding. Therefore, comparative tests are only meaningful if the same test person is used for running body box tests of different cleanroom garment systems or cleanroom garment that are old. Under the right test procedures, the body box is an excellent test for validating cleanroom garment systems (Figure 1).

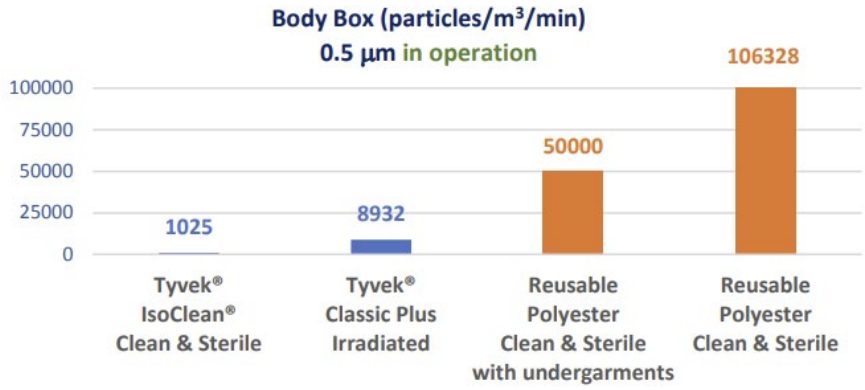

Figure 1. Body box test of various garments carried out by DuPont.

6 ASSESSMENT OF CLEANROOM GARMENT STERILITY

In aseptic manufacturing (grades A/B) only sterile cleanroom garment systems may be used. It is expected that the sterilization process is based on data, fully documented and is part of the contamination control strategy. Following a validated sterilization process which can guarantee a sterility assurance level of 10^{-6} as per ANSI/AAMI/ISO 11137-1 is recommended because it measures the bioburden before and after the sterilization process to guarantee the sterility assurance level. The sterilizer (manufacturer) or laundry of the cleanroom garments should be able to provide a certificate of sterility. A simple certificate of irradiation or a protocol stating the temperature and duration of the autoclaving process will not be sufficient anymore.

7 IN CONCLUSION

Since operators represent the highest contamination risk inside cleanrooms, the cleanroom garment systems are a critical part of the contamination control strategy. The new GMP Annex 1 is asking for a proactive, wholistic, risk-based and data-driven process validation. It will become necessary that the selection of the cleanroom garment systems is based on scientific data and not only on experience, wearers' comfort and/or costs. Using recognized testing methods like those suggested in this paper to assess the performances of cleanroom garment systems and to determine their end of life, should be part of a structured and well documented approach which would fit well into the QRM based contamination control strategy and thus meet the expectations of the latest regulatory requirements.

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Editors' comment:
The final version of Annex 1 in Manufacture of Sterile Medicinal Products (https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf) has been published in week 34 (2022). This document provides technical guidance on the principles and guidelines of good manufacturing practice (GMP) for medicinal products. The deadline for Annex 1 coming into operation is August 25, 2023, except for point 8.123, which is dealing with the frequency of lyophilizers' sterilisation and which deadline is August 25, 2024.

THE INFLUENCE OF INCUBATION TIME, TEMPERATURE, AND MEDIA ON MICROBIAL SAMPLES FROM CLEAN ROOMS

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Quite a few guidelines (Figure 1) can be found within the area of clean room, aseptic processing, and microbiological monitoring e.g., EU GMP Annex 1 (EC, 2008), FDA Aseptic Guidelines (US/FDA, 2004), EN 17141 (2020) and USP <1116> (PDA, 2015).

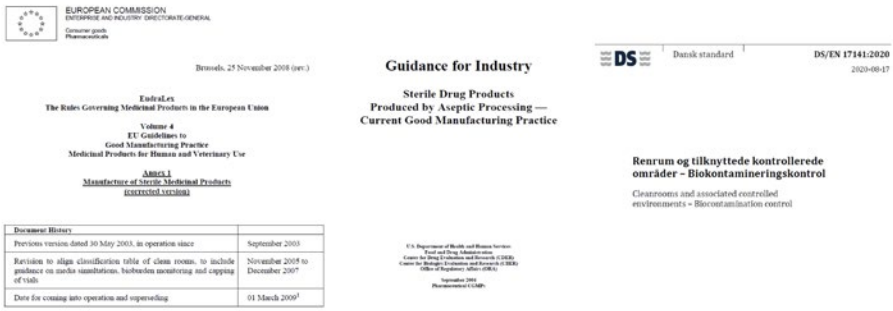

Figure 1. Some of the guidelines available for use in clean rooms, aseptic processing, and microbiological monitoring.

All these guidelines indicate the importance of the microbiological monitoring during aseptic production. Some of them even defines appropriate limits related to room grade. The incubation condition is not unambiguously defined. Some guidelines have no guidance values for incubation time, temperature, and media, and some have indicated a very broad range of suggested conditions. For microorganisms, the incubation regime is essential to ensure growth of the specific microorganism as microorganisms of different origin prefers different incubations regimes.

When performing monitoring in an aseptic environment it must be ensured that some microorganisms there, which might be injured and difficult to grow, get the best conditions allowing possible growth. Therefore, it is important to choose a suitable incubation regime to ensure the right environment for the microorganism (Figure 2). The aim must be that as many of the collected microorganism as possible are able to grow. The incubation temperature, media, and time are parameters of importance. If these parameters are not suitable for a specific microorganism, the growth of it will be delayed or the growth will not even take place.

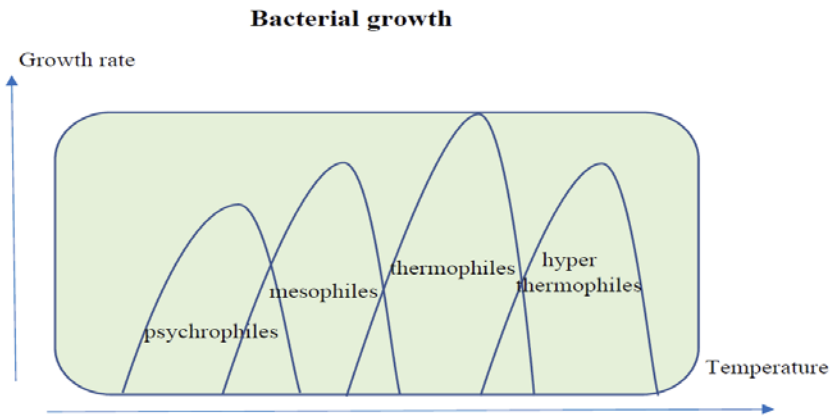

Figure 2. Various microorganisms grow in different temperature zones.

Therefore, it is very important to access set-up of the incubation regime using risk assessment. Questions e.g., what sources in the aseptic environment could contribute to microbial contamination, what are the growth optimum of these microorganisms, and which are the specific microorganisms of special interest, should be asked. Studies have been performed by comparing incubation temperature and time on a commonly selected growth media. The results indicate well how a suitable incubation regime can be set up. In this presentation data from comparison of different incubation temperatures somewhere in the Nordic countries will be discussed. To be able to set up a suitable microbiological monitoring program within a given zone the influence of the temperature zone will also be discussed.

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III

HOSPITAL

IS YOUR HOSPITAL PREPARED FOR THE NEXT PANDEMIC?

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1 INTRODUCTION

These two years of pandemic have shown how critical it is to be prepared for unexpected situations. By Stavanger university hospital they wanted to see how prepared the new hospital would be for an upcoming pandemic (or maybe the new normal). The first little task was: "....to make a risk analysis of the emergency entrance in the new hospital, with respect to a potential upcoming pandemic". This seemed to be manageable, until the task was revised: "...to make a risk analysis of the patient flow in the whole hospital, not limited to the emergency entrance". This was a significant change of scope, and no one had done anything like this before, so we had to sit down together and plan this task carefully.

To handle a pandemic is more about dividing of patient flows, organization, and routines, rather than physical space and technical solutions. Thus, the first key notes from the design group regarding increased number of patient beds, change of patient flow in the emergency entrance, isolation of parts of the hospital for infected patients – were all good suggestions, but had to be completed with how to organize this.

2 WORKSHOPS ON PLANNING HOSPITAL ACTIVITIES FOR A NEW NORMAL

All departments in the hospital should be included. Before engaging a huge number of already heavy loaded hospital staff, there were organized some tabletop exercises to develop the way we worked

with this topic. These exercises were very useful, and gave some key elements for the real workshops:

- our primary goal is to build a hospital with suitable patient flow and capacity for a normal situation
- we should implement only a minimum of changes in layout and technical systems, as the design process was more than halfway through
- but – we should discuss and consider the input from all the units

In the workshops, we followed the patient flow from outside (Figure 1) and all the way throughout the buildings (Figures 2–3). From the emergency entrance, the patient flow goes up to the isolation ward and intensive care unit, as well as into the whole hospital in the rest of the buildings.

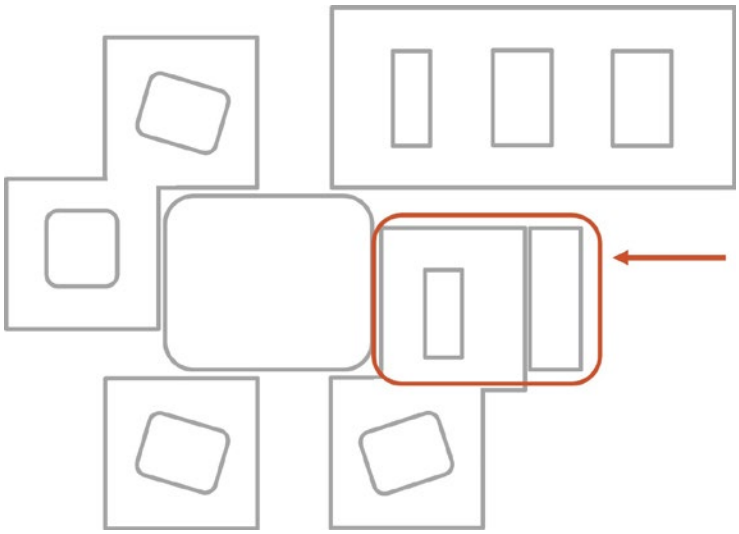

Figure 1. Patient flow into the hospital.

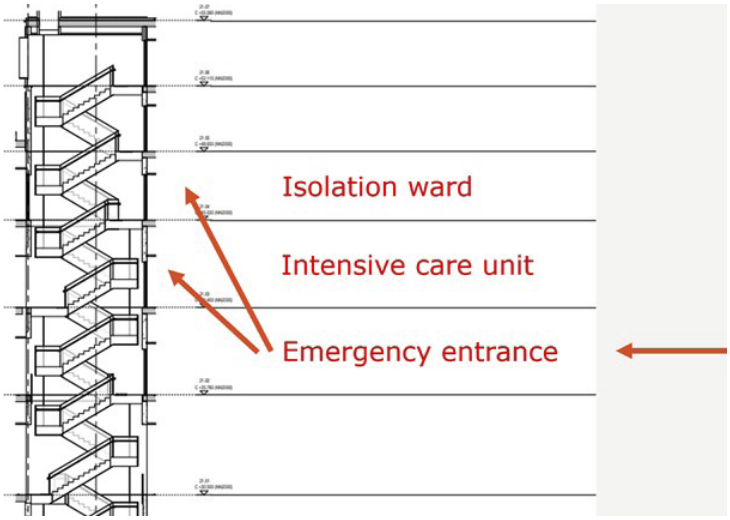

Figure 2. Vertical patient flow.

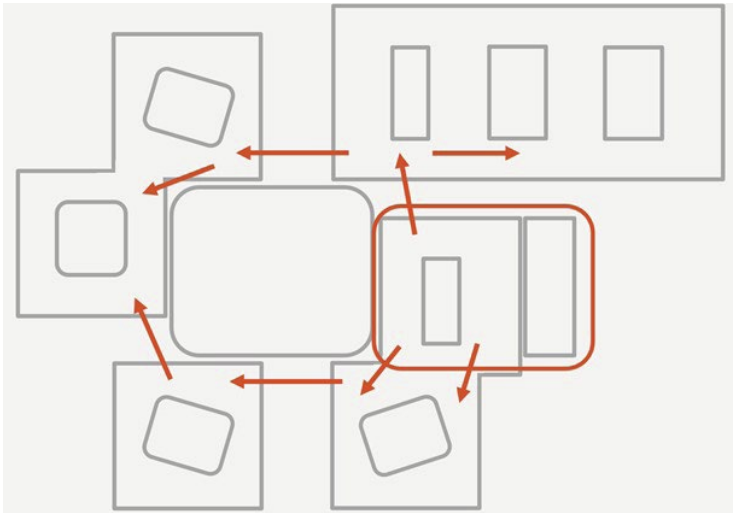

Figure 3. Horizontal patient flow.

For each department, the following key elements were discussed:

- How to divide into separate loops for infected/not infected patients
- How to handle the spread of infected patients into the other hospital units
- How to prepare for cohort isolation
- How to prepare the ventilation systems
- How to prepare the clinical routines.

Output from all workshops were collected. Thereafter, the participants had to prioritize actions dealt with. To handle this, we set up a specific risk matrix, where the pandemic steps were used instead of the probability. Based on that, we could sort the suggested actions according to how critical they were in normal situation and with different number of infected inpatients/patients on respirator.

3 IN CONCLUSION

As we now know more about the risk, we must set up costs related to each action. The cost elements were a bit different in different zones, due to the progress of detailed planning. If we change anything in an area where the design has been closed, it would be a noticeable cost related to re-design. And even worse, if we should change anything mechanical completed, the demolition and reconstruction would be added on top of this.

The total cost elements are important. At the end, these actions were prioritized:

- New door and re-arrangement of the emergency room
- Some new doors
- Windows in doors
- New laboratory for immediate diagnostics
- Pressurizing of areas and rooms
- Heat recovery units changed
- Some new anterooms
- Some new handwashing facilities
- .... and a lot of new pandemic routines.

This work is summarized in a report and accepted by the hospital board.

PEOPLE AS A CONTAMINATION SOURCE IN PHARMACEUTICAL CLEANROOMS

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1 INTRODUCTION

People disperse fragments from the skin and the resulting airborne dispersion will vary from person to person and from time to time. The prime function of cleanroom clothing systems is to work as a filter around people, protecting product and processes from airborne human contamination. Clothing systems should be designed to envelop a person and not allow significant amounts of contaminants be dispersed into the cleanroom. Properties of the fabrics used for cleanroom clothing can be assessed by measurements of, e.g., air permeability, particle retention, and pore size. The fabric itself should disperse the minimum of particles and be resistant to breakdown and tearing.

The combined filtration efficacy of fabric, construction, and design of the clothing system can be evaluated in a test chamber or body-box. The test chamber has been used for studying the protection efficiency of clothing systems in use by, e.g., Whyte et al. (1976), Hoborn (1981), Whyte & Bailey (1985), Reinmüller & Ljungqvist (2003), Ljungqvist & Reinmüller (2004) and Whyte & Hejab (2007). Measurements have been performed to relate the source strength of airborne particulates and/or viable particles (aerobic colony forming units (CFUs)) to the quality of fabrics and the design of evaluated clothing systems.

The increasing cleanliness demands in pharmaceutical manufacture require in-depth knowledge regarding both the performance of today's clothing systems for cleanrooms and the monitoring methods commonly used.

2 MATERIAL AND METHODS

2.1 Source Strength

The source strength is described as the mean value of the number per second of airborne particles and aerobic CFU, respectively, emitted from one person dressed in the system to be evaluated.

The source strength is a valuable engineering tool here describing the protecting efficiency of a clothing system against airborne particles, aerobic CFUs as well as total number of particles (Ljungqvist & Reinmüller, 2004).

In a room where supply, exhaust, and room air are completely turbulent mixing, the dilution principle is applicable. When also the airborne contamination sources have a constant total generation rate (source strength), the supply air is without contaminants and gravitational settling plays an inferior role, the expression for concentration, *c*, in the air during steady state becomes

$$c = (n \cdot q_s) / Q \qquad (1)$$

where
- c = concentration; total particulates, (number/m^3); aerobic bacteria-carrying particles, (CFU/m^3)
- n = number of persons (number)
- q_s = source strength; total particulates (number/s), aerobic bacteria-carrying particles (CFU/s)
- Q = total air flow (m^3/s)

When estimating the total supply airflow needed for a cleanroom, Equation (1) can be used in the following form, given the cleanliness level required for the designed cleanroom.

$$Q = (n \cdot q_s) / c \qquad (2)$$

In the same way, the source strength can be calculated with Equation (1) in the form

$$q_s = (c \cdot Q) / n \qquad (3)$$

In the test chamber where only one person at a time is present, Equation (3) is simplified and becomes:

$$q_s = c \cdot Q \qquad (4)$$

The source strengths of a clothing system evaluated in the test chamber or body-box are calculated by using the concentration (particles and CFUs, respectively per m^3) and the total air flow (m^3/s). The source strengths reported here are the mean values per clothing system in number of airborne aerobic colony-forming units (CFUs) per second from one person and in total number of airborne particles (≥0.5 µm,) per second from one person.

2.2 Test Chamber

The principal arrangement of the test chamber is shown in Figure 1. The supply air is HEPA-filtered. The air velocity (m/s) through the test chamber is measured, documented and the total supply air volume (m^3/s) is calculated. The concentration of airborne particles is measured in the exhaust duct of the test chamber/body-box (Ljungqvist & Reinmüller, 2004). In the test chamber, the supply air is unidirectional, and in the exhaust duct the air is turbulently mixed. The sampling is performed in the exhaust duct of the test chamber. The principal arrangement of the test chamber is shown in Figure 1.

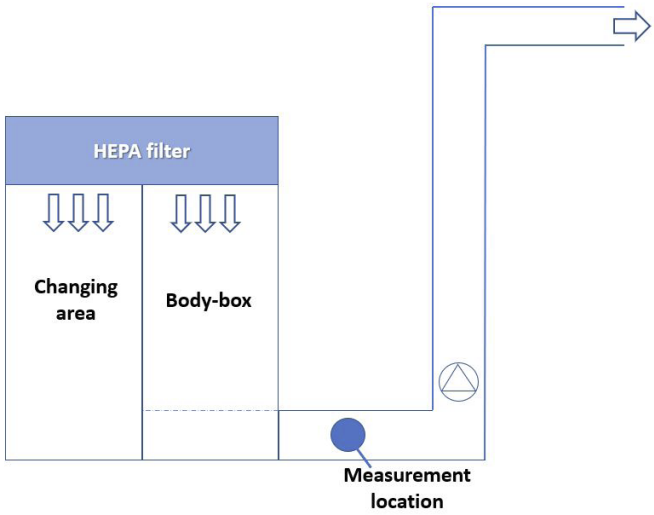

Figure 1. Principal arrangement of test chamber (body-box).

2.3 Test Performance

During measurements in the test chamber, the test subjects (male) perform standardized cycles of three movements, arm movements, knee bends, and walk in place at a set speed. Each kind of movement is performed for 3 min. Prior to each 3 min cycle of movement, the test subject stands still to avoid the influence of particle generation from the previous test cycle. This test is repeated a minimum of 4 times per test subject and usually with 5 test persons. The movements are, in principle, comparable with those described in IEST-RP-CC003.4 (2011).

2.4 Measuring Equipment

In the test chamber the air velocity is measured with an anemometer. In the exhaust duct of the test chamber, aerobic colony forming particles (CFUs) are collected using a slit sampler (FH3®, d_{50}-value 1.6 µm) and the total number of airborne particulates is determined using a particle counter (DPC; HiacRoyco 245A). The collection efficacy of the slit sampler FH3® in comparison with other microbial impaction air samplers has been published (Ljungqvist & Reinmüller, 1998; 2008). All instruments are calibrated and operated according to the manufacturers' instructions.

Microbial growth medium for all tests is standard Tryptic Soy Agar (TSA) in Petri dishes with a diameter of 90mm, pre-sterilized and double packed, with Quality Control Certificate. The TSA plates are incubated for not less than 72 hours at 32˚C followed by not less than 48 hours at room temperature. After incubation, the number of CFUs is counted and specified as aerobic CFU per m^3.

2.4.1 Gowning Process

The gowning process follows the SOPs, used in Grade B in the manufacturing of aseptic sterile products. For all tests, disinfected disposable gloves are worn during the gowning process and a single-use head cover is used under the textile hood all according to the SOP.

2.4.2 Evaluated Reusable Cleanroom Clothing Systems

The coverall "XR50", consists of a tightly woven continuous filament polyester fabric with ESD stripes, 97% polyester, and 3% carbon fiber, 3/2 twill weave, and weight 115 g/m^2. The underwear "BTS-75" consists of 100% polyester, weight 94 g/m^2, and plain weave.

The cleanroom clothing system consists of a reusable coverall, hood, and knee-length boots in combination with cleanroom underwear (long-sleeved t-shirt and long-legged pants), and cleanroom socks, sterile latex gloves, sterile facemask and sterile disposable goggles. The system is evaluated after 50, 60, and 70 cycles of use described as

- use in Grade B
- laundering, washing performed at a temperature of 75±2ºC for 12 min, followed by rinsing steps, dry-tumbling with HEPA-filtered warm air), and in Grade C environment inspected, folded, and packaged in disposable autoclavable bags.
- sterilized by autoclaving at 121°C for 20 min,

Additionally, the effect of a prolonged autoclaving process at 121°C for 25 min was evaluated after 50 cycles of use.

2.4.3 Additional Tests

Helmke Drum Tests according to IEST-RP-CC003.4 (2011) were performed by Berendsen Textil Service AB (Nyköping, Sweden). The cleanroom garments XR50 were tested after 25, 49, and 69 uses, washing and sterilizing cycles. Equivalent Pore Diameter Tests (Bubble Point Test) according to IEST-RP-CC003.4 (2011) were performed by Fristads AB (Fristad, Sweden). The cleanroom garments XR50 were tested after 50 and 60 uses, washing and sterilizing cycles.

3 RESULTS

The results of the performed evaluation in the test chamber are summarized in Table 1, mean values, and the min/max values of the measured concentrations (particles ≥0.5 µm and aerobic CFU) are given.

Table 1. Measured concentrations of airborne contaminants in the dispersion chamber when evaluating cleanroom clothing system (XR50) after 50, 60 and 70 cycles autoclaved (121°C, 20 min) and after 50 cycles and autoclaved (125°C, 25 min).

Number per m^3		
Number of cycles (uses, washes and autoclave cycles) and autoclave temp and time	**Particles ≥0.5 µm**	**Aerobic CFU**
50 cycles *121ºC for 20 min* Mean value Min/max value	 2 045 1 086 / 4 340	 0.5 0.1/4.4
60 cycles *121ºC for 20 min* Mean value Min/max value	 1 543 155 / 4 185	 1.5 0.1/3.3
70 cycles *121ºC for 20 min* Mean value Min/max value	 895 104 / 2 640	 2.1 0.5/5.4
50 cycles *121ºC for 25 min* Mean value Min/max value	 1 217 319 / 5 681	 0.6 0.1/2

Based on the air flow in the test chamber, which varied between 0.22–0.24m^3/s for the different test occasions, and the measured concentrations, the source strength for both airborne particles ≥0.5 µm and aerobic CFU is calculated. Table 2 shows results expressed as mean value source strength per second from one person of the evaluated cleanroom clothing systems. It should be noted that the calculated detection level of the microbial air sampler used here is about 0.25 CFU/s. Therefore, the CFU source strength values presented in Table 2 is around and below the calculated detection level. Results from the additional tests, Helmke Drum test and Bubble Point test are shown in Figures 2 and 3.

Table 2. Summary of source strength mean values for the evaluated cleanroom clothing system (XR50 with cleanroom underwear) autoclave sterilized at a temperature of 121ºC for 20 min and 25 min, respectively.

Number of cycles (uses, washes & autoclave cycles) and autoclave temp and time	Number per second (mean value)	
	Particles ≥0.5µm	Aerobic CFU
50 times at 121ºC for 20 min	471	≤ 0.25*
60 times 121ºC for 20 min	340	0.3
70 times 121ºC for 20 min	197	0.5
50 times *121ºC for 25 min*	292	≤ 0.25*
Mean value	325	<0.33
Min/max value	292/471	≤ 0.25/0.5

*value below the detection level (0.25CFU/s)

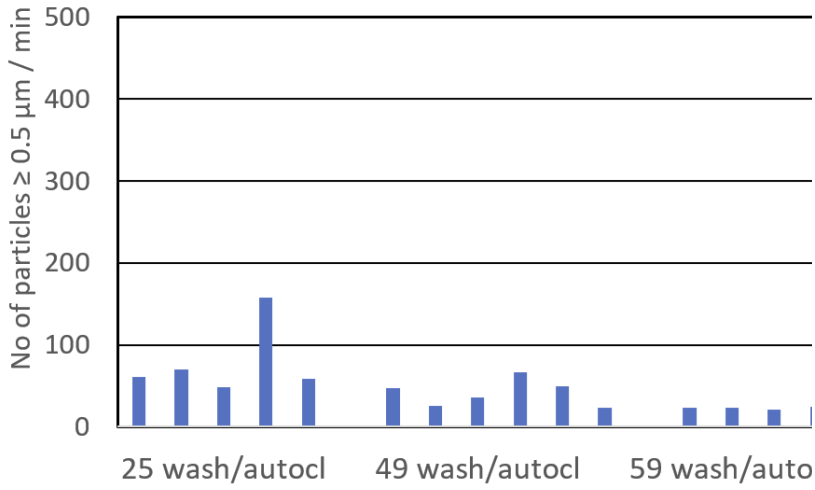

Figure 2. Helmke Drum test results for cleanroom clothing coveralls made of XR50 tested after 25, 49 and 59 uses, washing cycles, and autoclave cycles.

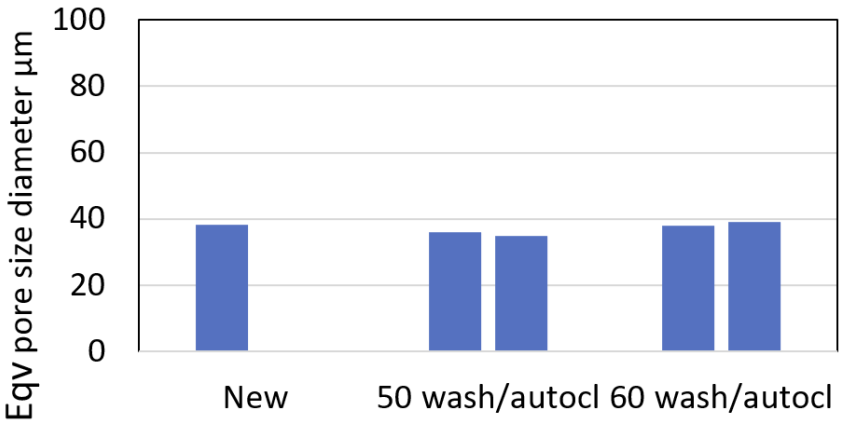

Figure 3. Equivalent Pore size diameter test (Bubble Point test) results for cleanroom clothing coveralls made of XR50 tested after 50 and 60 uses, washing and autoclave cycles.

Regarding particle generation and equivalent pore size, the results shown in Figures 2 and 3 do not indicate increased values over time of use.

4 DISCUSSION AND CONCLUSIONS

4.1 Cleanroom Clothing Systems

The summary of source strengths average values for the evaluated clothing system (XR50 in combination with cleanroom underwear) shown in Table 2 display a relationship between airborne particles ≥0.5µm and aerobic CFU, which seems to be in the range of 1 000 to 1.

The Helmke Drum Test shows the particle emission from the clothing system and increased values over time of use. This would be added to the particle emission from the test subject in the test chamber and give higher source strengths for particles. Figure 2 indicates no significant increase over time and use for the tested material XR50.

Increased values in the Bubble Point Test would affect the filtration efficacy of the textile material over time of use and thus affect the number of both particles and CFU emitted from the test subject. Figure 3 indicates no significant change over time and use for the tested material XR50. The development of cleanroom clothing system and its filtration efficacy regarding particles can be seen when compared to earlier published data, see Table 3.

Table 3. Evaluation according to Austin (1966) of earlier cleanroom clothing systems and calculated source strengths (numbers emitted per second from one person).

	Numbers per second		
	Particles		Aerobic CFU
	≥ 0.3µm	≥ 0.5µm	
Cleanroom clothes, walking	11 000	10 000	-
Good cleanroom clothing, walking	1 100	1 000	-

It could be mentioned that even the results are more than 50 years old (from 1966) in Table 3, they can be anticipated as valid, due to comparable monitoring methods now and then. If any change should have occurred in the monitoring methods (particle counting), it is

reasonable to estimate that the particle counters now a days are more sensitive, indicating that the results obtained in 1966 could have been even higher (and thereby means worst case for this experiment).

Today´s newer engineered textiles used in cleanroom garments has thinner fibers, lower particle dispersion from, and lower particle penetration through the material, thus higher protective efficacy. Improved design of the clothing systems seems also to contribute to low emission of airborne contaminants from people in cleanrooms. The studies indicate that the newer engineered textiles better control personnel contamination emissions, but that over longer time laundering, sterilization, and use can impact filtration properties.

4.2 Calculation of predictive air cleanliness during activity in cleanrooms

With reference to ISO 14644-16 (2019) and ISO FDIS 14644-4 (2020), the source strength for cleanroom clothing systems could be used for calculation of necessary air flow to achieve desired cleanliness levels. In cleanrooms and controlled environments with dilution mixing ventilation, where people are the main source of airborne contamination, a first approximation of the expected contaminant concentrations at steady state can be calculated using the Equation (1).

With reference to described results from the dispersion chamber and today´s cleanroom garments, the source strengths at very high activity level will approximately be ⩽ 0.3 aerobic CFU/s, and 300 particles ⩾ 0.5µm, respectively. Decisive for the calculation of expected concentrations is the air volume flow Q (m^3/s). Often a cleanroom has at least 20 air changes per hour (ach). With the assumption of a room height of 3 m and a floor area of 30 m^2, 40 m^2, 50 m^2, and 60 m^2 the air volume flows become 0.5 m^3/s, 0.67 m^3/s, 0.83 m^3/s, and 1 m^3/s respectively at 20 ach. Table 4 shows the calculated average concentration of aerobic CFU/m^3 in the respective cleanrooms, and Table 5 shows the calculated average concentration of airborne particles ⩾0.5µm. All calculations assume particle free supply air (HEPA-filtered), steady state, and that people are the main source of the airborne contaminants.

Measurements from ultra clean air operating rooms of airborne aerobic CFU, show that at high activity level, such as in total hip joint replacement, the source strength value is about 50% of the CFU source strength value evaluated from tests in the test chamber (body-box). The source strength of 0.3CFU/s as determined in the test chamber would exaggerate the expected concentrations but could here be assumed "worst case" for manual operations with very high activity, e.g., manual loading and unloading of freeze dryers, manual unloading of autoclaves, assembly of filling lines, and cleaning activities.

Table 4 shows that the calculated and predicted levels are close to the detection limit for many conventional microbial active impaction air samplers. However, at low activity level, the measured concentrations should be even lower. The calculated concentrations could be used as guidance values and compared to measured values from cleanrooms for aseptic production of sterile drugs.

Table 4. Predicted concentrations of airborne aerobic CFU/m^3 with a source strength of 0.3CFU/s and different number of persons at different air volume flows.

	Calculated Mean Value concentration of aerobic CFU/m^3 Air volume flow m^3/s			
Number of people in the cleanroom	0.5 m^3/s	0.67 m^3/s	0.83 m^3/s	1 m^3/s
1	0.6	0.4	0.4	0.3
2	1.2	0.9	0.7	0.6
3	1.8	1.3	1.1	0.9
4	2.4	1.8	1.4	1.2
6	3.6	2.7	2.2	1.8

When people are the main source of airborne particles ⩾ 0.5µm, Table 5 shows the calculated levels. At low activity level the measured concentrations could be even lower. The calculated concentrations could also here be used as guidance values and compared to measured values from cleanrooms for aseptic production of sterile drugs.

Table 5. Predicted concentrations of airborne particles ≥ 0.5µm/m³, with a source strength of 300 particles/s and person at different air volume flows.

	Calculated mean value concentration of particles ≥ 0.5µm/m³ Air volume flow m³/s			
Number of people in the cleanroom	0.5 m³/s	0.67 m³/s	0.83 m³/s	1 m³/s
1	600	448	361	300
2	1 200	896	723	600
3	1 800	1 343	1 084	900
4	2 400	1 791	1 446	1 200
6	3 600	2 687	2 169	1 800

4.3 Future possible applications

Should deviations of airborne contamination monitoring occur during aseptic production of sterile products, not only the operator might be the cause, but also the clothing system components. It could also be advantageous to have an improved tracing capacity of single clothing components. The lifetime of a system depends on the processes the clothing system is exposed to such as temperature, time, and type of process during laundering and sterilization, also the kind of use e.g., use of underwear, activity level, exposure to substances etc. The quality of push buttons, zippers and seams may also affect the lifetime of a system.

It is recommended to evaluate the source strengths (both particles and aerobic CFUs) as well at the beginning as at the end of the lifetime of reusable cleanroom clothing system, with the factual laundering, sterilization, and use processes. In the same way disposable cleanroom clothing systems should be evaluated about their source strengths. The presence of airborne contamination in pharmaceutical cleanrooms where the cleanroom dressed operator is the main source could be difficult to evaluate with today´s measuring instruments. The calculated concentrations, based on source strength and air volume flow, are close to or even below the detection limit of many microbial

active air-samplers. Should alert levels for the results of continuous monitoring of airborne particles ≥ 0.5µm be adjusted to the calculated concentrations, deviations might be detected early. To use class limits or half class limits for ISO Class 6 or ISO Class 7 of airborne particles ≥ 0.5µm as alert levels delays detection of deviations. A combination of particle counting and microbial active sampling could over time improve the monitoring efficiency and improve early detection of deviations.

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PROTECTIVE EFFICACY OF SURGICAL CLOTHING SYSTEMS WITH ADDITIONAL CLOTHING COMPONENTS CONCERNING AIRBORNE CFUS

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1 INTRODUCTION

The number of airborne bacteria-carrying particles, colony-forming units (CFUs), in the operating room is considered as an indicator of the risk of infections to the patient undergoing surgery susceptible to infections. To reduce surgical site infections, it is desirable to keep the bacteria-carrying particles at a low number in the operating room air, especially during orthopedic prosthetic surgery.

Whyte et al. (1983) suggested that the air in the wound area should, on average contain no more than 10 CFU/m^3 for surgery susceptible to infections. This level (⩽10 CFU/m^3) is nowadays international accepted and often called ultraclean air. A technical specification, SIS-TS 39:2015, published by the Swedish Standard Institute SIS, suggests half as large CFU-values as above.

The main source of airborne bacteria-carrying particles in an operating room is usually the personnel and patient, why the protective efficacy

of the surgical clothing system concerning bacteria-carrying particles plays an important role on the microbial air cleanliness. Measurements of airborne bacteria-carrying particles (aerobic CFUs) were performed in operating rooms during ongoing surgery to evaluate the protective efficacy, source strength, of a clothing system with various additional clothing components, such as disposable hood, textile hood, shoes without and with textile knee-length boots.

2 MATERIAL AND METHODS

2.1 Apparatus

Airborne viable particles were collected using a filter sampler (Sartorius MD8©) and gelatin filters and a slit-to-agar sampler (FH3©). The gelatin filters had a pore size of less than 3 µm. The impaction STA-sampler had a d50-value of less than 2 µm. Each sampling period with both instruments was 10 min.

The sampling volumes were 1m^3 for the filter sampler and 0.5 m^3 for the STA sampler. Both samplers were operated according to the manufactures' instructions.

The microbial growth-medium used, incubation time and locations are described by Ljungqvist et al. (2012), where also a comparative study of the two measuring methods of collecting airborne viable particles is discussed. The measurements of the comparative study (Ljungqvist et al., 2012) were performed in operating rooms during ongoing orthopaedic surgery. The results show that the two measuring methods, filter method and impaction with the STA-sampler gave values (CFU/m^3) in the same range. It was established with Mann-Whitney's U-test that there was no significant difference between the two measuring methods. These two methods with their difference in agar and incubation time are described as accepted methods in SIS-TS 39:2015.

2.2 Operating rooms

The measurements were performed in operating rooms at hospitals in the Stockholm area. The tests were performed during ongoing orthopaedic surgery in two operating rooms, where the air movements could be characterized as dilution mixing, i.e., the dilution principle is applicable. The supply air was HEPA-filtered with air volume flows in the two operating rooms of 0.62 m^3/s and 0.71 m^3/s, respectively, which for the two cases give about 18 air changes/h.

2.3 Clothing systems

The surgical clothing systems used were Olefin clothing system with three variations of additional clothing components. The fabric Olefin consists of 98% olefin and 2% carbon fibre. The blouse with cuffs at arms and neck and trousers with cuffs at the wrists were laundered about 20 times, but not antimicrobial treated. The weight is 125 g/m^2. Disposable facemasks, sterile disinfected gloves, two types of headcovers and two different footwear were also worn.

The two types of head covering were common disposable hoods and textile hoods with cuffs at the face and pushbutton below the chin (laundered about 20 times). One footwear system had clean socks of cotton and disinfected plastic shoes, the other had textile knee-length boots over the shoes. The textile knee-length boots with zip at the back of the leg were laundered approximately 10 times. Photos of the different clothing components are shown in Figures 1 and 2.

The tests have been performed with the following three variations of clothing components:

1. Olefin clothing system with disposable hood and plastic shoes
2. Olefin clothing system with textile hood and plastic shoes
3. Olefin clothing system with textile hood and textile knee-length boots.

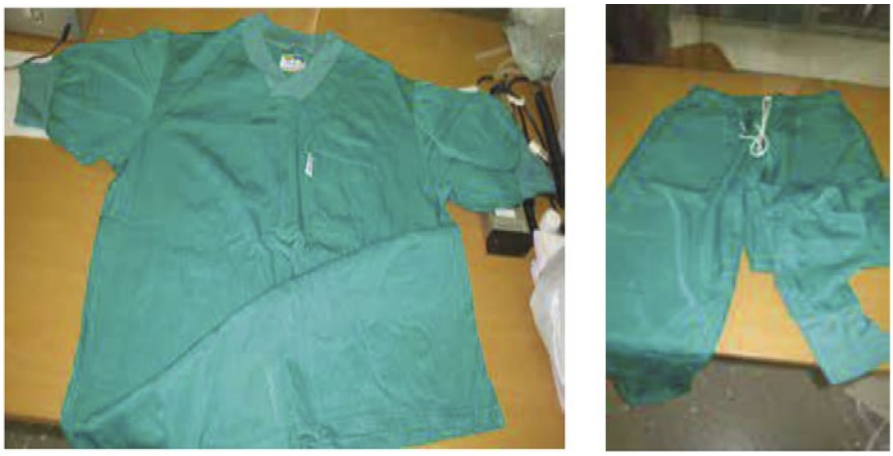

Figure 1. Olefin surgical clothing system, blouse, and trousers.

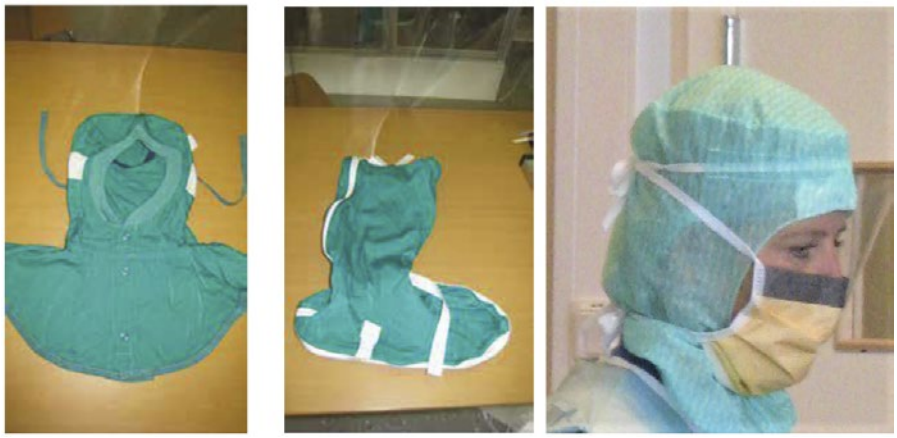

Figure 2. Olefin surgical clothing system, textile hood and textile knee-length boots, and the disposable hood.

2.4 Source strength

With the assumption of no leakage into the operating room and the HEPA-filters having efficiency close to 100%, the simplest possible expression, which is applied on the dilution principle, describe the source strength, protective efficiency of surgical clothing system (outward particle flow):

$$q_s = c \cdot Q/n \qquad (1)$$

Where q_s = source strength, bacteria-carrying particles (CFU/s)
c = concentration, bacteria-carrying particles (CFU/m^3)
Q = total air flow (m^3/s)
n = number of persons (number)

The source strength is here described as the mean value of the number of aerobic CFUs per second emitted from one person. Data are given as mean values based on several persons dressed in specific clothing systems. The source strength is a valuable tool in describing the protective efficacy of clothing systems against bacteria-carrying particles, e.g., a lower source strength gives a higher indication of a more suitable clothing system, (Ljungqvist & Reinmüller, 2004; Ljungqvist et al., 2014).

3 RESULTS

Data from measurements with the filter sampler (Sartorius MD8) performed by Blomfeldt (2014) are described by Kasina et al (2016) during ongoing hip-joint operations in an operating room with dilution mixing air and an airflow of 0.62 m^3/s. The surgical team (6-8 persons) was dressed in Olefin clothing system with disposable hood and plastic shoes.

In Table 1 concentrations of aerobic CFU are given from eight relevant operations and estimation of the source strength mean values is described with aid of Equation (1). Table 1 gives that the source strength mean value for Olefin clothing system with disposable hood and plastic shoes is 1.85 CFU/s. This value should be compared to values less than and equal to 1.5 CFU/s, which is the source strength level for clean air suits according to SIS-TS 39:2015. To improve the source strength value for the Olefin system additional clothing components should be used.

Ullmann et al. (2017) described measurements with the STA sampler when the surgical team (5-6 persons) had Olefin clothing system with textile hood and plastic shoes without and with textile knee-length boots over the shoes during ongoing orthopaedic surgery with high activity in an operating rooms with dilution mixing air and an airflow

of 0.71 m^3/s. Concentrations of aerobic CFUs and estimated source strength with aid of Equation (1) are for the two cases shown in Table 2 and Table 3, respectively.

Table 1. Concentration of aerobic CFUs and estimated source strength during ongoing orthopaedic surgery with high activity (hip-joint) in an operating room with dilution mixing air and an airflow of 0.62 m^3/s. The surgical team was dressed in Olefin clothing systems with disposable hood and plastic shoes. Measurements were performed with a gelatine filter sampler, Sartorius MD8.

Operation number	Number of persons	CFU concentration		Source strength* (CFU/s)
		Mean value (CFU/m^3)	Mean – Max (CFU/m^3)	
1	6	37.0	20–57	3.82
2	6	2.7	0–6	0.28
3	6	20.7	1–40	2.14
4	6	7.3	1–18	0.75
5	8	35.2	22–48	2.73
6	8	24.5	14–40	1.90
7	8	8.0	2–16	0.62
8	6	25.0	10–46	2.58
Grand mean value	6.75	20.05	--	1.85

*Source strength values are given with two decimal places.

Table 2. Concentration of aerobic CFUs and estimated source strength during ongoing orthopaedic surgery with high activity. in an operating room with dilution mixing air and an airflow of 0.71 m^3/s. The surgical team was dressed in Olefin clothing systems with textile hood and plastic shoes. Measurements were performed with the STA sampler (FH3) with the sampling time of airborne CFUs for 10 min per sample.

Air sample number	Number of persons	Concentration (CFU/m^3)	Source strength* (CFU/s)
1	6	4	0.47
2	6	10	1.18
3	6	10	1.18
4	6	14	1.66
5	5	12	1.70
Mean value	5.8	10	1.24

*Source strength values are given with two decimal places.

Table 3. Concentration of aerobic CFUs and estimated source strength during ongoing orthopaedic surgery with high activity. in an operating room with dilution mixing air and an airflow of 0.71 m^3/s. The surgical team was dressed in Olefin clothing systems with textile hood and with textile knee-length boots. Measurements were performed with the STA sampler (FH3) with the sampling time of airborne CFUs for 10 min per sample.

Air sample number	Number of persons	Concentration (CFU/m^3)	Source strength* (CFU/s)
1	5	<2	<0.28
2	5	<2	<0.28
3	5	2	0.28
4	5	6	0.85
Mean value	5	<3	<0.42

*Source strength values are given with two decimal places.

Measurement with clothing system described in Table 2 and Table 3 have also been performed in a dispersal chamber and the source strength mean values without and with boots become 2.3 CFU/s and 1.0 CFU/s, respectively, (Ullmann et al., 2017; Ljungqvist & Reinmüller, 2016). The source strength mean value of a specific clothing system from operating room measurements during orthopaedic surgery with high activity (hip joint) seems to be about half the mean value obtained in dispersal chamber tests (Ljungqvist & Reinmuller, 2014; Ljungqvist et al., 2014; Ullmann et al., 2017; Gandra, 2018). This gives, as a first approximation, an expected source strength mean value of 1.15 CFU/s for the system without boots and a mean value of 0.5 CFU/s for the system with textile boots. These two values should be compared to the source strength mean values given in Table 2 and Table 3. It should be noted that these values fulfil the source strength level for clean air suits according to SIS-TS 39:2015.

Table 2 and Table 3 show that the reduction of the number of aerobic CFUs with boots compared to without boots is about two third. Even if the number of measurements during ongoing surgery is limited, the results indicate that the reduction during ongoing surgery is in the range as in the dispersal chamber tests. Figure 3 shows exposed agar plates used in the measurements of airborne bacteria-carrying

particles with the Olefin clothing system described in Tables 2 and 3. The upper four plates are showing the results from measurements with knee-length boots and the plates below are the results without knee-length boots.

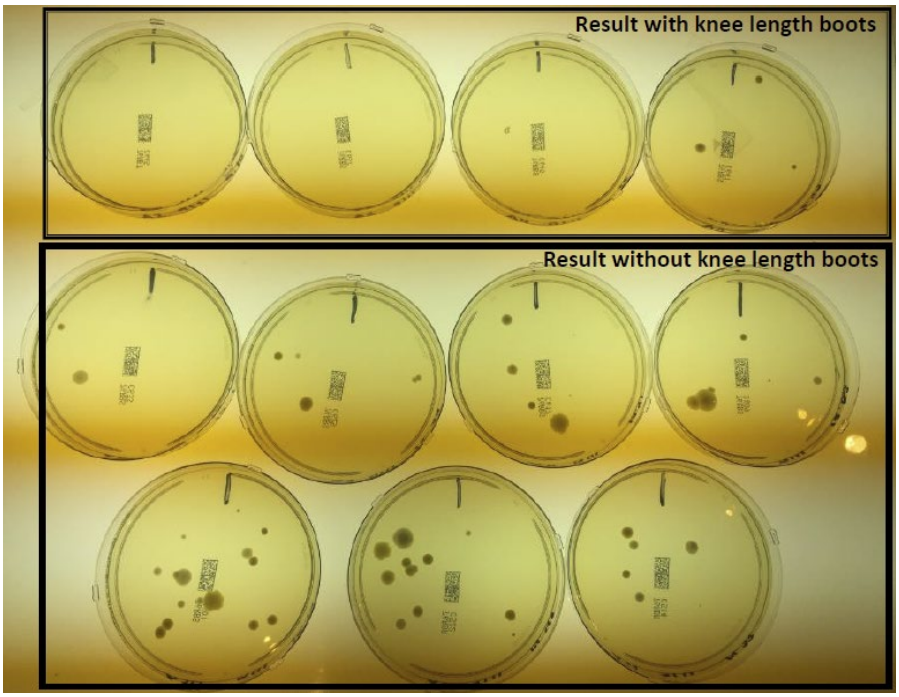

Figure 3. Agar plates used in the measurements of airborne bacteria-carrying particles in the operating room when the personnel are wearing the Olefin clothing system with textile hood and with and without textile knee-length boots (from Ullmann, 2019).

4 DISCUSSION

Tables 1-3 show that the reduction of the number of aerobic CFUs is one third when the Olefin clothing system is used with textile hood instead of disposable hood and the total reduction becomes almost 80% when both textile hood and knee-length boots are used. The difference in protective efficacy (source strength) between disposable hood and textile hood depends on how occlusive the fabrics are. The difference in poor size of the two fabrics are shown with microscopic photos in Figure 4.

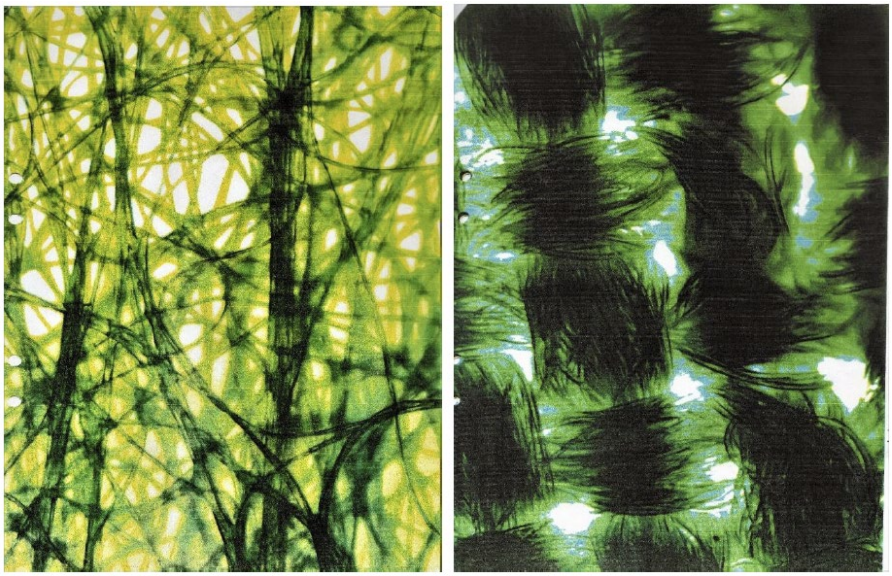

Figure 4. Disposable hood (left) and textile hood (right) seen under microscope with the same magnification.

It should be noted that the effect of knee-length boots is established in the pharmaceutical industry. Reinmüller (2001) describes tests in an aseptic filling room for aseptic production of sterile products, where the operators were dressed in cleanroom coveralls and hoods, face masks and sterile gloves. The effect of knee-length textile boots compared to without knee-length boots was evaluated. When knee-length boots were used a reduction of airborne particles and aerobic CFUs of about 90% was achieved. The high reduction with cleanroom clothing might depend on that the cleanroom operator being better covered than the surgical staff within an operating room.

The theoretical mean value concentration of bacteria-carrying particles in an operating room can be calculated, when the dilution principle is applicable, if the total airflow, the number of people and their source strength are known.

In this case, the Equation (1) becomes:

$$c = n \cdot q_s/Q \quad (2)$$

In the following example, some estimations are given with Equation (2).

Calculate the mean value concentrations of bacteria-carrying particles (aerobic CFUs) during ongoing orthopaedic surgery with high activity in three different operating rooms with dilution mixing air and airflows of 0.6 m^3/s, 1.5 m^3/s, and 2.5 m^3/s, respectively. The surgical team was six persons dressed in Olefin clothing system with different additional clothing components, three cases.

Case 1 Olefin clothing system with disposable hood and plastic shoes (Table 1).

Case 2. Olefin clothing system with textile hood and plastic shoes (Table 2).

Case 3. Olefin clothing system with textile hood and textile knee-length boots (Table 3).

The calculations are performed with Equation (2) and the numbers are given with one decimal place. The results are shown in Table 4.

Table 4. Estimation of mean value concentrations of aerobic CFUs during ongoing surgery with high activity in three operating rooms with dilution mixing air and airflows of 0.6 m^3/s, 1.5 m^3/s, and 2.5 m^3/s, respectively. The surgical team (6 persons) were dressed in Olefin clothing system with different additional clothing components, see example.

Olefin clothing system	Source strength* (CFU/s)	Mean value CFU concentration* (CFU/m^3)		
		Airflow 0.6 m^3/s	Airflow 1.5 m^3/s	Airflow 2.5 m^3/s
Disposable hood & plastic shoes	1	19	7.6	4.6
Textile hood & plastic shoes	1.2	12	4.8	2.9
Textile hood & textile knee-length boots	0.4	4	1.6	1

*Source strength values and mean value concentrations are given to one decimal place.

The results in Table 4 show that use of additional clothing components can considerably improve the microbial air cleanliness in operating rooms during ongoing surgery. It should be noted that the European Standard EN 13795-2:2019 (14) states that to manufacture a functional clean air suit, design shall also be considered. Arms and feet openings

shall therefore be closed. A barrier hood should be worn, tucked into the gap at the neckline. If the clean air suit consists of blouse and trousers, the blouse should be tucked into the trousers or designed with a tightly fitting waist. In addition, it could be mentioned that the Swedish Standard SS 8760164:2020 (15) contains the construction pattern for all three parts (hood, blouse, trousers) of the clean air suit.

5 IN CONCLUSION

The main source of airborne bacteria-carrying particles is the staff and the patient. To reduce airborne bacteria-carrying particles from the staff, it is important that the surgical team wears a functional clothing system. This paper compares results from measurement studies of the protective efficacy, i.e., source strength, of a surgical clothing system with different additional clothing components.

The studies were performed during ongoing surgery. The results show that the use of disposable hood or textile hood and the use of knee-length textile boots have considerable influence on the source strength, i.e., microbial air cleanliness in the operating room.

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HUMIDIFICATION IN HEALTHCARE FACILITIES

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1 INTRODUCTION

Humidification is not a common procedure in many buildings in the Netherlands. An important exception are buildings that are used for healthcare, especially hospitals. There, e.g., in operating theatres, relative humidity (RH) generally is controlled stringently at levels around 50% (Figure 1). From an energy point-of-view humidification is an energy-intensive activity.

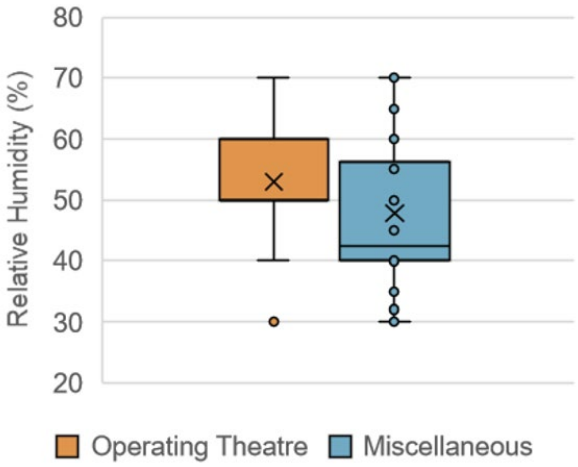

Figure 1. Distribution of RH set-points as applied currently in practice in the Netherlands.

Currently, more than 10% of the total energy used in buildings for healthcare is spent on humidification. The basis for an RH of around 50%, however, is not clear. Therefore, we pursued a scoping review to find evidence for specific RH thresholds in such facilities. In addition, an inventory was made of the current practice in the Netherlands. In the literature review, references were selected based on keywords. After analyzing the title and abstracts, the remaining references were read by two persons and scored on several topics. Guidelines and current practice were analyzed by referring to existing (inter)national guidelines and standards, and by contacting experts from Dutch hospitals through a survey and semi-structured interviews. Outcomes from the literature review were grouped into four different topics: 1) micro-organisms and viruses, 2) medical devices, 3) human physiology and 4) perception. No scientific evidence was found for the currently generally applied RH set-point of ~50%. Some studies suggest a minimum RH of 30% but the evidence is weak, with exception of medical devices if specifications require it, Figure 2. A lack of research that addresses more long-term exposure (a couple of days) and includes frail subjects, is noted. Following current practice related to humidification, it was found that RH requirements are strictly followed in all hospitals consulted, some only focusing on the hot zones, but in many cases extended to the whole hospital. For humidification, steam is mostly applied for hygienic reasons. Steam humidification is quite energy intensive.

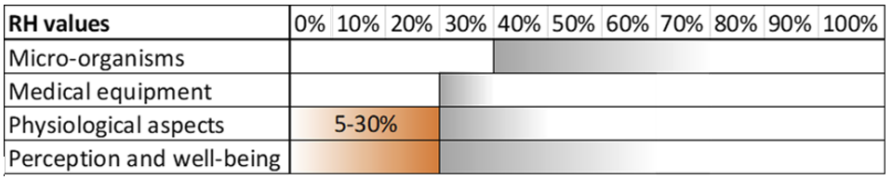

Figure 2. Summary outcome literature study for the four identified topics investigated. The gradient in colour indicates that there is no fixed value. The orange colour indicates that there is room for lower RH-levels to be applied. An upper RH-limit could not be identified.

Alternatives are available but nearly not considered yet. The conclusion, therefore, is that there is no solid evidence to support the RH-setpoints as currently applied in the Netherlands. It merely appears a code of practice. Therefore, there appears room for quick and significant energy savings, and CO_2 emission reductions, when considering control at lower RH values than currently applied and because of that may be refrained from humidification at all, while still fulfilling the indoor environment requirements and not negatively influencing the health risk. This outcome can be applied directly in current practice with the available techniques.

Making healthcare real estate more sustainable is also an important topic for achieving the climate objectives. Healthcare facilities are an important energy consumer and effort is put in reducing the energy demand of such type of facilities. The Dutch government initiated a program the reduce the reduce CO_2-emission of the health care sector (Anon., 2019).

Temperature, relative humidity, and air quality are examples of indoor environment parameters which are controlled to support the healthcare process. From literature, we know that the indoor environment affects health, well-being, comfort, and productivity (Fang et al., 2004; Hall & Dusseldorp, 2008; Razjouyan et al., 2020). The conditions that are set for the parameters that constitute the indoor environment, determine the energy demand in the end. Energy efficient solutions for realizing these conditions support the reduction of the energy demand. Requirements (conditions) with respect to the indoor environment may also help in reducing the demand or support the energy flexibility (Papachristou et

al., 2021). However, energy savings in healthcare cannot be realized at the expense of the primary process, i.e., availability of functions, patient safety, quality of care and the preconditions within which this care must be provided. The quality of the healthcare and the performance of the building to support that process cannot be compromised.

Nevertheless, we see that assumptions for indoor environment requirements are not that rigorous. Guidelines for health-based criteria exist when dealing with the indoor air quality (Dusseldorp & van Bruggen, 2007; WHO 2021). However, for much parameters scientific evidence is still lacking. Focusing on relative humidity (RH), if values are provided, they generally refer to (thermal) comfort. For healthcare, when related to RH, in the Netherlands current practice heavily relies on past assumptions and codes of practice (Bouwcollege, 2007). As a result, in the Netherlands, RH in healthcare environments is generally controlled at around 50%. Due to the climatic conditions, then air humidification is required, which therefore is a standard component of the air treatment in HVAC systems for healthcare facilities, particularly in hospitals, but also in long-term care. Nevertheless, the scientific evidence for this code of practice is meagre. Notably, air humidification, applying central steam humification, is an energy-intensive process. As a result, humidification is a relatively large energy consumption item (>10%) (Ferreira Porto, 2020).

We see two directions for addressing the sustainability requirement in healthcare settings, related to the RH. First, there is a need to derive more (scientific) evidence for the code of practice as applied currently, that assumes RH values in a relatively small range around 50%. Secondly, current practice with respect to RH-settings and air humidification can provide further insights into how humidification in the Netherlands, in healthcare facilities, is dealt with and what options are available as an alternative.

In view of the situation outlined above and the two clearly different subjects which relate RH to sustainability, this research has been divided into two parts. On the one hand, a literature study was conducted into what limits for relative humidity conditions are in place for the indoor environment, specifically in healthcare settings, to achieve

a safe environment for patients and staff from the point of view of health and comfort. On the other hand, using current practice as a starting point, an inventory was made to summarize RH set-points and humidification solutions, as currently applied within Dutch hospitals, and assess possibilities (techniques) that could be considered for realising humidification safely and sustainably.

This has been translated into two research questions: 1) What is the necessity of humidification, i.e., which RH condition is required in care facilities from the point of view of safety and comfort of the patient and the nursing staff and is there a distinction in functions? & 2) In which alternative, more energy-friendly way, can humidification be realised? This considering patient safety and comfort requirements of the building users.

2 METHODS

2.1 Scoping review (knowledge base)

To answer the first research question, a literature study (so-called scoping review) was conducted. The scoping review included studies till November 2020, with a specific supplement on electrostatic discharge till February 2021. It consisted of five different steps: 1. identify the research question, 2. identify relevant studies, 3. select studies, 4. identify themes, 5. report. The steps are based on the framework of (Arksey & O'Malley, 2005) and assume an iterative process. The iterative process makes it possible to go back to earlier steps if new insights are gained that can give more direction to the next step in the review process.

The literature study focused on the necessity of humidification in healthcare buildings from the point of view of patient and staff safety and comfort, and process support. For that, the literature study focused on the following four topics: 1. The effect of RH concerning survival of micro-organisms and viruses; 2. The effect of RH on the functioning of medical equipment; 3. The effect of RH on human physiology; & 4. The effect of RH on perceived human well-being and comfort.

The included databases for the scoping review were: Scopus, Pubmed, Web of Science and Science Direct. The choice was made to search databases from a health perspective and from a building perspective so that the theme of air humidification in healthcare buildings was mapped as broadly as possible. The search terms applied were based on the categories indoor air quality, environment, perception, experience and comfort and micro-organisms and viruses.

The screening process and its outcome are summarized in Figure 3. After processing the results from the search on duplications and a first screening on title and abstract, in total 78 publications were read completely and assessed by two team members. The assessment was performed based on an assessment matrix (rubric) covering topics such as reliability, context, method, usefulness of the results and conclusion. The assessment resulted in a score. The maximum score that could be arrived at was 27. Inclusion or exclusion of an article was discussed if opinions for a publication differed by 5 points or more between the reviewers, or if the score was around 10-20. In general, only articles with a score higher than 15 were included. In the end, a total of 46 publications were included after the screening process. In the analysis of the information, the effect of RH on the four topics identified above was treated separately.

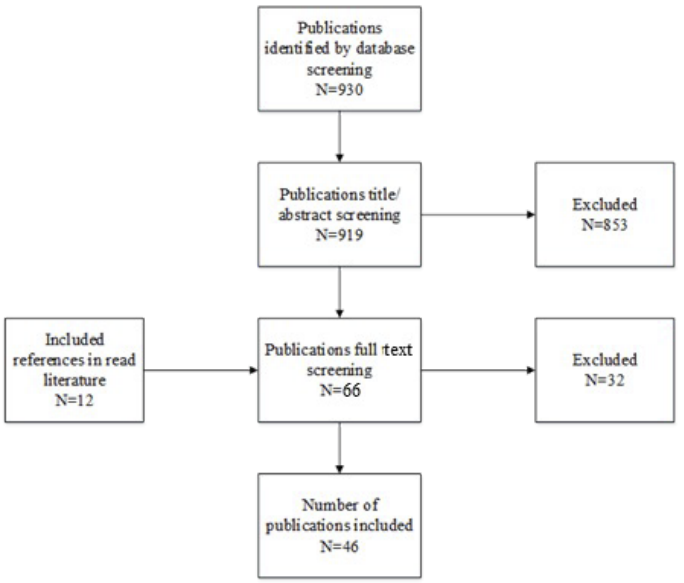

Figure 3. Flow diagram screening process publications.

2.2 Practice (inventory)

In the second part of the study, an inventory was made of the current practice, with regard to humidification in Dutch hospitals. This information was obtained through semi-structured interviews with relevant experts in The Netherlands, selected from the research network e.g., facility management staff and clinical physicists, employed by hospitals and manufacturers of medical equipment. The interview was designed to discuss issues related to (i) requirements set for the relative humidity, (ii) whether requirements differ between functions in the hospital, and (iii) what humidification principles are used for humidification. In total experts from 20 different hospitals were consulted in this way.

In addition, desk research was applied to gather information on standards and guidelines and with respect to techniques applied for humidification, apart from steam humidification. The concept reports from both studies were presented to a group of experts and persons from practice for peer-review and content validity. These were experts in different fields such as medical specialists (pulmonologist, medical microbiologist), doctors, infection prevention specialist, and technical related experts such as a building services engineer and facility manager. In combination with a rebuttal document to answer the remarks made, their comments were implemented in the final version of the report.

3 RESULTS AND DISCUSSION

3.1 Knowledge base

The outcomes of the literature study have been gathered in tables that provide information on the type of study performed (e.g., Experiment, Intervention, Case study, Literature study), the environment in which the research was performed (e.g., Hospital, Office, School), and a summary of the specifics of the outcome. A full overview of the tables developed has been published by Loomans et al. (2021). Below we summarize the main findings from the literature review and the subsequent analysis. The information obtained has been grouped according to the four topics

indicated: 1) Micro-organisms and viruses, 2) Medical equipment, 3) Physiological aspects and 4) Perception of comfort and well-being. The included studies indicate that RH is often not investigated as a separate parameter but in combination with various other aspects. It, therefore, is not always straightforward to quantify the individual effect of the RH on the outcome.

From the point of view of microbiological organisms, there is a dependency on the type of organism. Temperature and RH conditions outside the host determine the chance/time that for example, a virus, can remain infectious. However, the conditions under which the chance of survival is greatest differ per organism and it is not possible to state a specific value for this. In general, low and high RH values should be avoided. Studies regarding the relationship between RH and transmission of micro-organisms and viruses have not been found. The lower RH limit used for medical equipment is associated with electrostatic discharge (ESD). To limit ESD, a lower limit of 30% RH is found for medical equipment. The specifications of such equipment are leading for the minimum RH value to be applied, because this can influence the functioning of the equipment. From a comfort point of view, it is also desirable to prevent ESD (shocks when touching surfaces and other people). The RH can reduce this form of ESD, but it cannot completely prevent it. For that, it needs to be accompanied by the right material, e.g., footwear (conductive) and bedding (cotton).

Physiological symptoms such as dry eyes, nose complaints, respiratory complaints and headaches can be caused by low RH levels. Many complaints related to physiological symptoms seem to increase at RH lower than 30%. The studies considered, however, often have the limitation that the duration of exposure to these conditions is not explicitly given or is limited (up to a few hours). More long-term exposure (a few days, e.g., related to patient hospitalization) has not been investigated, while this will be the case for the most critical persons (patients) within the care facility.

The results available generally are more representative of an outpatient situation. For that matter, there are almost no studies available that address optimal RH-conditions for personnel in such facilities.

In general, significant effects of RH on the perception of dry air seem to be limited. Individual sensitivity may influence this perception. With respect to thermal comfort, the sensitivity to RH, when in normal ranges, is low (Loomans, 1998). Figure 4 summarises the outcomes of the literature review. It again distinguishes the four topics that were investigated in the context of healthcare buildings. We conclude from the literature available that strict guidelines on RH for healthcare facilities are not to be derived from the current (scientific) information as available in literature. From the overall results, a minimum level of 30% RH may be suggested, but the evidence is weak. In Figure 4 the orange colour indicates that there is room for lower RH-levels. We do not propose a higher limit for RH as no information is available to support such a limit for a healthcare environment. Specifications for medical equipment, however, may require such a limit. With respect to air humidification, the lower limit is of most interest, though in practice of course higher RH levels remain possible due to climatic conditions.

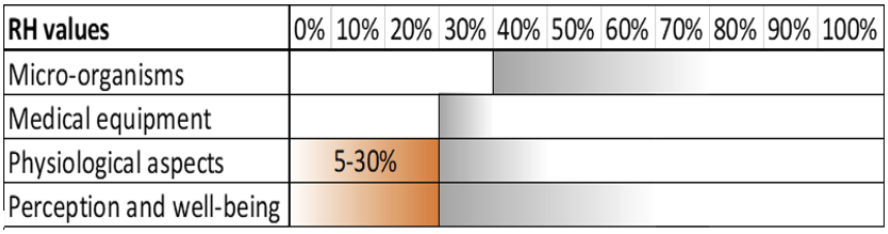

Figure 4. Summary outcome literature study for the four identified topics investigated. The gradient in colour indicates that there is no fixed value. The orange colour indicates that there is room for lower RH-levels to be applied. An upper RH-limit could not be identified.

The outcome deviates somewhat from reviews e.g., by Sterling et al. (1985). Sterling et al. (1985) proposed a RH-range between 40% and 60%, at normal room temperatures. The focus of that review is mainly on micro-organisms and a few physiological outcomes and did not focus on healthcare environments. The current review is wider and focuses on healthcare environments. The concept of dry air in relation to perception and physiological outcomes is complex (Wolkoff, 2018). The closely related link between low RH and indoor air pollution is an underlying explanation for that. In line with the conclusion from Wolkoff

(2018) we also find that current research with respect to the effect of RH on physiological and perceived outcomes is missing. Especially research that resembles realistic situations, in space and time. In this respect there also is an urgent need to distinguish between the 'average' person and the average type of person that is expected to frequent healthcare more often, i.e., frail, and aging people.

Following the information gathered from the literature review, there currently is no actual scientific support to keep the RH-level in Dutch hospitals at the generally applied 50% RH. Put otherwise, there is no information available in the current scientific literature that indicates that a RH-level of 50% is best for the people working and staying in healthcare environments. A lower value would still provide for a similar performance on the separately identified topics.

3.2 Inventory in Dutch hospitals

From the inventory, it is concluded that 100% of the surveyed Dutch hospitals (n = 20) apply air humidification as part of their HVAC system for conditioning the supplied air. 72% of the respondents indicated that they use steam humidification as a source for that. The remainder (28%) uses a combination of steam and water humidification. Water humidification alone or combined with steam humidification generally is restricted to low-risk rooms, such as offices. For high-risk rooms, such as operating theatres, steam humidification is applied in all cases because of hygienic assumptions. This is generally done centrally. Decentralized solutions are only applied due to in-use changes of function or rooms. Most of the hospitals (83%) apply humidification for the entire building. The set-points applied vary per hospital surveyed and depend, amongst other things, on the chosen grouping of functions. In 89% of the cases the users of the building are not able to change the RH set-point. That is done centrally by the facility management.

Almost all respondents indicated a subdivision for the operating theatre (hot zone) and the category 'miscellaneous' which can be considered the remaining functions. Some respondents distinguished these other function groupings with different climatological requirements (e.g.,

office function, patient room, ICU/CCU, laboratories, pharmacy, lung department, scope department and MRI room). Most of the set-points used in practice for the operating theatre were ≥50% RH. For the other rooms this was 42.5% RH, with a wider spread in outliers due to the many different function groupings in this category (Figure 5). According to the respondents, the reason for using strict RH requirements is based on the requirements for medical equipment, comfort, hygiene, and perception of wound dehydration, and from guidelines, history, and experience.

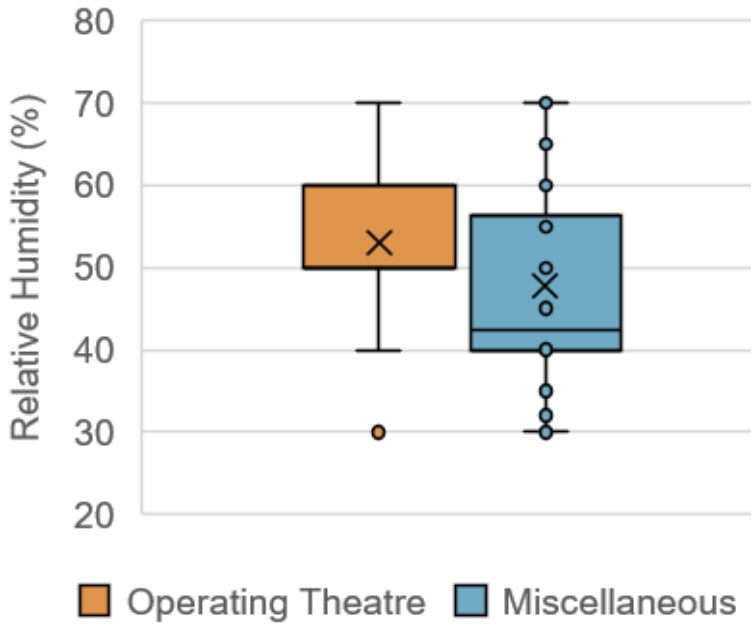

Figure 5. Distribution of RH set-points as applied currently in practice in the Netherlands.

The inventory of (inter)national standards and guidelines results in an overview of the current recommendations for air humidification. This overview is summarized in tables and has been published by Kompatscher et al. (2021). Standards and guidelines do not show unanimity with respect to the required RH conditions in healthcare settings, and do not provide a scientific knowledge base for suggested RH requirements. An RH of 20% is the lowest lower limit found (ANSI/ASHRAE/ASHE. 2017), while a lower limit of 50% RH is used in publications of the former Bouwcollege (2007).

As could be concluded from the survey, steam humidification is currently the most common technique in Dutch hospitals, when humidification is applied. By heating water (>100°C), steam is produced and supplied to an air stream. The advantage of this technique is the very likely elimination of pathogens. An alternative to steam humidification is water humidification (i.e., adiabatic humidification). With water humidification, water in its liquid state is supplied into the air stream (i.e., spraying, vaporizing, or atomizing) so that no heating of the water is required before addition. However, evaporation of moisture in the air stream removes heat from the air stream, causing it to cool and requiring additional energy to bring the air stream up to the required temperature before being supplied into a room.

Different type of humidification techniques can be applied when using water humidification. Figure 6 provides an overview of the techniques currently available. Techniques with and without recirculation are present. Water humidification with recirculation uses collected water to minimize water consumption. In any case, the microbiological safety, e.g., because of legionella, of this form of humidification still needs to be monitored, to gain sufficient certainty about the functioning and safety of such systems in healthcare applications.

Standards and guidelines reflect this precaution by preferring steam humidification over water humidification. Some standards, e.g., DIN194604 (2008) only allow the use of steam humification in operating theatres. In the case of water humification, additional requirements are prescribed to assure hygienic performance.

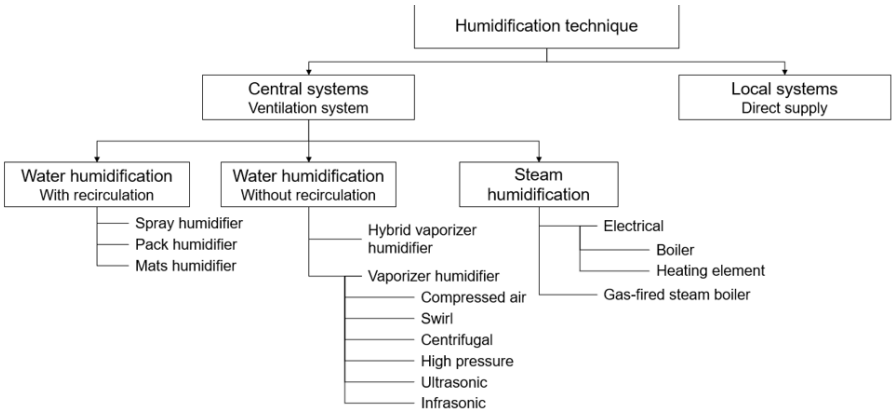

Figure 6. Overview of available air humidification techniques.

The advantage of water humidification is found in the possibility to apply renewable forms of energy, in combination with a heat pump, to condition the supply air. This is nearly not possible for steam humidification, due to the high temperatures required for that process. On the other hand, hydrogen gas and electricity can be applied to produce steam. Steam production generally is done centrally and therefore prone to heat losses in the distribution process.

4 IN CONCLUSION

This study has shown that, in practice, strict requirements are often set for the relative humidity, while the justification for these strict requirements cannot be found in the scientific literature or is only very limited available or very weak. In general, research on this specific subject, related to healthcare environments, is scarce. This also limits the possibility of providing a good quantitative foundation for the values to be set for the RH in such environments.

Based on the available information, an indicative lower limit of 30% RH may be desirable, considering issues such as medical equipment, physiological aspects and well-being and comfort. For micro-organisms and viruses, no general relationship has been found between the occurrence and inactivation of these and the RH. For that matter, more aspects than humidity alone play a role in the transmission and development of infections.

An upper limit for RH cannot be advised, as there is no unambiguous optimum for all four topics described in the knowledge base. The emphasis of the studies found and analysed is on low values for RH. In the context of humidification, the lower limit is of most interest.
In addition to the fact that information on the effect of RH on the identified topics is limited, the connection with the healthcare environment is even more limited. It is concluded that the available research is not well aligned with the situation as found in a healthcare setting. That mainly relates to the duration of the studies performed, generally in the order of hours, and to the subjects involved, healthy (young) people. That is not representative for an in-house patient that is required to stay for a

few days in a patient room. There is an urgent need to have research outcomes available that reflect this actual situation better.

Per room or function, primarily a balance will have to be found between presence of (medical) equipment, presence of patients and perception of comfort, regarding humidity on the one hand and the resulting energy consumption for humidification on the other hand. If there are rooms where medical equipment is used that is sensitive to humidity (high/low RH-values), such as MRI and CT scanners, or other critical equipment, specific requirements can be leading. While in other situations, where no critical equipment or critical processes take place, the need for humidification can be questioned, based on the knowledge base gathered in this research.

ACKNOWLEDGEMENT

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RISK ASSESSMENT IN UNIDIRECTIONAL AIRFLOW AT DIFFERENT AIR VELOCITIES

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1 INTRODUCTION

The number of airborne bacteria-carrying particles, colony-forming units (CFUs) in operating rooms is considered as an indicator of the risk of infection to the patient undergoing surgery susceptible to infections. An international accepted level of the mean concentration during surgery measured close to the wound is less than 10 CFU/m^3. The main source of microorganisms in an operating room is the personnel and the patient.

Operating rooms for patients undergoing infection prone surgery often have unidirectional flow (UDF) supply air systems. In the past 25 years, many UDF supply air systems installed in Europe have low air velocity, i.e., equal or below 0.3 m/s. It should be noted that Whyte (2015a, 2015b) in his review paper in two parts states that the UDF system, to be able to work effectively, shall have a minimum average velocity of 0.38 m/s for partial-walled system (0.3 m/s for a full-walled system) when velocity readings are taken 2 m above the floor and minimum average velocity

0.2 m/s taken 1 m above the floor. This agrees with results presbented by Nordenadler (2010). In this paper microbiological risk assessment with the method for limitation of risks (LR-Method) is used for the evaluation of contamination risks in UDF without obstacles at different air velocities at laminar as well as turbulent airflows.

2 MATERIAL AND METHODS

2.1 The LR-Method

The LR-method provides a reliable procedure for assessing potential microbiological risks of airborne contamination in clean zones in a systematic way. The LR-Method is performed in the following three steps:

- The first step is to visualize (e.g., by using isotherm smoke technique) the main air movements and identify turbulent regions and critical vortices where contaminants can be dispersed or accumulated in an unpredictable way. The illustrative technique of smoke studies provides a useful technique for visualizing air movements and the dispersal of contaminants. This technique requires that isothermal smoke is released continuously and almost momentum free using a diffuser. The smoke pattern can be recorded by means of still photography and video. Visualizing the air movements improves the understanding of potential risks of airborne contamination.
- The second step - the challenge test – is to identify potential risk situations. The particle challenge test involves placing the probe of a airborne particle counter in the critical area where during normal operations the process/product is exposed and taking continuous total particle counts (sampling flow 1cft/min) while generating particles in the close surrounding air (e.g., by using Air Current Test Tubes) to a challenge level of more than 300 000 particles equal to and larger than 0.5 µm per cubic foot (approx. 10^7 particles per m^3). These measurements must be carried out during simulated process activity. At least three samples of one minute are sampled at each location or during each process step.

- The third step is to evaluate the risk situation by calculating the Risk Factor, which is defined as the ratio between the maximum measured particle concentration (number/ft^3) in the critical region and the challenge level in the surrounding air. Due to limited measurement accuracy at high concentrations, a value of 300 000 particles per cubic foot is used as a challenge level in all Risk Factor calculations.

When the Risk Factor is less than 10-4 (0.01%) during the challenge test, there are no risks of airborne microbiological contamination during normal operational conditions according to experimental findings from more than 50 studied aseptic production lines. Experiences from the use of the LR-Method have been presented in the literature (Ljungqvist & Reinmüller, 1995, 2002, 2018; Ljungqvist et al., 2016).

2.2 Performed tests

The tests have been performed in a special designed clean zone test chamber with a UDF-system of 1.2 m x 1.5 m, where the supply air is HEPA-filtered. The vertical air velocity is adjustable from 0.1 m/s to 0.6 m/s. To stabilize the airflow the test chamber is equipped with partial side walls. Temperature and relative humidity are not controlled but have during the tests been in the range 20–26°C and 25–55% RH, respectively.

Figure 1 shows the principal arrangement of the tests with a person present in the test chamber. The probe of the particle counter HiacRoyco 245 is in all tests situated on the table in the test chamber at 60 cm from the test person. Figure 2 shows the principal arrangement of the particle generation regions in the test chamber.

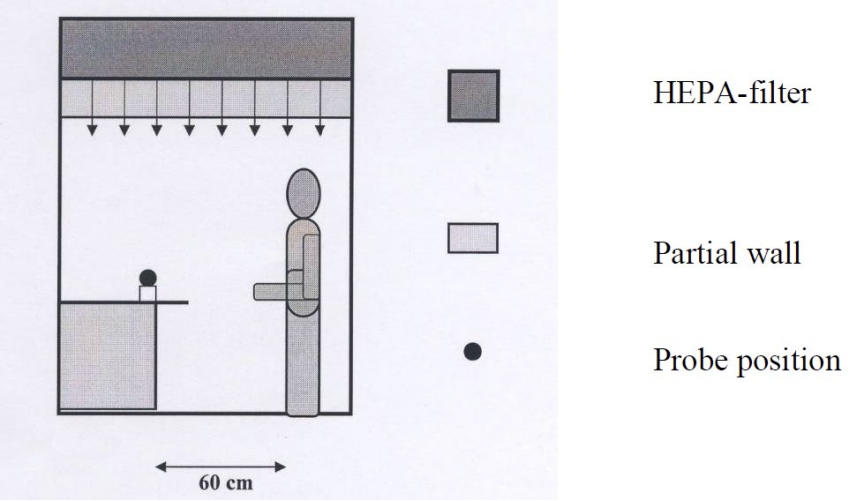

Figure 1. Principal arrangement of the tests in the chamber, section view.

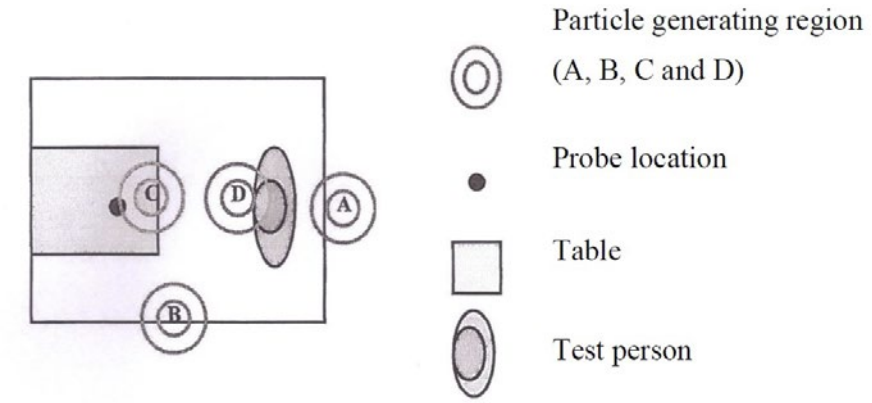

Figure 2. Principal arrangement of the particle generation regions in the test chamber, plan view.

The particle generation regions A and B were situated at floor level at the outer edges of the clean zone and the particle challenge was performed without a test person in the clean zone of the test chamber. The particle challenge in particle generation region C was performed below the table without a test person in the clean zone. In particle generation region D, the particle challenge was performed in the clean zone in front of a cleanroom dressed test person, who was standing still, or calmly moved his arms in standardized cycles, moving the arms forwards and back (Figure 3).

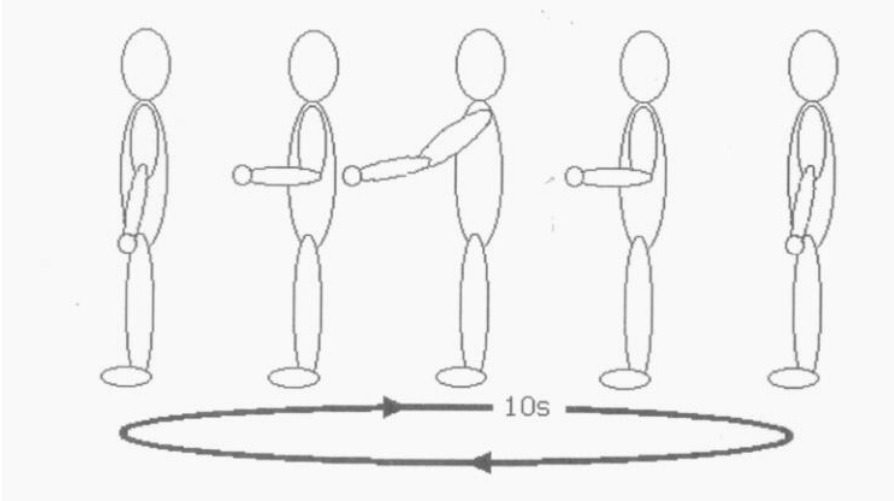

Figure 3. Standardized cycle of arm movements, time 10 s. (from Sipilä, 2006).

The supply air filter screen creates a low turbulence airflow, which in practical situations often should be called laminar. By using a turbulence generating grid placed just below the filter screen a turbulent airflow should be achieved. The turbulence generating grid was made of tubes with a diameter of 20 mm and the tubes were situated at the distance of 55 mm. A Reynolds Number of about 400 and 660 was achieved at velocities of 0.3 m/s and 0.5 m/s, respectively at normal room temperature. According to photographs presented by Schlichting (1979), it is to be expected that a change to turbulent flow principally consisting of interfering Karman vortex streets will occur at a Reynolds Number of approximately 100. This gives that in the described tests with the turbulence generating grid that turbulent flow is well established and is in the following called flow with high degree of turbulence. Note that the value of Reynolds Number is an indicator of the degree of turbulence in the parallel flow.

The velocity measurements were performed 0.2 m below the filter screen according to ISO 14644-3 (2005), which gives that the readings were taken about 2 m above the floor. For velocities between 0.3-0.5 m/s measurements have been performed in the test chamber with the LR-method of flows with low degree of turbulence (almost laminar) as well as with flows with high degree of turbulence. Figure 4 shows these two types of flow visualized with aid of smoke.

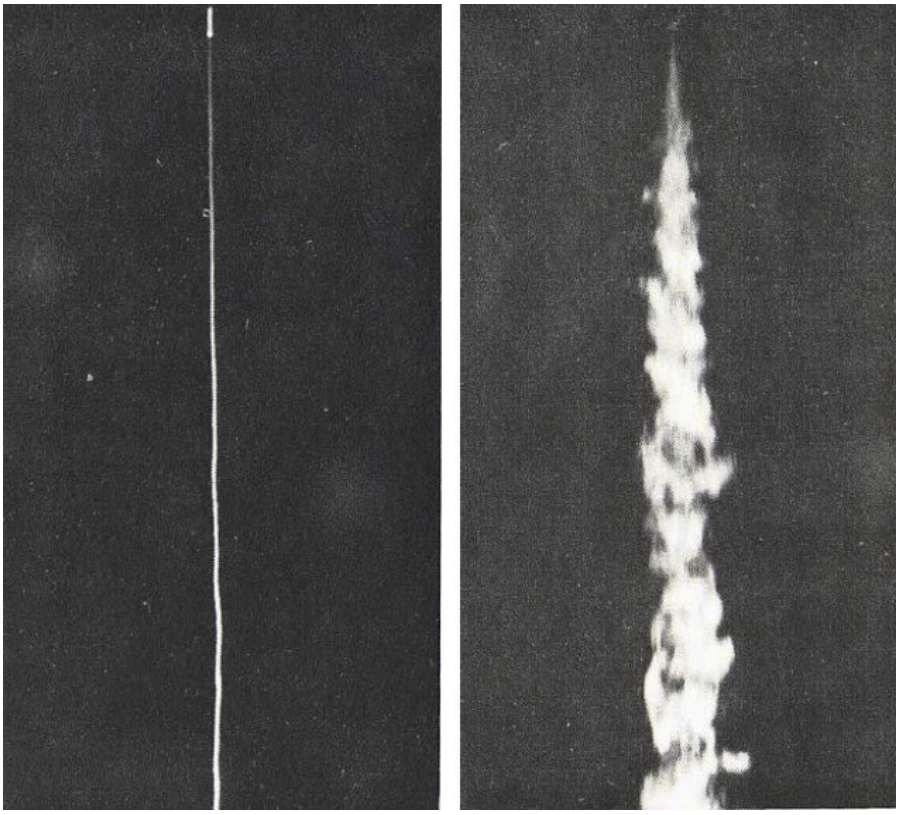

Figure 4. Dispersion of smoke in laminar (left) and turbulent (right) flow.

3 RESULTS

Results from the measurements with the LR-method at UDF with low and high degree of turbulence at different air velocities are shown in Tables 1 and 2. The results in Tables 1 and 2 show, independently of the turbulence degree of the UDF, that the air velocity should exceed 0.4m/s to achieve a good protection efficacy, i.e., a Risk Factor less than 10-4.

Indicative measurements have also been performed at air velocities of 0.25 m/s, 0.35 m/s and 0.45 m/s. The values for the air velocity 0.25 m/s are for particle generation regions A, B, and C in the same range as the values given for the velocity 0.3m/s, while the values in particle region D (person present) become higher than those given for the velocity 0.3 m/s.

The values for the air velocity 0.35 m/s are in a level between the values for the velocities 0.3 m/s and 0.4 m/s. The values for the velocity 0.45 m/s are close to the values for the velocity 0.5 m/s. The results show clearly that the convection flows from the test person and arm movements have a great impact on the particle dispersion at air velocities below 0.4 m/s.

Table 1. Measured particle levels (max. values) during the challenge tests and calculation of the Risk Factor at UDF with low degree of turbulence.

Velocity m/s	Region	Challenge	Number of particles ≥0.5µm/ft³	Risk Factor
0.3	A	Without person – with particle challenge	8 839	$2.9 \cdot 10^{-2}$
0.3	B	Without person – with particle challenge	3 625	$1.2 \cdot 10^{-2}$
0.3	C	Without person – with particle challenge	18 469	$6.2 \cdot 10^{-2}$
0.3	D	Person still – without particle challenge	<10	-
0.3	D	Arm movements – without particle challenge	1 138	-
0.3	D	Person still – with particle challenge	>100 000	$>3 \cdot 10^{-1}$
0.3	D	Arm movements – with particle challenge	>100 000	$>3 \cdot 10^{-1}$
0.4	A	Without person – with particle challenge	0	$<10^{-4}$
0.4	B	Without person – with particle challenge	0	$<10^{-4}$
0.4	C	Without person – with particle challenge	0	$<10^{-4}$
0.4	D	Person still – without particle challenge	<10	-
0.4	D	Arm movements – without particle challenge	41	-
0.4	D	Person still – with particle challenge	<10	$<10^{-4}$
0.4	D	Arm movements – with particle challenge	1 623	$5.4 \cdot 10^{-3}$
0.5	A	Without person – with particle challenge	0	$<10^{-4}$
0.5	B	Without person – with particle challenge	0	$<10^{-4}$
0.5	C	Without person – with particle challenge	0	$<10^{-4}$
0.5	D	Person still – without particle challenge	0	-
0.5	D	Arm movements – without particle challenge	0	-
0.5	D	Person still – with particle challenge	0	$<10^{-4}$
0.5	D	Arm movements – with particle challenge	0	$<10^{-4}$

Table 2. Measured particle levels (max. values) during the challenge tests and calculation of the Risk Factor at UDF with high degree of turbulence.

Velocity m/s	Region	Challenge	Number of particles ≥0.5µm/ft^3	Risk Factor
0.3	A	Without person – with particle challenge	73	$2.4 \cdot 10^{-4}$
0.3	B	Without person – with particle challenge	7 006	$2.3 \cdot 10^{-2}$
0.3	C	Without person – with particle challenge	18 394	$6.1 \cdot 10^{-2}$
0.3	D	Person still – without particle challenge	130	-
0.3	D	Arm movements – without particle challenge	1 296	-
0.3	D	Person still – with particle challenge	83 224	$2.8 \cdot 10^{-1}$
0.3	D	Arm movements – with particle challenge	>100 000	$>3 \cdot 10^{-1}$
0.4	A	Without person – with particle challenge	<10	$<10^{-4}$
0.4	B	Without person – with particle challenge	0	$<10^{-4}$
0.4	C	Without person – with particle challenge	392	$1.3 \cdot 10^{-3}$
0.4	D	Person still – without particle challenge	<10	-
0.4	D	Arm movements – without particle challenge	<10	-
0.4	D	Person still – with particle challenge	<10	$<10^{-4}$
0.4	D	Arm movements – with particle challenge	167	$5.6 \cdot 10^{-4}$
0.5	A	Without person – with particle challenge	0	$<10^{-4}$
0.5	B	Without person – with particle challenge	0	$<10^{-4}$
0.5	C	Without person – with particle challenge	0	$<10^{-4}$
0.5	D	Person still – without particle challenge	0	-
0.5	D	Arm movements – without particle challenge	0	-
0.5	D	Person still – with particle challenge	0	$<10^{-4}$
0.5	D	Arm movements – with particle challenge	0	$<10^{-4}$

4 DISCUSSION

When the test person is within the UDF region the results show, when the air velocity is 0.3 m/s or less, that the airflow pattern occurs in a disordered manner in the region around the table and the test person. However, when the air velocity exceeds 0.4m/s, the airflow pattern

more closely resembles undisturbed airflow, and the sweeping action seems to be significantly improved.

UDF vertical downwards airflow has been used for decades in industrial cleanrooms as well as in many ultraclean air operating rooms worldwide. If the main concern in an operating room is to achieve an almost bacteria-free environment by the sweeping action of the air in a region around the operating table during ongoing surgery, a UDF-based room air distribution system with an inlet velocity about 0.4m/s is needed. This agrees with results presented by Nordenadler (2010), Whyte (2015a, 2015b), and Gandra (2018) and Whyte & Lytsy (2019).

While most UDF-based room air distribution systems for operating rooms, such as those which have been installed in Europe in the last 25 years, have air velocities below 0.3 m/s, the air movements during ongoing surgery just above the operating table become partly turbulent mixing. For operating rooms with UDF systems with air velocities below 0.3 m/s, one can assume that the dilution principle starts to become valid in the operating zone during ongoing surgery. In such cases the number of people in the operating room and chosen clothing system should be taken into consideration when the microbial air cleanliness is of importance.

5 IN CONCLUSION

Operating rooms for patients undergoing infection prone surgery often have unidirectional flow supply air systems. Many systems installed in Europe have low air velocities, i.e., equal, and below 0.3 m/s, while other supply air systems have velocities about 0.4 m/s. The velocity, given by the supplier, is mostly the inlet air velocity just below the filter screen of the unidirectional flow system. The purpose of this paper is to describe contamination risks in unidirectional airflow without obstacles at different air velocities.

To evaluate contamination risks the method for limitation of risks, the LR-Method, has been used. The results show that the convection flows and arm movements from a person standing in the unidirectional

airflow system have a great impact on the contamination risks at air velocities below 0.4 m/s and that the air velocity should at least be 0.4 m/s to achieve a good protection efficacy.

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PLANNING OF A STERILIZATION DEPARTMENT

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1 INTRODUCTION

The sterilization department in a hospital is a factory for producing sterile goods. This means, we need to understand the sterilizing process to design and construct the right solution for each hospital. This case is from the planning of the New University Hospital in Stavanger, Norway. The sterilization department is placed in the treatment building, where we also could find the surgical department. The sterilization department is in the basement, level U1, whereas the surgical department is in the upper floor, level 3.

2 FLOW

The first issue to consider is the connection between these two departments regarding the flow of used and sterile instruments. In this case, the transportation between the two departments is planned in two different elevators. One of them is directly connected to the sterilization department, and the other one is outside, across the main corridor. When inspecting the flow, it turned out that the flow of sterile instruments originally was planned in the elevator across the corridor (Figure 1).

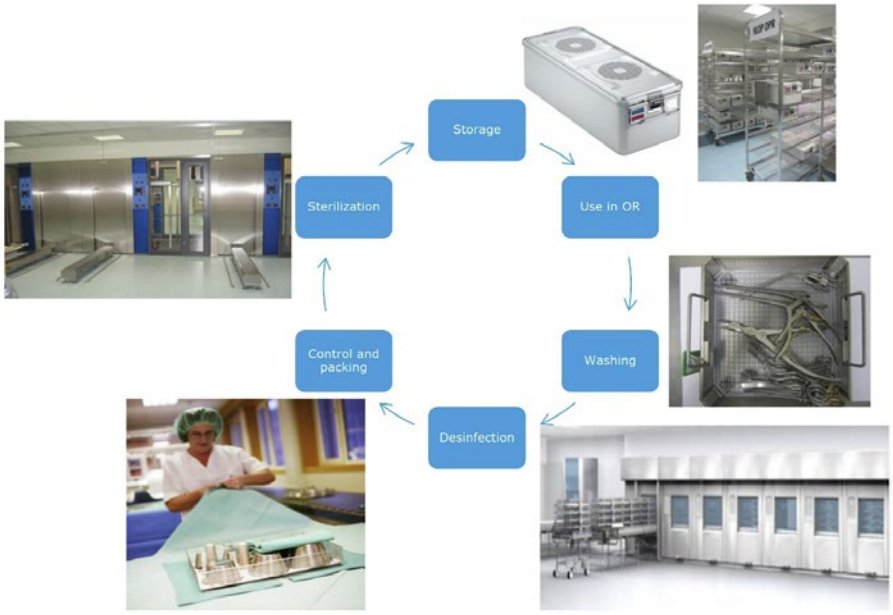

Figure 1. Sterile flow.

However, this was not acceptable, if the transportation was planned without using closed wagons. Thus, the first thing that was decided, was to mirror the layout of the sterilization department, to ensure the flow of sterile instruments within the containment barrier. The next step is to inspect the internal flow in the department and see how this can be solved in the actual building, and how to ensure the best possible layout according to the flow. In the layout, an example is given in Figure 2, we can see where the different zones are and classify them.

Figure 2. Different zones.

3 SWEDISH REQUIREMENTS ACCORDING TO SIS-TR-57

According to the Swedish requirements in SIS-TR-57 there are a lot of requirements to the clean zones. These parameters are given in Table 1. To reach these parameters, we organize the work according to the project process for critical rooms. The phases in the project are given in Figure 3.

As a result of the requirements in SIS-TR-57, and an increasing focus on the air quality in sterilization departments in Norway in general, we do have to acknowledge the need of humidity control. The limit of 30–70% RH is quite challenging and leads to a lot of components in the ventilation system. Each zone with this requirement needs an extra cooling coil, heating coil and a steam speer, in addition to HEPA-filters and VAV-dampers to ensure the cleanliness and the right pressure difference.

Table 1. Parameters from SIS-TR-57.

Parameter	Value
Microbiological cleanliness	≤100 cfu/m³ (GMP class C)
Temperature	22 ± 3°C
Humidity	30 – 70% RH
Airflow	10 – 20 air changes/h
Pressure difference	≥ 10 Pa

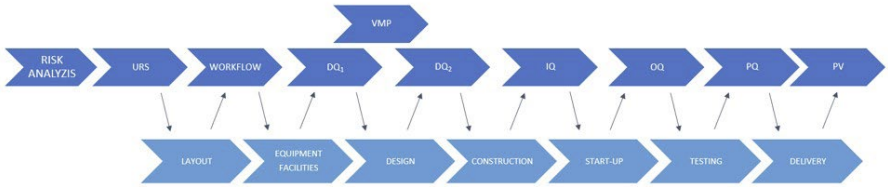

Figure 3. Project process.

4 IN CONCLUSION

But the most challenging topic is what it leads to when it comes to cooling capacity. Although Norway is known as a country with a relative cold climate, we do have summer temperatures about 30°C. The key question is: "How many hours can we accept to exceed the limit for air humidity?" In this case, the normal summer conditions in Stavanger are about 23°C and 60% RH. This value is normally exceeded 50 hours pr year. The next value is about 25°C and 60% RH, which is exceeded

20 hours pr year, and the extreme temperature is 31°C and 70% RH. When discussing these values and what to set as dimensioning conditions, it was obvious that exceeding the limits 50 hours pr year was not acceptable.

As a result, the dehumidifying capacity should be dimensioned according to the extreme summer condition. This again would lead to huge dimensions in the air handling unit and individual cooling coils, and a cooling capacity far above the maximum of the cooling system. So, we had to go one step backwards, to see if the extreme conditions really were necessary, and to go for a compromise in the middle.

Furthermore, there are a lot of subsystems to be planned and designed in a sterilization department. For example, there are many different doors, with individual requirements to surfaces, functionality and intersections. And the core process equipment does need different supply infrastructure. All this must be coordinated in the process of designing, installing, and commissioning a new sterilization department.

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DESIGN CONSIDERATIONS FOR ATMP FACILITIES

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1 INTRODUCTION

Advanced Therapeutic Medical Products (ATMPs) form a group of therapies that have been developed and categorized over the past decades. The categorization of various therapies based upon EC directives is quite complex (Figure 1).

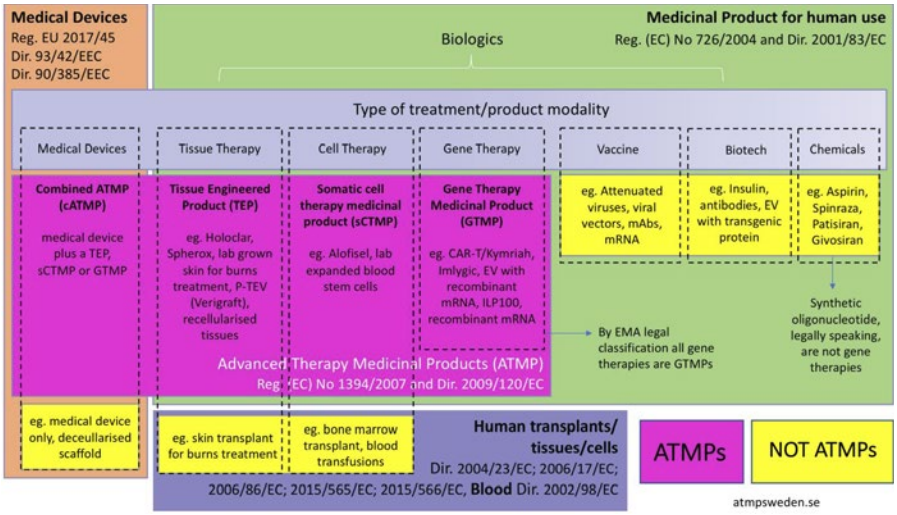

Figure 1. Overview of therapies and their categorization (http://atmpsweden.se).

As shown the ATMP distinguishes between Cell Therapy, Tissue Therapy and Gene Therapy. In this case study the focus is on Cell therapy facility design. Cell therapy is based upon living cells that are manipulated before introduction into the patient to treat a disease. The

cells that are manipulated and introduced can be cells derived from the patient itself (autologous) or from a suitable donor (allogenic). Both autologous and allogenic manipulation and introduction into the patient require aseptic processing of live cells during transport, in the facility and administering to the patient. The essential difference between autologous and allogenic cell therapy is the origin of the cells: 1) Autologous cell therapies derive the cells from a single specific patient whom after the manipulation will receive its modified cells back; & 2) Allogenic cell therapies derive the cells from one/more donors and the manipulated cells will be introduced into multiple patients.

Both autologous and allogenic therapies start with cell materials, for common therapies by blood samples, where via an apheresis step the starting cell material for the manipulation is separated and collected. In case of allogenic cell therapy, the collected cells can be used for many different patients, so the scale of cell culturing is much larger than that for the autologous cell therapies as that is related to a single individual patient only. Table 1 shows the essential difference.

Table 1. Different steps for autologous and allogenic cell therapy.

Step	Autologous	Allogenic	
	Material – Patient	Patient	Material
Selection of patient	At related hospital	At related hospital	Donor selection
Collection of blood	Patient material	NA	Donor material
Cold chain transport	Yes	NA	Yes
Receipt and Verification	Yes	NA	Yes
Cell manipulation Cell multiplication	Single therapy	NA	Batch
Filling	1 lot	NA	Batch to multiple lots
Inspection	Per lot/patient	NA	Multiple lots
Storage	NA	NA	Multiple lots
Labelling	Per lot/patient	Per patient	NA
Cold chain transport			
Treatment	Single patient	Multiple patients	NA

Autologous and allogenic cell therapy types both require a well-developed cold chain employing cryo-techniques as the distance between patients and the facility is significant. Both types of facilities employ disposable technology. Allogenic cell therapy uses batch processes based upon selected donor cells. Those batch sizes can reach up to 1000 litre or more. Allogenic facilities are resembling more well-known biological facilities. Autologous cell therapy production by its nature and scale of production requires multiple parallel production workstations where the individual patient material is processed. As the handling is so labour intensive it also poses a challenge with respect to aseptic processing. The process not only includes quite a few manipulations but also many in process control checks and sampling. As autologous means one therapy for one patient the loss of a single therapy means the danger of (to) late treatment of the patient. Allogenic however provides the option of having several overlapping runs and therapies in store. Now, however, about 75% of the clinical cell therapies and 100% of those for CAR-T cells, the most commercial successful therapy, are autologous. For this case study the more common and intriguing 'autologous' ATMP facility design is further explored.

2 DESIGN IMPLICATIONS

2.1 Logistics and contamination control

A facility layout must consider the routing of all utensils, starting material, media, samples, product, and waste. As the operational processes use manual production with consequent connection, feed, manipulate and sample steps the open handling requires an EU GMP Grade A environment. This is commonly done in Bio Safety Cabinets (BSCs). Due to the use of BSC's not being Isolators or RABS (restricted Access Barrier Systems) a background environment Grade B is required.

This requires all materials as well as operators to transfer from ambient conditions via personnel airlocks (PALs) and material airlocks (MALs) to increasingly cleaner conditions. Considering the manual nature and the large number of items needed at various stages this poses a

real challenge to the contamination control strategies employed. For personnel in common gowning steps can be used. For all aseptically packaged utensils, starting materials and media (order of magnitude up to 200 different items) the clean introduction into the B grade suite and A grade BSC require bioburden reduction on the outside. The huge variety both in format of packaging and source combined with the large quantities per therapy, makes this bioburden reduction step complex. The most favourable way would be unwrapping to an inner cleaned packaging. However, this expensive way of packaging is available only to a limited extend. Therefore, the local bioburden reduction by IPA wiping of VHP processing can be employed. A qualification of the method is required as the influence of the cleaning agent on the contained item is important when this has direct contact to the patient material being processed. As most ATMP processes have been developed using common laboratory techniques and are filed accordingly a change in the bioburden reduction process poses a significant challenge.

For the transition of all materials into the production suite after outer bioburden reduction, dedicated pass-through boxes can be employed. This greatly facilitates linear logistics and separation between supplies, product, samples, and waste.

2.2 Production suite size

Manual processing requires workstations with multiple equipment such as wave reactors, cell counters, cell processing units, tube sealers, incubators and BSCs. The arrangement of a workstation requires study of the activities and the space required for safe aseptic procedures. The challenge is to design the process in the workstation in such a way that a mix up of different therapies is prevented. This can be done by separation in time or physical. To achieve a sustainable economy of scale for commercial production this requires a thorough exercise where procedures and lay out must be optimized.

Based upon a single workstation the number of workstations per suite can be assessed. Here again the design must include ergonomic and contamination control aspects such as undisturbed aseptic

work in a BSC and concentrated work on product handling. The traffic with all materials and sample needs to be very well organised. Understandably the number of operators and aids is much higher than normally encountered in Grade A/B environments. The result of these studies can lead to up to a maximum of 15 workstations per suite for manual processing. Larger numbers would make the suite also very susceptible to disturbances for maintenance of equipment and would make the impact on production capacity of a maintenance of upgrade shutdown to big. Therefore, arrangements of multiple suites each with 6 -10 workstations are common. When processes are becoming more automated and with less or no aseptic handling the number of workstations as well as the general arrangement of all equipment can be further optimized.

2.3 Auxiliary spaces

In the processing suites inbound and outbound PAL and MAL are to be designed, also storage room for all production materials as well as cleaning equipment. Around the processing suites itself the logistics do require an adequate corridor system that allows the flows to be separated in inbound and outbound with clean segregation between processed product and incoming patient material. In multiple B-suites with A BSCs and surrounded by a C-Grade corridor the PAL and MAL need a single grade step: Inbound C to B and outbound B-C. assessing the large number of movements and personnel in the corridor system a choice can be made to have a D-Grade corridor and two step inbound PAL and MAL arrangement from D-C-B. The outbound can be a single dual step when there is directional flow B-D. Other areas are the general gowning, inbound material transfer, waste out, product out and maintenance and service room. Also, a cleaning / washing room might be needed if some equipment and used materials must be periodically cleaned. A typical arrangement is shown in Figure 2.

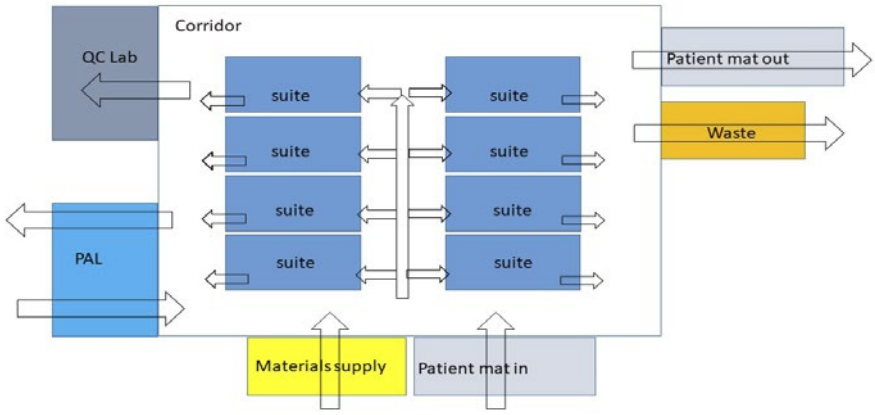

Figure 2. Schematic arrangement of a multi suite Advanced Therapeutic Medical Product (ATMP) facility.

2.4 Viral vector segregation

Cell therapy requires manipulation of the starting material by adding functional elements into the cell. This is done by using a viral vector, containing the intended functionality, that conveys the functionality into the cells. As these viral vectors are therapy specific cross contamination between various suites with different therapies needs to be prevented. In the case of manual aseptic operation this can be done by segregating the operators per suite, proper de-gowning, and waste disposal as well as single suite heating, ventilation, and air conditioning (HVAC) systems see Figure 3. This has the drawback that each suite has a single HVAC unit only without redundancy.

A fully redundant HVAC system is shown in Figure 4. The suites are all connected to a main supply and return header that is connected to n=1 HVAC units. This allows for full redundancy as well as easy expandability. This however connects the return air from one suite to the supply air of another. This could be potential considered leading to transfer of viral vectors unless the effect of high efficient air filter (HEPA) filters is considered. The possible viral vector containing air would be filtered in the BSC exhaust HEPA, the fine filters in the recirculation air handler as well as the supply HEPA. This would lead to a total filter efficiency of at least 99.9999999% which seem a good a protection as compared to the possible transfer via de-gowning activities.

Additional to the option of Figure 4 extra HEPA filtering the of exhaust air would lead to an even better overall filter efficiency of at least 99.999999999999% which is even better.

2.5 Redundancy and modularity

As shown in Figures 3–5 the make-up air as well as the air towards the supporting rooms all are equipped with n+1 air handlers for redundancy and maintainability purposes. As autologous therapies are patient based both the start as the duration of the process cannot be full planned. A maintenance stop of a suite causes a much larger loss of capacity than in case of batch production of allogenic therapies. Therefore, redundancy and modularity of moderate sizes suites are optimal.

When all suites are modular designed, the supporting technical systems as the BMS motor control center, the monitoring system, the door interlock system, the electrical distribution cabinet as well as branched connections of the clean gasses used. Such a modular set-up will allow maintenance and modifications to be performed while other suites are not/minimal affected. Furthermore, when the building volume allows, expansion additional suites can be constructed and connected.

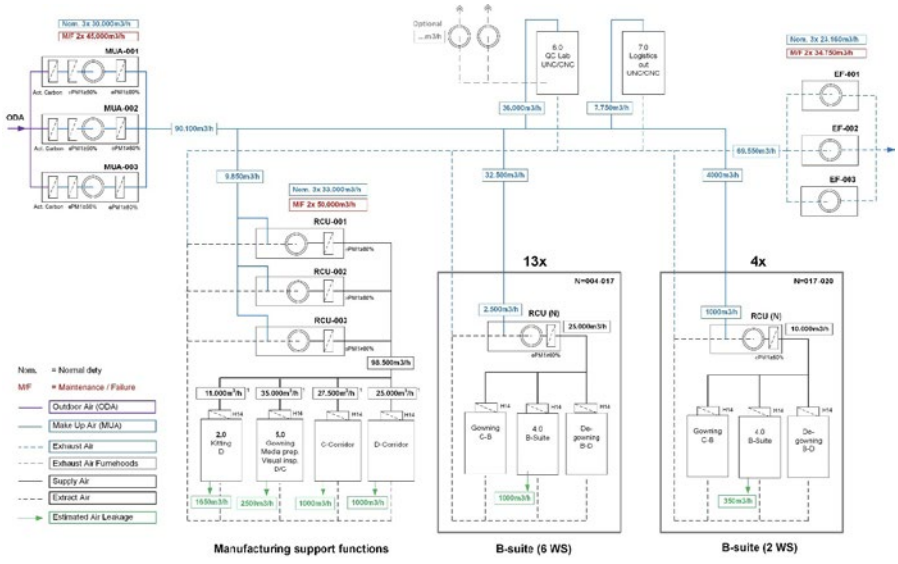

Figure 3. Heating, ventilation, and air conditioning (HVAC) schematic with single HVAC per suite.

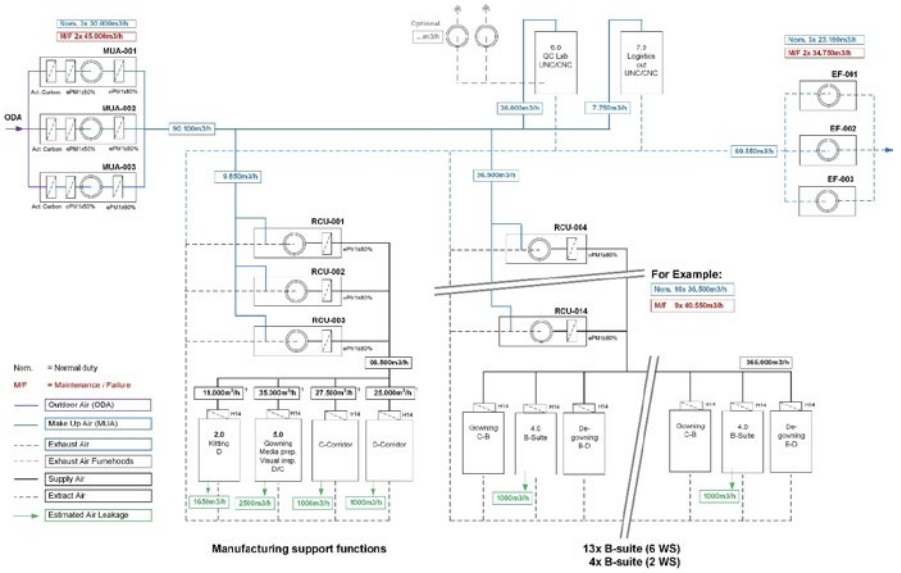

Figure 4. Heating, ventilation, and air conditioning (HVAC) with set of multiple and redundant RCUs connected to a main supply header and main return header with all B-suites.

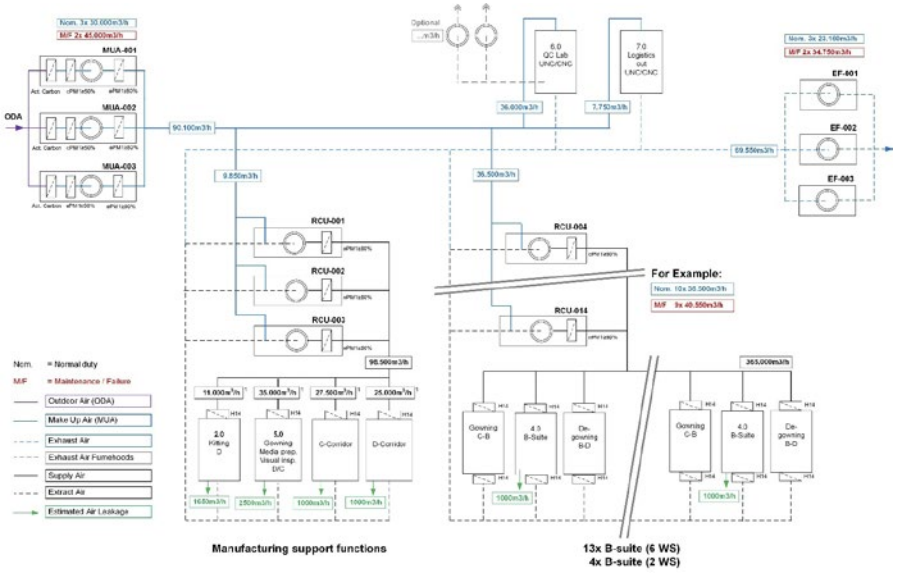

Figure 5. Heating, ventilation, and air conditioning (HVAC) Figure 4 with additional high efficient air filter (HEPA) filters in the return of all B-suites.

3 EVALUATION

ATMP facility design requires an integrated approach where production, operation, QC, and the design team need to work together and evaluate all design elements. As the development of processing equipment from manual aseptic is moving towards more closed systems flexibility and redundancy in the suite layout design as well as in the HVAC and supporting systems is mandatory.

4 IN CONCLUSION

ATMPs form an increasing part of the pharmaceutical market. The Eudralex Vol 4 ATMP-guideline deals with their specific requirements. As diverse as they are they generally require a flexible and modular approach. Furthermore, logistics on product, materials and in process quality control pose requirements on routing and layout. This is particularly of importance when autologous products are processed. Developing from manual lab procedures the expected developments to more closed and automated systems require adaptable designs. Based on recent projects and considering the contamination control strategy aspects, design concepts and solutions will be presented including lay-out concepts, flow/pressure cascades including GMP and containment.

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VENTILATION SOLUTIONS FOR HEALTHCARE PATIENT ROOMS TO CONTROL RESPIRATORY INFECTIONS

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1 INTRODUCTION

The pandemic has caused to develop and study indoor air solutions, because in the past the safety of indoor air has been taken for granted. One of the most significant factors is ventilation in indoor air environmental solutions. Novel indoor air environment solutions are needed to make safe indoor air the default again. Studies have emphasized the critical role of airflow in the spread of airborne infectious diseases in closed spaces (Ren et al. 2021).

2 METHODS

The study investigates the coronavirus infection risk and ensure safe indoor air with 3D computational fluid dynamics. The target room is the standard hospital reception room for two people (patient and doctor or healthcare staff). The heat produced by one person in this study is 60 W. There is 4-way supply air terminal. The supply air temperature is 21°C and air speed per inlet way is 0,0833 m/s. The room ACH is 2.7. The present study investigates what is the optimal exhaust terminal location in a type of room for the extraction of aerosols caused by human breathing. The study compares the exhaust terminal placement in six different locations. (Figure 1) The ventilation is mixing ventilation.

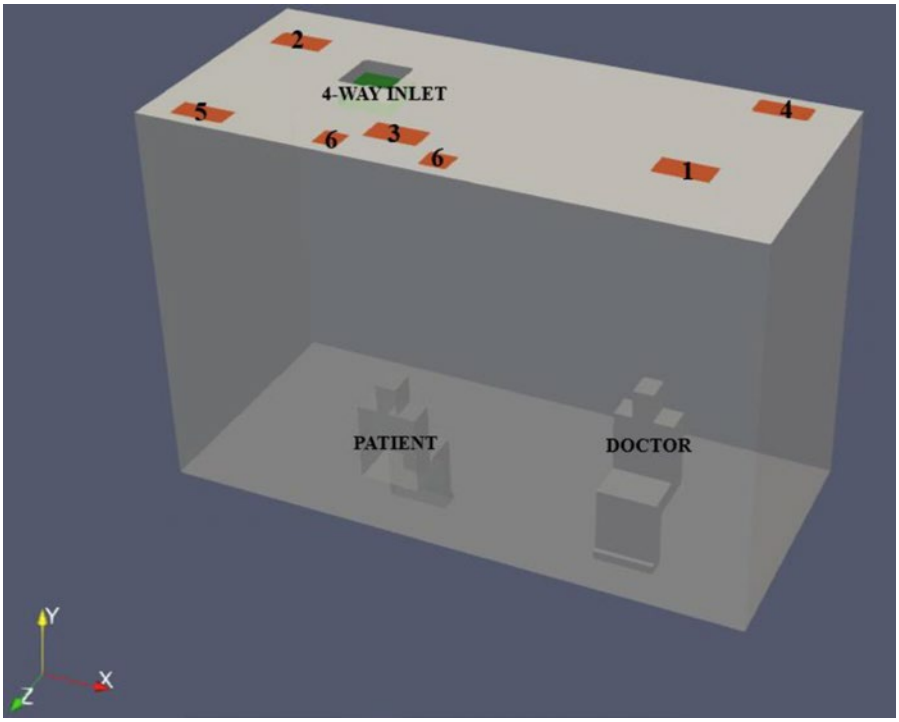

Figure 1. The hospital room layout with different exhaust terminal options (6), inlet terminal and people. The exhaust terminals are numbered 1-6.

3 RESULTS

The RANS approximation was used in the simulation, and the k-omega-sst model as the turbulence model. The positions of the exhaust terminals affect the movement of the air flow in the room (Figure 2). The movement of air flow in the room also affects the movement of aerosols. The research is still in progress and in this extended abstract examined the differences in the velocity profiles of exhaust terminals 1 and 2.

Figure 3 shows the spread of breathing in the room, exhaust terminal 1 is used in the breathing simulation. Breathing was implemented for the simulation as a passive scalar, which can be thought of as continuous steady breathing.

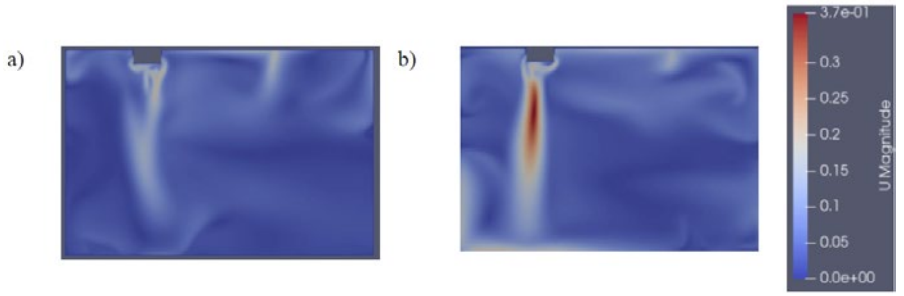

Figure 2. Velocity profiles xz -plane. a) Exhaust terminal 1 b) Exhaust terminal 2 is used in simulation.

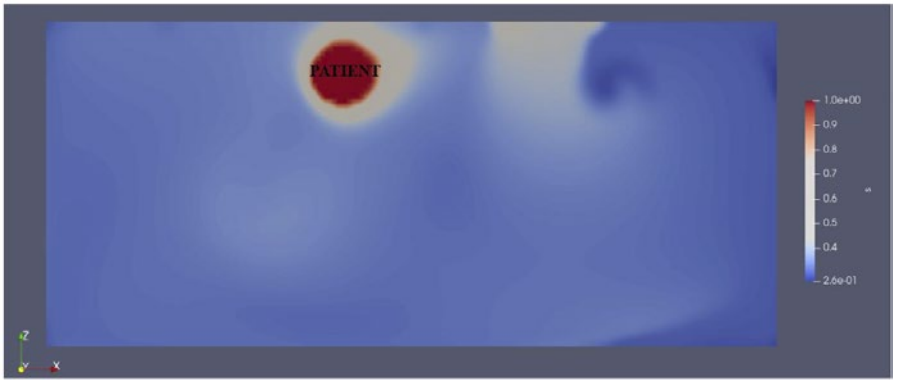

Figure 3. The patient's breathing profile, modeled as a transient simulation in the room as a passive scalar.

4 DISCUSSION

Simplifications were used in the simulation, such as heat produced by humans has been considered as a heat source, and heat radiation has not been considered. Breathing was also not modelled at the droplet level but as a passive scalar to maintain simplicity and efficiency. All the simulations are not ready yet, so the best exhaust terminal placement in the room cannot yet be said with the first two simulations and one breathing profile.

5 IN CONCLUSION

During the COVID-19 pandemic, more attention has been paid to healthy indoor conditions and safety, as air is the main route of transmission of the Sars-Cov-2 virus. The airborne spread of the virus highlights the importance of a ventilation strategy, as well as the development of new ventilation solutions. Current studies have shown that sufficient ventilation reduces potential exposure to the virus. The aim of the study is to optimize the location of ventilation terminals in a typical hospital emergency reception room.

In this study different computational fluid simulation models (CFD) implemented in the room were compared. The location of the exhaust air device has been changed in the various cases. The research methods of the work are CFD, literature research and comparison of ventilation solutions.

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VENTILATION SOLUTIONS ENHANCING HEALTH CARE WORKER'S SAFETY IN ISOLATION ROOMS

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1 INTRODUCTION

According to recent studies, there is a high risk for health care worker's (HCW) to be exposed to microbes exhaled by patients especially, while they are conducting their work close to patient as shown in Figure 1. Current ventilation solutions that are used in Isolation rooms are not designed to address this challenge. With high airflows rates that are used in isolation rooms, ventilation airflow can reduce the average microbial concentrations in the room, but they are not able to affect the HCW's exposure to patients' outbreath close to patients. These may lead to substantially higher exposure levels compared to general room air conditions. The results of the study by Kalliomäki et al in Figure 2 indicate that it can be even 5 to 10 times higher. It is worth to notice that this difference is at the same magnitude as if HCW was using FFP2 mask or not.

Figure 1. Health care worker's (HCW) exposes to patient exhalation in close proximity treatment situation, mixing ceiling air diffusion (Kalliomäki & Koskela, 2018).

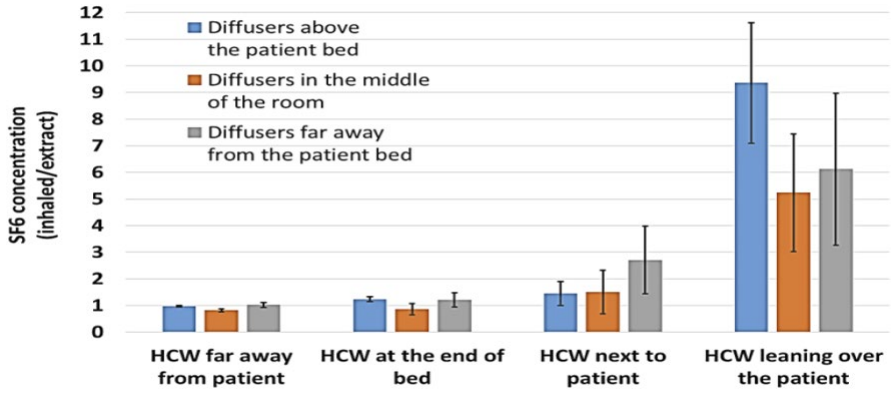

Figure 2. Influence of room position and ventilation outlet location on the HCW exposure in an isolation room with mixing ceiling air diffusion (Kalliomäki & Koskela, 2018).

2 PERFORMANCE REQUIREMENTS FOR ISOLATION ROOMS

The performance requirements for isolation rooms have been considered from first principles in standardization work at CEN TC156 WG18 (2022). The airflow dimensioning of a patient room airflow is considered based on steady-state emission of an infected person and expected dilution factor leading to an airflow rate /patient rather than room air change rate that has been used quite often traditionally. Also, the defined verification requirements for ventilation systems aim to account both for general and local exposure risks acknowledging above presented research evidence. Also, sustainable operation is considered when the room is used for other patients without isolation need. Recently with COVID-19 pandemic, there has also raised a need for isolation of multi-patient intensive care rooms for patients with a same infection.

A new dynamic protective flow ventilation approach has been developed for isolation rooms allowing different operation modes for isolated and normal patient needs. The airflow pattern used in Isolation rooms is illustrated in Figure 3.

The protective airflow ventilation system was tested according to same test protocol as in the publication reported by Kalliomäki & Koskela (2018) as well as according to principles emphasized in CEN working draft to assess, whether it would provide enhanced protection for HCWs while working close to patient. The smoke visualization of the situation is shown in Figure 4. Figure 5 shows the data of the HCW exposure with protective flow and with mixing ceiling air diffusion using intake fraction. Intake fraction illustrates the share of patient exhalation that is inhaled by HCW. The intake fraction with protective airflow system was more than 5 times lower compared to traditional mixing air diffusion and the inhaled concentration was also below room exhaust level.

Figure 3. Protective airflow system concept in an isolation room (Halton, 2021).

Figure 4. Reduction of HCW exposed to patient exhalation in proximity treatment using protective airflow.

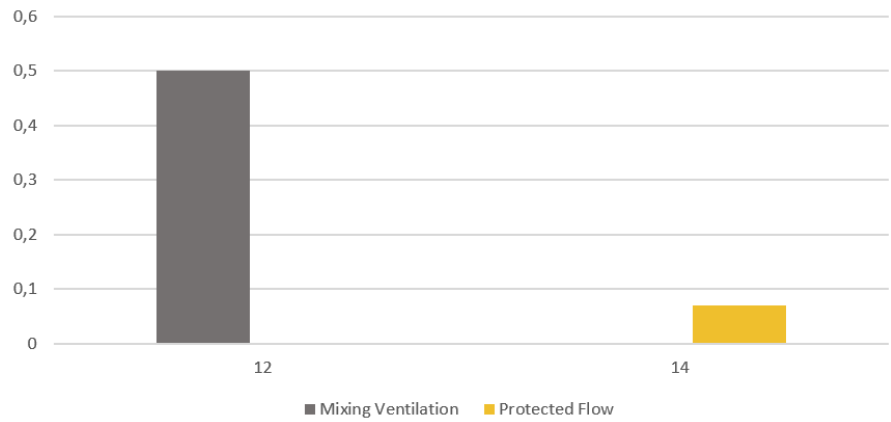

Figure 5. Health Care Worker intake fraction with mixing ventilation (grey) and protective airflow (yellow). The intake fraction with protective airflow system was more than 5 times lower compared to traditional mixing air diffusion.

As protective airflow principle is based on more localized air diffusion it was important also to verify thermal comfort of a patient. This was made in the first stage by using thermal mannikin and finally with human subject experiment using 15 persons (8 females and 7 males). The thermal environment was found acceptable in both tests. The sensation vote by test subjects was found neutral with perceived dissatisfaction below 15%.

3 IN CONCLUSION

The protective airflow principle was found a promising approach for HCW protection in isolation rooms and superior to traditional air diffusion method with high exposure risk. The same principle has also been implemented for normal patient rooms; more information of that application may be found in the publication written by Hagström et al. (2022).

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SURFACE HYGIENE IN HOSPITAL ENVIRONMENT

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1 INTRODUCTION

The current COVID-19 situation challenges and highlights the importance of hygiene and cleaning expertise and skills in all operation environments. The actors of the hygiene and cleaning sector as well as their customer companies face today various new challenges in different crisis situations, which must be responded acutely by changing materials, chemicals and working procedures. In addition, the hygiene and cleaning industry actors are in key roles not only during the crisis and extraordinary circumstances such as pandemic waves but also when the restrictions are removed, ensuring the safe return to normal conditions e.g., in terms of quality surface cleaning.

In the hospital environment cleanliness and clean surfaces must be self-evident. Surfaces are always contaminated with dirt, dust, micro-organisms and condensed matter. This is why cleaning has a long history, but the criteria for what we want to obtain by cleaning differ: to obtain an acceptable perception both visual and tactile, for hygienic and health concern reasons, and to prevent surface degradation (Dancer, 2011; SFS 5967, 2010).

There are several studies concerning persistence of coronavirus (SARS-CoV-2) in surfaces in the hospitals and for example Wu et al. (2020), Ye et al. (2020) and Zhou et al. (2020) all had similar conclusions of the need to strict environmental surface hygiene practices and enhanced hand hygiene to prevent the spread of the virus.

Assadian et al. (2021) compiled a review focusing on routine environmental cleaning and disinfection including areas with a moderate risk of contamination, such as general wards. The review provides expert guidance for healthcare workers in their daily practice. Boyce (2021) has been studied different wipes and wiping techniques and their effect on cleaning quality.

Kampf et al. (2020) assume that virus in not likely spread though surfaces if there is no external secretion so that is why we are not supposed to use disinfectants unnecessarily. According to CDC Science Brief on April 5th 2021 cleaning surfaces just with daily used detergent should be enough and disinfection should be used only in risk situations. So, the risk of fomite transmission is easily reduced with normal hygiene procedures used in this situation.

An article in the Lancet magazine has summarized studies that have investigated the C_t (Cycle threshold) values of coronavirus findings. The C_t value gives an idea of the amount of virus in the sample. The lower the C_T value, the greater the number of viruses and the chance of infection. The authors consider the spread of the virus through surfaces to be minimal unless there are secretions on the surfaces. Therefore, they would limit the use of disinfectants only to those situations (Kampf et al., 2021).

2 MATERIALS AND METHODS

The purpose of the study was to determine whether COVID-19 patients secrete SARS-CoV-2 virus into their environment and whether cleaning removes the spread of virus contamination from surfaces. The study was carried out at Tampere University Central Hospital in the emergency, intensive care, infection, and children's emergency departments. The samples were collected from the surfaces with a moistened cotton swab into a sample tube with salt buffers. The collection was carried out before and after cleaning from a total of 48 patient rooms.

Samples were collected from different parts of the patient room, e.g., from door handles, windowsill, air conditioning duct, different parts of the patient bed, treatment equipment, floor, toilet facilities, e.g., toilet seat, sink and faucet. Totally 921 samples were taken, and 465 samples were examined before cleaning and 456 after cleaning.

The swab samples were analyzed using the SARS-CoV-2 specific nucleic acid amplification method (RT-qPCR). The nucleic acid contained in the samples was isolated with Qiagen's Viral RNA putty according to the instructions. Potential virus positivity was tested using SARS-CoV-2 specific RT-qPCR methods targeting the N1 and N2 genes. The reactions were made with QuantiTect Probe RT-PCR putty (Qiagen) according to instructions with 900mM CoV2019 N1 F primer, 900mM CoV2019 N1 R primer and 200mM CoV2019 N1 P probe. In the N2 gene method, the template was amplified and identified using a 300mM CoV2019 N2 F primer, a 900mM CoV2019 N2 R primer, and a 200mM CoV2019 N2 P probe. RT-qPCR conditions were as follows: The RT-PCR reaction was done at 56°C for 30 minutes. In the qPCR method, initial

denaturation was done at 95°C 5min and amplification at 94°C for 15 seconds, the adhesion of the primers to their target was done for 60°C 15 seconds and amplification at 72°C for 1 minute, there were 50 cycles in the method.

3 RESULTS

A total of 921 samples were examined 465 before cleaning procedures and 456 after cleaning. There were 48 patient rooms, and no virus was found in 32 patient rooms. At least one virus positive sample was found in 15 rooms. The viral numbers in the samples were very low, the samples contained from a single to a few dozen viruses. An exceptionally high number of virus-positive samples were found in two patient rooms. In the first room 18 samples were tested and 11 were positive and in the other room 8 of the 18 samples were viral positive. In those rooms exceptionally high amounts of viruses were found and three of the samples contained an estimated thousands of viruses. Ten positive samples were also tested for the ability to infect viruses. No indication of infectious viruses was found in the samples tested. SARS-CoV-2 virus was found in 32 samples collected before cleaning, 13 of these sample points were positive even after cleaning. In addition, after cleaning, 2 positive sample points were found, which were negative before cleaning. An example of the results of a one-person patient room is in the table 1.

Table 1. The presence of coronavirus on the surfaces of the patient room. Coronavirus was found in the patient's room before cleaning on seven surfaces and after cleaning on four surfaces.

	Before cleaning	After cleaning
Patient room door handle	NEG	NEG
Floor next to the bed	POS	NEG
Sideboard of the bed	POS	POS
Footboard of the bed	POS	NEG
Bedside table	POS	POS
Toilet faucet handle	POS	POS
Toilet door handle	POS	NEG
Inner side of the toilet seat cover	NEG	POS
Toilet seat ring	POS	NEG

4 IN CONCLUSIONS

Cleaning reduced the amount of viruses on the surfaces of the hospital environment but did not always remove them completely. However, the amount of virus was so low that it no longer caused the disease. More studies of cleaning efficiency, cleaning procedures and usage of cleaning detergents is needed.

The research project was funded by Business Finland Co-Innovation, and it was carried out during the winter of 2020-21 in the Tampere higher education community. The researchers thank the financier and the companies involved.

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THE PROPOSED CHANGES TO ANNEX 1 DRAFT FEBRUARY 2020: REVIEW OF IMPACTS ON THE REQUIREMENTS FOR CLEANING AND DISINFECTION

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1 RELEVANCE OF ANNEX 1 BEYOND THE EU

As stated in the EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use – Introduction: *"The pharmaceutical industry of the European Union maintains high standards of Quality Management in the development, manufacture, and control of medicinal products…Manufacturing authorisations are required by all pharmaceutical manufacturers in the European Union whether the products are sold within or outside of the Union."*

Pharmaceutical manufacturers within the EU, or manufacturers supplying products to the EU are therefore required to conform to EU GMPs. EudraLex Vol.4 Annex 1 is common to the member states of the EU, but also the participating authorities of (PIC/S). As of June 2018, 48 countries have acceded as state members of PIC/S. Updates or revisions therefore have significant and wide-reaching consequences.

2 HOW THE DRAFT ANNEX EVOLVED

On December 20th, 2017, the European Commission produced a draft of a revised Annex 1. The draft revision had attempted to reflect many of

the advances in sterile manufacturing technology that had occurred in the preceding 10 years since the Annex had been updated, particularly with regards to RABS, isolators and single use technologies. There was an acceptance and alignment with ICH Q9 (Quality Risk Management - QRM) and ICH Q10 (Pharmaceutical Quality System - PQS) and the new draft implicitly encouraged using the principles of QRM, with numerous references to QRM made throughout the document.

3 THE IMPACT OF THE ANNEX 1 UPDATE ON CLEANING AND DISINFECTION

Of the many changes in the draft Annex, this article will look particularly at the impact the draft had on the requirements for cleaning and disinfection, and whether the latest version (Annex 1 v.12 February 2020) has changed the guidance significantly in this respect.

It would be considered prudent for sterile manufacturers to compare the proposed changes in the draft to the procedures and practices at their own sites to determine if adjustments to site CCS will be needed to remain compliant.

3.1 Cleaning versus disinfection and the focus on disinfectant residues

Annex 1 v.12 February 2020: *"4.36 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed..... Cleaning programs should effectively remove disinfectant residues."*

It has been accepted for some time that the terms 'cleaning' and 'disinfection' should be considered as two distinct terms, and it can often be helpful to consider them as two distinctly different processes within cleanroom environments. The Annex 1 section previously called 'Sanitation' had already been renamed 'Disinfection' and been expanded

in the Annex draft issued in 2017, indicating that this was an area of increased focus.

The separation of these two processes is now clearly stated. The process of cleaning is to remove physical dirt, soiling or disinfectant residues from a surface which could otherwise present a risk of physical, chemical or particulate contamination to the cleanroom area or products being manufactured within it. The presence of dirt, soil or residues on a surface could also present a physical barrier impeding the contact of any disinfectants that may be applied to a surface or to any microorganisms present, potentially impacting on the disinfectant efficacy.

By contrast, disinfection refers to the application of a chemical with a known antimicrobial activity or effect, for a specific contact time to reduce any bioburden present to an acceptable level. The presence of visible residues has often been seen in the past as an indication that a cleaning and disinfection process is not fully in-control, as the activity itself is leaving a 'contaminant' on the surface. The Annex draft now goes further, raising the concern that the residues themselves can have some hidden effects.

3.2 Rotation and use of disinfection agents

Annex 1 v.12 February 2020: *"4.36 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme... More than one type of disinfecting agent should be employed to ensure that where they have different modes of action and their combined usage is effective against all bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection program and to detect changes in types of microbial flora (e.g., organisms resistant to the disinfection regime currently in use)."*

"4.38 Disinfectants and detergents used in Grade A zone and Grade B areas should be sterile prior to use (disinfectants used in Grade

C and D may also be required to be sterile). Where the disinfectants and detergents are made up by the sterile product manufacturer, they should be monitored for microbial contamination. Dilutions should be kept in previously cleaned containers and should only be stored for defined periods. If the disinfectants and detergents are supplied "ready-made" then results from certificates of analysis or conformance can be accepted subject to successful completion of the appropriate vendor qualification."

Disinfectants are usually divided into broad-spectrum disinfectants or sporicides (usually more aggressive, oxidising chemistries capable of penetrating and killing bacterial endospores). Whilst the requirement to rotate a broad-spectrum disinfectant with a sporicide 'in accordance with a written programme' (i.e., not using sporicides only reactively) remains, the Annex draft v.12 issued in February 2020 has changed slightly. It now appears to imply the use of two different (possibly broad spectrum) disinfectants with different modes of action in addition to the periodic use of a sporicidal agent, however this needs clarification.

Whilst this practice is sometimes seen, there may be little value in rotating two broad spectrum disinfectants that are exerting an effect on a similar spectrum of organisms. Having two broad spectrum disinfectants that need to be rotated can also increase complexity in terms of SOPs, and procedures, and increases the burden of validation and control of materials on site.

The Annex draft v.12, perhaps disappointingly, continues to reference organisms 'resistant' to the disinfection regime. The concept of acquired rather than innate resistance occurring at a site has been a contentious point for years, with little evidence of this phenomena forthcoming. The requirement for disinfectants and detergents used in Grade A zone and Grade B areas to be sterile prior to use (termed Grades A and B areas in Annex 1 2008 and in the 2017 draft) and for solutions to be monitored for microbial contamination, remains in place. Interestingly, Annex 1 daft v.12 highlights that disinfectants used in Grade C and D may also be required to be sterile. This is again an indication that QRM principles must be applied. The use of sterile products in lower grade areas should not be ruled out if a contaminant present in a disinfectant

could detrimentally impact on a production area and/or the products being manufactured within that area.

3.3 In house preparation of disinfectant from concentrates

Annex 1 v.12 February 2020: *"4.38 …Where the disinfectants and detergents are made up by the sterile product manufacturer, they should be monitored for microbial contamination. Dilutions should be kept in previously cleaned containers and should only be stored for defined periods. If the disinfectants and detergents are supplied "ready-made" then results from certificates of analysis or conformance can be accepted subject to successful completion of the appropriate vendor qualification."*

Concentrate versions of disinfectants have long been used and are considered by many to be a practical and cost-effective means of producing large volumes of disinfectant for use. However, the Annex 1 draft issued in 2017 made it clear that there were increased considerations that impact on disinfectants being prepared and filtered into sterile areas.

3.4 Validation of disinfectant efficacy and in use expiry periods

Annex 1 v.12 February 2020: *"4.37 The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and should support the in-use expiry periods of prepared solutions."*

The Annex is clear that the effectiveness (efficacy) of disinfectants should be validated, and that the validation should be representative of the specific way they are used. This reinforces that end users of disinfectants should carefully consider the contact times, surface materials and methodology used to validate disinfectants.

It also requires that the 'in-use expiry' or hold time of a disinfectant solution is demonstrated through validation. This may represent a further increased burden on users preparing detergent or disinfectant products from concentrate rather than using "ready-made" or ready-to-use products. Here the Annex draft concedes that certificates of analysis or conformance from approved vendors may be sufficient, negating the need for additional testing.

4 IN CONCLUSION

The revised version 12 of the Annex 1 draft issued February 2020 retains much of the 'direction of travel' of the 2017 draft with regards the guidance for cleaning and disinfection as an integral part of a Contamination Control Strategy (CCS). The final version of the Annex will invariably still contain some text that may be open to interpretation and will of course never be able to be a perfect guide for all readers. Further targeted consultation with a select number of relevant industry groups and organisations is complete, and suggest clarifications and amendments submitted to the to the Annex1 Inspectors Working Group (IWG). It is hoped that this process will now result in a final version of Annex 1 in Q3 2022.

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Editors' comment:
The final version of Annex 1 in Manufacture of Sterile Medicinal Products (https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf) has been published in week 34 (2022). This document provides technical guidance on the principles and guidelines of good manufacturing practice (GMP) for medicinal products. The deadline for Annex 1 coming into operation is August 25, 2023, except for point 8.123, which is dealing with the frequency of lyophilizers' sterilisation and which deadline is August 25, 2024.

IV

CLEANROOM NEWS / GENERAL

THROUGH PROCESS OPTIMIZATION TO REDUCE PRODUCTION TIME, ENERGY AND COSTS

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Thinking of the warming of the Earth's atmosphere, we all have a responsibility, starting with each of us, companies, and states, because the air is common to us. A good example of this is how all these benefits can be achieved by optimizing production stages by shortening production time and reducing energy use, i.e., energy costs.

Here's an example new production plant of the Ecoflac-Plus infusion bottles® at B. Braun, those responsible - among many other criteria – have demanded a time optimization of the process, a short implementation phase and a significant reduction in operating costs for the drying of the bottles between the sterilization autoclave and the bottle labeling.

The mission of this kind of drying tunnels is reducing the drying time spend in between the autoclave and labelling system. During sterilization process, the autoclave in flooded with pressurized water, which creates a problem in labelling, as it will not be possible to stick the labels on the humid bottles. To achieve a complete drying process, air flows are created and directed to the exterior surfaces of the bottles, absorbing the water and humidity of the products. The air involved in the process is treated inside the Air Handling Unit. Then, the air is insufflated and recirculated in the interior of the tunnel, removing the water and the humidity and cooling the product. Water is drained through the inclined trays and pipeline system (Figure 1).

Figure 1. Recirculation of the air in the interior of the tunnel is made by 8 fans situated on the lateral plenum.

Thanks to the "plug & play" design, the new drying tunnel is largely delivered in ready-to-use modules approved by the customer. The integral and modular design of the system allows initial start-up in the plant. During the FAT, the dryer was extensively tested together with the B. Braun project team and at the same time around 80% of the IQ and OQ tests were successfully carried out with regard to the functions. Just 4 weeks after the start of the installation work at B. Braun, the qualification was completed as planned and the system was handed over to the customer. After a thorough evaluation, the

new drying tunnel from was able to convince with a drying time of less than 2 hours with a capacity of 9 pallets (36,000 bottles) per batch, as well as with a significantly lower energy consumption due to the drying principle efficient drying principle.

In view of constantly increasing demands on flexibility, scalability, and efficiency in production processes as well as on quality, the planning and integration of old and new plants requires a profound understanding of the specific processes and regulations in addition to great technical competence. Our responsibility for the environment, such as global warming, is the responsibility of all our companies as part of developing new and improving the energy efficiency of old processes in use for future generations, thereby contributing to our global common goal. More information is available in the presentation.

RE-QUALIFICATION OF CLEAN ROOMS

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Different qualification activities expected to be conducted in clean rooms in GMP areas are described in guidelines such as EU-GMP Annex 1 and FDA Aseptic Guide as well as in the standards within the ISO 14644-series and the EN standard 17141 (2020).

Figure 1. The standards cover activities, requirements, and tests to be performed in qualification of a clean room.

The standards and guidelines given in the literature list cover activities, requirements, and tests, to be performed from the first stages of qualification of a new cleanroom to the final commissioning of the clean room. This presentation covers an explanation of the guideline and standard "puzzle". What, how where and when to be used will be discussed with a detailed background in the requirements according to the new expected EU-GMP Annex 1 regarding qualification and re-qualification of clean rooms. Expected tests for qualification in the new version of the EU-GMP Annex 1 are given in Table 1 and Figure 2.

Table 1. Parameters to be checked in re-qualification (EN 17141, 2022; EC, 2020).

Grade	Determination of the concentration of airborne viable and non-viable particles	Integrity Test of Terminal Filters	Airflow volume measurement	Verification of air pressure difference between rooms	Air Velocity test
A	Yes	Yes	Yes	Yes	Yes
B	Yes	Yes	Yes	Yes	*
C	Yes	Yes	Yes	Yes	*
D	Yes	Yes	Yes	Yes	*

i. Installed filter leakage and integrity testing.

ii. Airflow measurement - Volume and velocity.

iii. Air pressure difference measurement.

iv. Airflow direction and visualisation.

v. Microbial airborne and surface contamination.

vi. Temperature measurement.

vii. Relative humidity measurement.

viii. Recovery testing.

ix. Containment leak testing.

Figure 2. Expected qualification tests in new version of the EU-GMP Annex 1 (EN 17141, 2022; EC, 2020).

The (re-)qualification tests will be explained in detail in the presentation. The use of each test will be presented from a practical point of view.

The principles of testing can be found in standards given below:

- ISO 14644-1 regarding
  - Airborne non-viable particles
- ISO 14644-3 regarding
  - Installed filter leakage and integrity test
  - Airflow test - volume & velocity
  - Air pressure difference test
  - Airflow direction and visualization
  - Temperature measurements
  - Relative humidity measurements
  - Recovery testing
  - Containment leak testing
- EN 17141 regarding
  - Microbial (viable particles) airborne and surface contamination

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RESPIRATORY AEROSOL PARTICLE EMISSIONS AND CONTROL IN THE CLEAN ROOM ENVIRONMENT

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1 INTRODUCTION

The current COVID-19 pandemic has highlighted the importance of understanding better the rapid aerosol transmission of pathogens, especially in respiratory aerosol particles (Greenhalg et al., 2021; Pai et al., 2016). Respiratory aerosol particle and droplet emissions vary widely between individuals and various activities such as breathing, speaking, singing, and coughing (Alsved et al., 2020; Asadi et al., 2019; Morawska et al., 2009). Important parameters in assessing the risk of infection with pathogens are respiratory particle emission rates and size distributions, as well as dispersion and dilution (Peng et al., 2022).

In this study, the emission mechanisms, and dynamics of aerosol particle emissions from respiratory tract are presented based on our pilot studies and the recently published articles. A new developed portable measurement system for respiratory particle emission experiments and some preliminary results are presented.

2 METHODS

The portable measurement system (Figure 1) enables the investigations of absolute and time-resolved exhaled aerosol emission rates with controlled drying and dilution processes of generated droplets. The system has an aerosol chamber having background aerosol concentration ca 0 after feeding clean pressurized air through HEPA filter. Temperature in the chamber was about 20°C and relative humidity was less than 1%, allowing the respiratory droplets to dry quickly. The relative humidity of the environment affects the final size and dynamics of the respiratory droplets, so it is an important parameter in the measurement system. Aerosol emissions were collected with aerosol sampling tubes at about 20 cm from the subject. The aerosol sample was fed to the real-time aerosol instruments (TSI 3776 CPC, Airmodus A20 CPC, TSI APS, Palas Fidas Frog) that are installed under the aerosol chamber. Parallel CO_2 concentration was measured (LI-840A, LI-COR Inc) to obtain information on aerosol dilution.

Figure 1: Portable measurement system for respiratory aerosol emission studies.

3 RESULTS AND DISCUSSION

Using the current measurement system, we can study respiratory aerosol particles generation rate in real time over a wide particle size range (0.01–10 µm). CO_2 measurement allows us to estimate dilution ratio of the aerosol emissions, so we can estimate the absolute aerosol emission concentrations. The results showed that most of the aerosol particles were smaller than 0.5 µm in size. The results are in line with the previous observations in which the highest number

concentration of respiratory particles was estimated to be around 0.1 µm in size (Pöhlker et al., 2021). The results indicate that the number of respiratory viruses may also be significant in this particle size range. However, the smallest particles are not necessarily relevant carrier of the virus, as individual viruses are typically larger than about 0.08 µm. Particle emissions varied between the speaking, singing, and coughing. Interestingly the particle emissions correlated with CO_2 concentration, which can be a useful indicator for assessing airborne aerosol particle emissions and dilution in indoor environments. An interesting question is whether emissions by particle volume concentration are more critical than particle number concentration because larger particles may have more infectious pathogens than smaller ones. That is one of the most important questions in future studies.

4 IN CONCLUSION

The results will help us gain new insights on aerosol transmission events, especially on the differences between common spreaders and potential super-spreaders. The study also indicates the efficiency of some potential aerosol control measures in the clean room environment such as face masks, air purifier and filtration. Because most respiratory particles are small, it is recommended that the performance and leakage of face masks, air purifiers and filtration equipment be tested over a size range of 0.1 to 10 µm.

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MICROBIAL RISK ASSESSMENT IN SAFETY CABINETS/CLASS II BENCHES WITH THE LR-METHOD

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Microbiological risk assessment with the method for limitation of risks, the LR-Method is described in this paper. Results from excerpts of case studies in Safety cabinets/Class II benches are discussed. The LR-Method which relies upon visualization of air movements, particle challenge testing, and calculation of a risk factor presents an effective way for identification and limitation of potential microbial risks.

1 INTRODUCTION

Experiences from risk assessment with the method for Limitation of Risks (LR-Method) can be applied to the assessment of airborne contamination risks of products and processes in Grade A conditions in cleanrooms and controlled environments. To identify and monitor potential microbiological hazards, a risk assessment should consider the following points:

- Identification of all potential hazards associated with the process, product, and staff.
- Assessment of the risk of occurrence of a hazard and identification of preventative measures for its control.

- Designation of risk zones, and in each zone, determination of suitable control points, procedures, operational steps, and environmental conditions that can be controlled to eliminate a hazard or minimize its risk of occurrence.
- Establishment of contamination control limits.
- Establishment of scheduled monitoring.
- Establishment of corrective actions to be taken when the monitoring indicates that a procedure, operational step, or environmental condition is not under control.
- Establishment of procedures to verify that the system is working effectively.
- Establishment and maintenance of appropriate documentation.

The key to this risk assessment is to understand the process, which in this case includes the Grade A and its surrounding and its performance, as well as the process and its vulnerability to airborne contamination. The risks of airborne contamination could result from the potential leakage of unfiltered air, entrainment of air from adjoining areas of lower cleanliness conditions, and accumulation of contaminants in turbulent or stagnant regions within the clean zone.

Whyte (1986) presented a model for predicting the product contamination from the concentration of airborne bacteria. Bradley et al. (1991) showed by a microbiological challenge test, that the level of airborne microorganisms in the filling environment has a profound effect on the level of product contamination. A direct relationship was reported between the extent of product contamination and the concentration of airborne microorganisms.

Using common microbiological methods currently available (such as active sampling of air, surface sampling, and media fills (APS)) it is difficult to identify, measure, and evaluate single potential hazards under clean room conditions. The detection level of common microbiological methods and the time needed for analyses makes it difficult to ascertain how, e.g., the performance of single operations and interventions affect microbiological risks. Due to low contamination levels in the surrounding environment real time measurements for detection of airborne microbial contamination might yield results that are difficult to interpret.

The use of challenge tests for evaluation of clean room processes (such as sterilization processes, sterile filtration methods, and HEPA-filter installations) to achieve microbiologically safe processes is well established. Microbiological challenge tests are not suitable for use in clean zones, clean rooms, and manufacturing areas. Assessment of potential microbiological hazards from airborne contamination can be performed with a non-microbiological challenge method using airborne particles as quick-response tracers. The LR-Method is a non-microbiological approach consisting of

- visualization of air movement study,
- challenge test with airborne particles as direct response tracers and
- calculation of the risk factor for the micro-biological evaluation of potential hazards.

Since this method does not rely upon highly variable microbial air sampling methods, it yields results that are more reliable and less subjective.

2 AIR MOVEMENTS AND DISPERSION OF CONTAMINANTS

Within a clean environment the predominant source of airborne microbial contaminants is people. Potential risk situations created by interaction among people, air movements, and airborne contaminants are difficult to predict and to evaluate.

In a unidirectional air flow, wakes and vortex streets are created behind obstacles, causing regions of turbulence. In front of equipment, the unidirectional airflow causes stagnation regions, and on working surfaces situated perpendicular to the main flow direction, the unidirectional airflow changes the flow direction and vortex regions can occur. Examples of visualized air movements in vertical UDF-units are shown in Figures 1-2.

Air movements in these cases are mostly irregular and difficult to predict. Contaminants emitted in such areas might accumulate or

disperse in an unpredictable way. Factual situations are complex and should be mapped and assessed empirically. The presence of people can cause unstable wakes and entrainment. These unstable situations are in most cases caused by the movements of arms and hands. Unstable situations within the clean zone can cause ambient (less clean) air to be entrained into the clean zone. Contaminants can also be dispersed from people moving arms and hands.

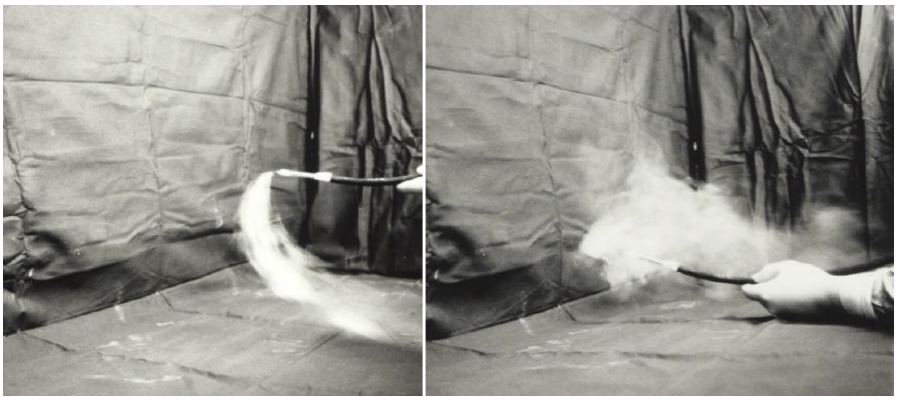

Figure 1. Change of airflow direction from vertical to horizontal (left) and occurrence of vortices (to the right) in a UDF unit with vertical airflow (from Ljungqvist & Reinmüller, 2006).

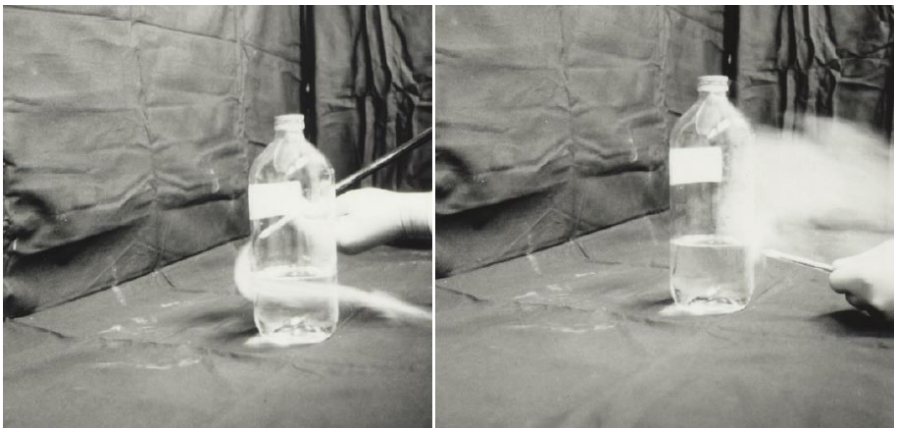

Figure 2. Air movements around an object (left) and wake vortex behind the same object with risk of entrainment from surrounding region(right) in the UDF unit shown in Figure 1, (from Ljungqvist & Reinmüller, 2006).

3 THE METHOD FOR LIMITATION OF RISKS (LR-METHOD)

The method for limitation of risks (LR-method) provides a reliable procedure for assessing potential microbiological risks of airborne contamination in clean zones in a systematic way. Experiences from the use of the LR-Method have been described earlier by Ljungqvist and Reinmüller (1993, 1995, 1997, 2006), Thomasin et al. (1987) and Ljungqvist et al. (2016).

The LR-Method is performed in three steps:

- The first step is to visualize (e.g., by using isotherm smoke technique) the main air movements and identify turbulent regions and critical vortices where contaminants can be dispersed or accumulated in an unexpected way.
- The second step - the challenge test – is to identify potential risk situations. The particle challenge test involves placing the probe of a light scattering airborne particle counter (LSAPC) in the critical area where during normal operations the process/ product is exposed and taking continuous total particle counts while generating particles in the close surrounding air (e.g., by using Air Current Test Tubes) to a challenge level of more than 300 000 particles equal to and larger than 0.5 µm per cubic foot (approx. 10^7 particles per m). These measurements should be carried out during simulated process activity. At least three samples of one minute are sampled at each location or during each process step.
- The third step is to evaluate the risk situation by calculating the Risk Factor, which is defined as the ratio between the highest measured particle concentration (number/ft^3) in the critical region and the challenge level in the surrounding air (number/ft^3). Because of limited measurement accuracy at high concentrations, a value of 300 000 per cubic foot is used as a challenge level in all Risk Factor calculations.

The illustrative technique of smoke studies provides a useful technique for visualizing air movements and the dispersal of contaminants. This technique requires isothermal smoke released continuously and

almost momentum free using a relevant diffuser. The smoke pattern can be recorded by means of still photography and video. To see the air movements improves the understanding of potential risks of airborne contamination

During the challenge test, the process simulation and operating conditions should preferably exaggerate the human interference and interventions to identify potential risk situations more rapidly. To assure the result, generally not less than three measurements of not less than one minute each should be performed at each representative location and for each intervention. The maximum concentration (number/ft^3) value of each intervention and location respectively forms the base for Risk Factor calculations. The advantage with this approach is the uncomplicated, immediate registration of results using a particle counter (LSAPC). The critical regions become contaminated only by non-viable particles, and this approach can be safely used in microbiological clean zones with no added risk of microbial contamination from the challenge tests.

When the Risk Factor is less than 10^{-4} (0.01%) during the challenge test, there are no risks of airborne microbiological contamination during standard operational conditions according to experimental findings from more than 50 studied aseptic production lines

4 RISK ASSESSMENT IN SAFETY CABINETS/CLASS II BENCHES

Microbiological risk assessment was performed and compared for three manual aseptic process steps. All process steps were sensitive to airborne contamination and had to be carried out in safety cabinets (Class II microbiological safety cabinets, Grade A conditions). The principle of the safety cabinet is shown in Figure 3.

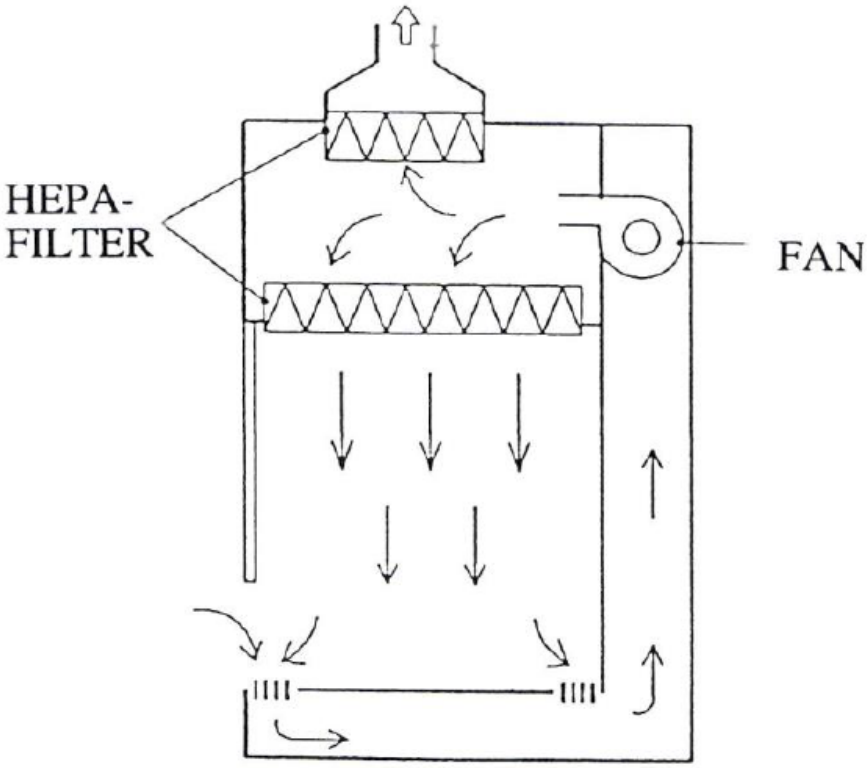

Figure 3. Principle of a safety cabinet

Three cases (I, II and III) were evaluated. The process specifications for the test cases were:

I Transfer of microbial inoculates in small vials to large flasks with sterile media (3L) but with no use of a gas flame. The safety cabinet is situated in an environment of ISO Class 8 operational (US customary class 100,000).

II Transfer of microbial inoculates in small vials to large flasks with sterile media (3L) and occasional use of a gas flame. The safety cabinet is situated in an environment of ISO Class 8 operational (US customary class 100,000).

III Small equipment, aseptic tube filling from a larger container to sterilized vials, 10 mL, no gas burner, the safety cabinet is situated in an environment of ISO Class 7 operational (US customary class 10,000).

All three safety cabinets were checked after installation regarding filter integrity, air flow velocity, and maximum allowed front opening. The results fulfilled the preset requirements. Visualization of air movements in empty cabinets showed that the main air movements were acceptable and similar for all three safety cabinets.

5 RESULTS OF RISK ASSESSMENT WITH THE LR-METHOD IN SAFETY CABINETS/CLASS II BENCHES

During the challenge test, the measuring probe of the particle counter was placed inside the cabinet, 0.15 m from the front edge and 0.1 to 0.3 m above the work surface depending on where the critical region for the process was established. The height of the front opening of the safety cabinet was 0.20–0.25 m, which is the common aperture height during working conditions. Particles (³ 0.5 µm) were generated (using Air Current Test Tubes) to a challenge level of more than 300 000 particles per ft3 in the ambient air close to the front opening of the safety cabinet. Results from the measurements are shown in Table 1. Maximum levels from samples of 1 ft3 for 1 min sampling time are reported.

Table 1. Measured maximum particle levels during the challenge tests and calculation of the Risk Factor (excerpts from a case study).

Case	Condition	Particle Levels (Number of particles ≥ 0.5 µm per ft³)		Risk Factor
		Ambient air in front of aperture	Maximum values within the cabinet	
I	Empty cabinet Simulated activity and disturbances	>300 000 >300 000	<30 30	$<10^{-4}$ 10^{-4}
II	Empty cabinet Simulated activity Disturbances	>300 000 >300 000 >300 000	<30 400 4 500	$<10^{-4}$ $1.3 \cdot 10^{-3}$ $1.5 \cdot 10^{-2}$
III	Empty cabinet Simulated activity and disturbances	>300 000 >300 000	<10 <10	$<10^{-4}$ $<10^{-4}$

The results in Table 1 show that the Risk Factor is satisfactory ($\leq 10^{-4}$) for the cases I and III, while in the case II, the Risk Factor is $1.5 \cdot 10^{-2}$, which indicates a potential microbiological risk. Further investigations of potential risk situations were performed, and these results are presented in Table 2.

Table 2. An example of mapping potential risk situations, in case II (excerpts from the study). Measured maximum particle levels during the challenge tests and calculation of the Risk Factor.

Condition	Particle Levels Number of particles ³ 0.5 µm/ft3		Risk Factor
	Ambient air in front of aperture	Maximum values within the cabinet	
Empty cabinet	>300 000	<30	$<10^{-4}$
Burner on and simulated activity	>300 000	600	$2 \cdot 10^{-3}$
Burner on and opening of door behind the operator	>300 000	2 800	ca $<10^{-2}$
Burner on and rapid passage behind operator	>300 000	4 500	$1.5 \cdot 10^{-2}$
Production activity. Transfer of equipment into the cabinet	>300 000	500	$1.7 \cdot 10^{-3}$
Burner on and critical operation ongoing	>300 000	200	$7 \cdot 10^{-4}$
Active air sampler located close to the front aperture. Sampler not operating	>300 000	<10	$<10^{-4}$
Active air sampler located close to the front aperture. Sampler operating.	>300 000	30 000	$1 \cdot 10^{-1}$

6 DISCUSSION

From Table 1 can be seen that the risk factor varied for the three cases. The clear differences between case I and III without use of a gas burner, and case II with the use of gas burner, showed that gas burners or heat sources within a safety cabinet cause serious disturbance. The

true outcome of the process performed during conditions simulated in case II showed a low but significant frequency of microbiological contaminated products.

Table 2 gives an example of mapping risk factors, and how potential hazards could be identified and evaluated. Within the cabinet, the use of a heat source, transfer of large equipment into the cabinet, and active air sampling represented risk situations. Further studies revealed that opening of doors in the room, and rapid passage behind the operator caused risk situations. The outcome was a redesign of the side walls of the safety cabinet and of the process laboratory.

During the investigation, the LR-Method was used simultaneously with traditional microbiological tests. The results from the microbiological samples taken outside and inside the cabinet did not show any significant difference between the various conditions. The Biotest Air Sampler, Reuter Centrifugal Sampler® (an earlier model) has often been used for active sampling of air during critical aseptic environments supplied with unidirectional air flow. The results here indicated that this operating RCS® air sampler, placed on the working surface close to the front edge (less than 0.2 m from the edge), entrained ambient air into the cabinet and thus increased the risk of airborne contamination to the process.

To evaluate the risks of airborne biocontamination in class II benches as well as in open UDF units, visualization of the air movements is not enough, see Thomasin et al (1987). The risk of entrainment and disturbances of movements during manual interventions, occasional heat sources, and large equipment is not assessed detailed enough by visualization of air movements alone. To avoid aseptic processes in existing stagnation regions in safety cabinets/class II benches or in vertical UDF units the aseptic interventions should take place above the table surface and preferably allow for air flow beneath the objects.

A rule of thumb for safety cabinets and effective protection of the operator is that the average air velocity through the maximum allowed front opening should not be below 0.4 m/s, see Clark (1983). This air volume should represent not less than1/3 of the total flow through the HEPA-filter. The KI-discus method is an important method for

evaluation of operator protection, see Clark (1983). Heat sources should not be used inside safety cabinets or UDF units, necessary disinfection had to be performed in other ways. Use of sterile disposables is recommended. Clothing system used in Grade C might need addition of disposable sterile accessories, such as arm or sleeve covers, during aseptic processes to minimize the risk of airborne contamination.

7 IN CONCLUSION

To design and evaluate microbiologically safe aseptic processes, several evaluation methods ought to be combined during the different stages of process development. To the common methods include computer simulations of airflow, installed filter leakage tests, airflow visualization, measurements of air velocity, environmental monitoring methods, and the LR-Method.

When an aseptic process is performed in a safety cabinet or UDF unit, sidewalls and openings might have to be customized to the process equipment and the necessary process interventions. Here, visualization of air movements studies gives valuable information provided that the smoke or particles are emitted continuously and momentum free under isothermal conditions. However, the visualization studies alone do not ensure microbiological safety against airborne contamination during dynamic conditions. The protection efficiency of the sidewalls during dynamic conditions can be evaluated with the LR-Method. For example, the LR-Method can be used to evaluate individual details such as the tools constructed for interventions.

The method also can be used to optimize safe aseptic interventions when detailed standard operation procedures (SOPs) are developed. In addition, monitoring locations can be evaluated with a modified LR-Method (Ljungqvist & Reinmüller, 2006).

Aseptic processes in Class II benches or UDF units require detailed instructions due to the limited working space within the units and the special conditions regarding the airflow pattern. Presence of stagnation regions, vortices, and in Class II benches especially the division line that

affects the dispersion of contaminants and thus the way of working. Each unit and process must be assessed separately.

The LR-Method, which relies upon visualization of air movements, particle challenge testing and calculation of the Risk Factor presents an effective way for limitation of potential microbiological risks. It can be used for

- tracing the dispersion routes of airborne contamination,
- identification of risk situations,
- evaluating risks connected to single process steps,
- immediate evaluation of changes,
- assessment of potential risks.

With a systematic use of the challenge test with particles and the use of a particle counter it is possible to identify specific risk situations and thus avoid them or reduce their frequency or duration. Changes in working procedures can be evaluated without delay. Detailed work instructions (SOPs) containing exact recommendations for risk reduction can be written based upon the information obtained from the use of the LR-Method. In addition, the identification and documentation (e.g., video) of risk situations has been found to facilitate the operator training.

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PREPARING FOR THE NEXT PANDEMIC – SIMULATION-BASED SOLUTIONS

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1 INTRODUCTION

At the beginning of 2020, frightening news emerged around the world. The unknown threat caused a lot of pneumonia and other several illnesses. Soon it turned out that the cause was the coronavirus closely related to 2002–2003 Severe Acute Respiratory Syndrome (SARS) virus. New virus was later named SARS Corona Virus 2 (SARS-CoV-2) and the disease was named COrona VIrus Disease 19 (COVID-19) in order to avoid name SARS and fear it could cause (Miller et al., 2022).

At first, it was thought that the virus would not be transmitted from human to human, but when this turned out to be the case, it was time for urgent measures. Different methods to prevent the spread of the disease were applied, including full lockdowns. At first, it was thought that the virus was transmitted mainly through droplets and fomites. The research community started soon, however, to speculate whether the virus can also be transmitted by small particles floating in the air called aerosol particles (Vuorinen et al., 2020). When this transmission route turned out to be important (Morawska & Milton, 2020), perhaps even dominant (Zhang et al., 2020), it was time to start look for, research, and develop the methods to prevent aerosol transmission.

In this paper, we present one technique for studying different airborne contamination control methods and devices. The method is computational fluid dynamics (CFD), which was successfully used in the aviation industry in the first place, but now also in many other sectors including construction industry.

2 METHODS

As a CFD simulation software, OpenFOAM (Weller et al., 1998) is used which is based on finite volume method (Patankar, 1980). Taking turbulence into account is one of the biggest challenges of flow simulation (Pope, 2000). In the case of indoor air flows, traditional Reynolds Averaged Navier Stokes (RANS) models are not usable due to the nature of the flow situation. Another option, namely Large Eddy Simulation (LES), is not feasible as a daily design tool because of its very high computing power requirements, if boundary layers of the surfaces are also to be simulated correctly, which is necessary to predict the deposition of small particles appropriately.

The turbulence modelling procedure used in this study is Detached Eddy Simulations (DES) and shear stress transport (SST), particularly the k-ω SSTDES model (Menter et al., 2003), in which core region of the domain is simulated using LES, while the vicinity of the walls is simulated using traditional RANS model. We do not present the equations of the method in this short paper, see them in the literature. Instead, developed method and simulation procedure is introduced using practical examples.

3 CASE STUDY

In the following examples, droplet size distribution is taken from literature (Alsved et al., 2020; Duguid, 1946) and a flow velocity profile as a function of time is also taken from literature (Gupta et al., 2009). It is assumed that the coughed droplets contain 6% solid material (mass content) at the emitting time the rest being liquid. Large portion of the liquid content of the droplets evaporates fast, time of evaporation and size of remaining particle depending on for example ambient relative humidity and ambient temperature. If the remaining droplets are small enough to remain in the air, they are called aerosol particles. All these physical factors are considered in the examples. Droplets emitted by inhalation are assumed to be completely dry, but the method also allows the use of other assumptions.

3.1 Masks as a source control

In this first example, we present the use of the simulation method to visualize the effect of the mask in normal indoor ventilation conditions (Figure 1).

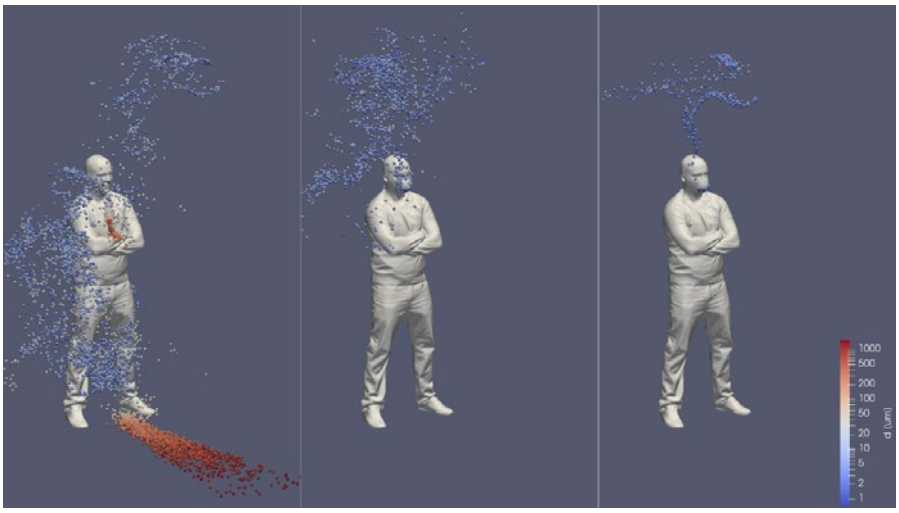

Figure 1. Effect of mask as a source control under realistic ventilation situation. On the left without a mask, in the middle with a mask with typical side leakages and on the right with non-leaking mask. All masks are surgical masks with typical efficiency. Particles coloured by a diameter. The snapshot is taken 10 s after coughing.

The figures show how the largest particles fall in front of the cougher (without a mask) while the smaller ones are left floating in the air. The images also show how the mask significantly reduces the number of emitted particles so that the non-leaking mask is by far the best with the respect of source control. It should be noted that there is always some side leakage in real masks. The images also show the upward flow close to human (plume) caused by human temperature; the smallest particles rise upwards (Sun et al., 2021).

3.2 Effect of ventilation rate and air purifiers

This example shows the use of the developed method for comparing the effectiveness of different ventilation and purifying approaches

(Figure 2). The gentleman on the left is sick and on the right is a healthy susceptible lady. The locations of the different ventilation units are also marked in the figure.

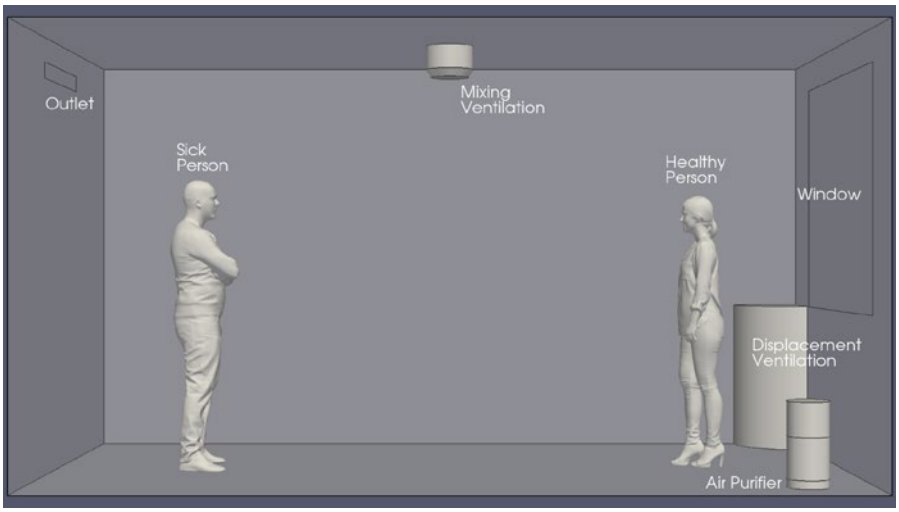

Figure 2. Example case simulated.

Both individuals breathe sinusoidally. Particles inhaled by a susceptible person can be calculated by the simulation method. When information on the number of viruses contained in particles (Johnson et al., 2022) and information on how many viruses are needed to get sick (infectious dose) (Prentiss et al., 2022) is added to a knowledge of a number of inhaled particles, the probability of the susceptible person getting sick and the severity of the disease can be estimated (Basu et al., 2022; To et al., 2020). This information can be used to guide the design process.

Natural convection due to skin temperatures (30°C), underfloor heating (floor temperature is 35°C, other walls and ceiling are well insulated), colder window (17°C), and warmer caught air is considered. Inlet air temperature is set to value 20°C.

As the results show (Figure 3), the rate of the ventilation significantly affects the number of particles in the space. The results also show that the air purifier has a significant impact. In the case of displacement ventilation, in this single simulation, the results are influenced more by the amount of ventilation than by the type of ventilation itself. In general,

larger ventilation rates can be used in displacement ventilation without the risk of draught. In addition, displaced ventilation can be designed in such a way that a clean particle free space is created in the living zone.

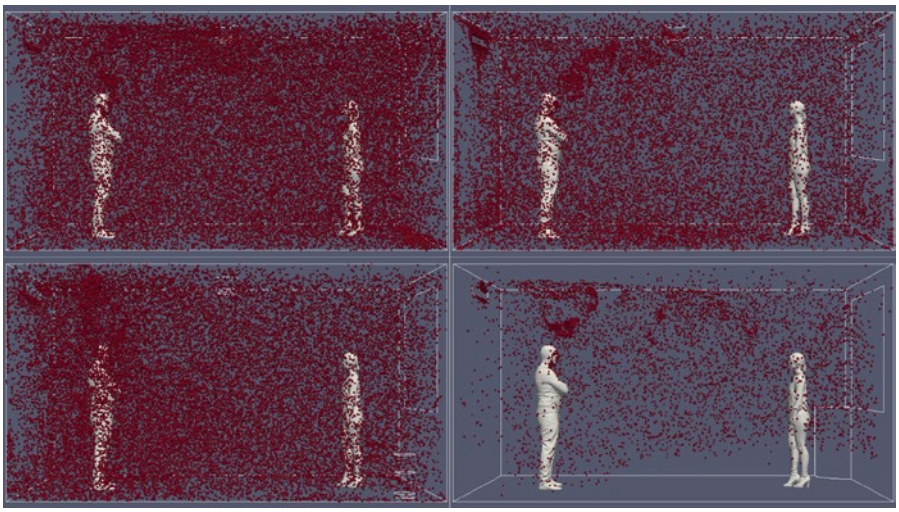

Figure 3. Effect of ventilation rate and air purifiers.
Top row: Mixing ventilation with 0.5 (l/s)/m^2 and mixing ventilation with 10.0 (l/s)/m^2.
Bottom row: Mixing ventilation with 0.5 (l/s)/m^2 with air purifier (330 m^3/h) and displacement ventilation with 40.0 (l/s)/m^2.

3.3 Pandemic safe office

This example compares a traditional office with mixing ventilation with an office where efforts have been made to redesign ventilation on the terms of the pandemic (Figure 4). It should be noted that the number of particles in the redesigned office is significantly lower, although only the first version of the new plan has been presented here. More detailed planning could further significantly improve the situation.

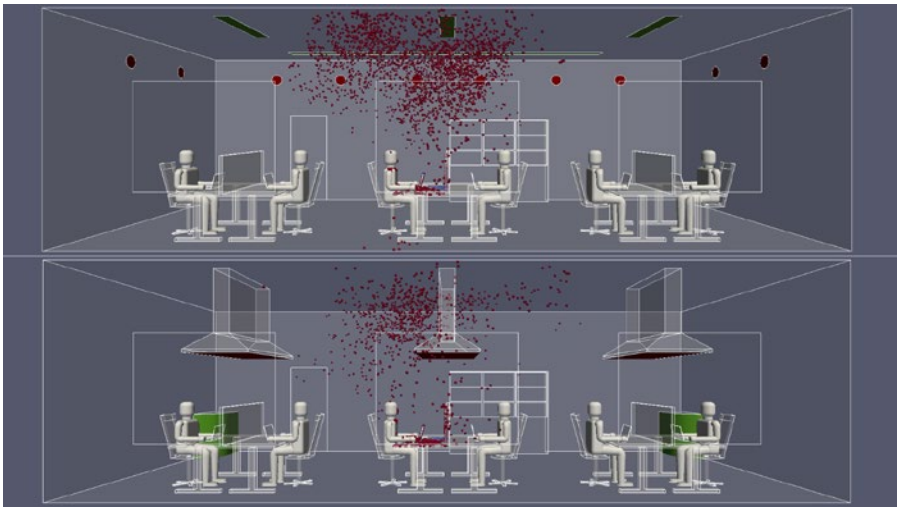

Figure 4. Coughed aerosol particles after 30 s of the cough. In the top image, traditional mixing ventilation and, in the bottom image, displacement ventilation with local discharges. Green means supply air and red means discharge. Red particles are dry and blue ones (mainly on the table) wet. Coughing person in the middle left (the third one from the left).

3.4 Air filter

This last example shows how to include the realistic air filter with measured efficiency curve in the simulation method (Figure 5). This makes it possible to consider various air purifiers and, for example, the realistic filter for recycled air and compare them with each other. Different ideal filters with step functions as efficiency curve have been used in the images shown, but the method allows the use of arbitrary efficiency curve.

4 DISCUSSION

The simulation method presented is useful in designing different pandemic prevention methods and comparing their efficiency. The method makes it possible to assess the risk of infection if sufficient information is available on the disease in question, such as the number of viruses in particles and the number of viruses needed to get sick

(infectious dose). The videos produced by the method facilitate the design of preventing methods and allow the methods to be demonstrated in an easily understandable format.

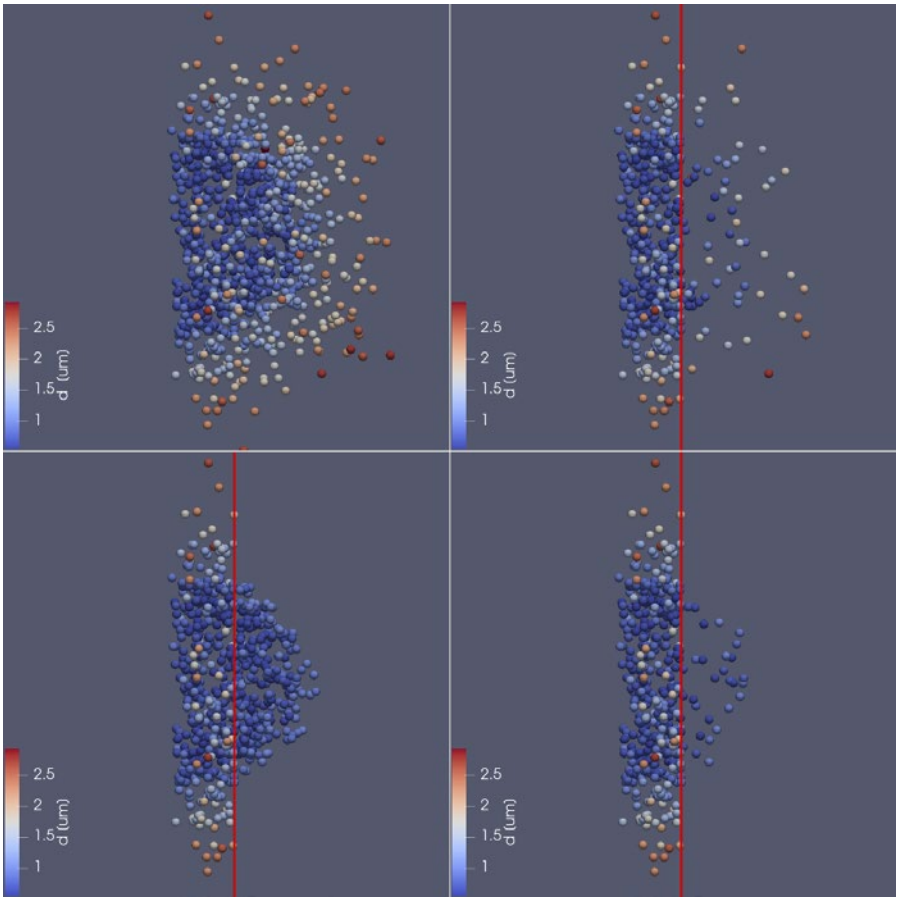

Figure 5. Different kind of filters in action. Flow direction is from left to right. Filter is marked by a red vertical line.
Top left: Without filter. Top right: Filter with 90% efficiency.
Bottom left: Filter with 100% efficiency for ≥ 1 µm particles.
Bottom right: Filter with 100% efficiency for ≥ 1 µm particles and 90% for others.

In the future, the method will be expanded by a method that enables inactivation based on the age of particles to consider natural decay (van Doremalen et al., 2020). In addition, a method for volume-based inactivation, e.g., the effect of Far-UVC, will be developed (Eadie et al., 2022).

5 IN CONCLUSION

This paper describes how computational simulation can be used to study different methods to prevent the aerosol transmission of diseases. The main simulation tool used is CFD, which allows the movement of individual droplets and aerosol particles to be predicted and visualized in different situations, such as in different ventilation strategies. The simulation also enables the assessment of the effectiveness and development of various methods of preventing transport, such as mobile air purifiers and UV (ultraviolet) lights. In addition to simulation of the movement of aerosol particles i.e., an airborne route of the disease, the method also enables the study of transmission via droplets and surfaces (fomites). The method has also been used to illustrate for the community how the virus spreads, facilitating, among other things, daily decision-making on which facilities are safe and when for example the use of a respirator is necessary. In addition to help societies out of the ongoing COVID-19 situation, the methods developed can and will be used to prepare for the next pandemic.

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V

FOOD & BIOTECH

THE HYGIENE FACTOR AS AN IMPROVED DESCRIPTION OF THE HYGIENIC QUALITY OF FOOD CONTACT SURFACES

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1 INTRODUCTION

The surface characteristics of product contact areas impact the cleanability of the materials that are in contact with, foodstuffs and other products. This is evident from published studies. However, a clear correlation between surface topography and cleanability has not yet been established. FORCE Technology is working to achieve this through the development of a hygiene factor. The goal is for the hygiene factor that it can be used on all types of materials and across different surface finished to assess the hygiene quality without carrying out any experimental work.

The statutory requirements specifies that surfaces in contact with products must be smooth and free from cracks and crevices and must not exchange substances with the products. Furthermore, they must be cleanable at a level that ensures that they are clean and free from

substances that may contaminate the products before process plants are commissioned in production. In practice, random sampling is used in production to verify that the product contact areas are clean. It is, of course, a prerequisite that good materials have been chosen with cleanable surfaces in the construction of machines and process lines.

This general goal is, however, of little use for manufacturers of process equipment. They need specific knowledge about material qualities and surface characteristics to be able to make the right choices. The current guidelines and rules of thumb are based on the characterization of surface roughness given by the R_a value. This is a measure of the mean distance between top and bottom over 6 mm on the surface originally according to ISO 4287 (see ISO 21920-2:2021), and it is often measured only in one direction. Traditionally, this measurement takes place with a physical pickup, which is moved across the surface, but laser technologies and 3D microscopy is becoming more used. The characterization of a surface by only one number is a crude simplification, which is quite easy to infer by observing surface topographies for steel surfaces, as seen in Figure 1 where microscopy images of two different hygienic surface qualities are shown.

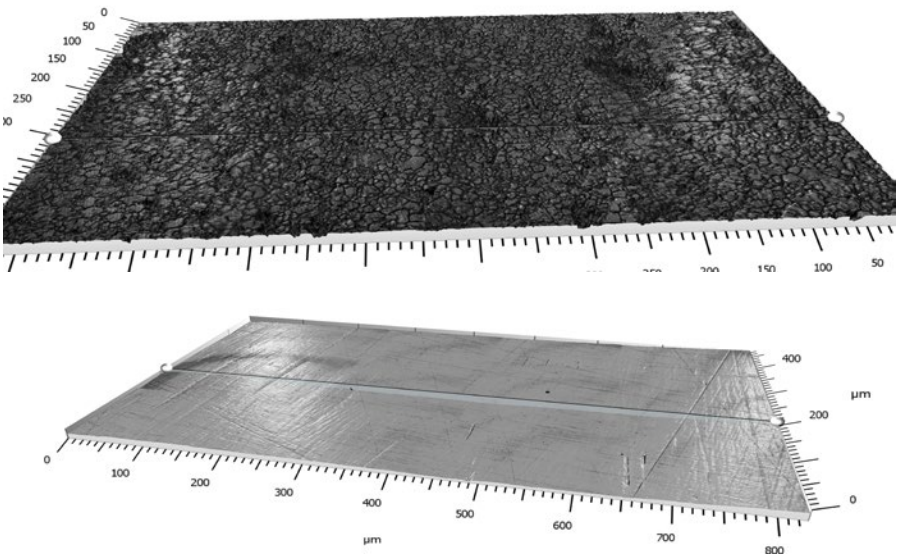

Figure 1. Microscopy image of surfaces on various types of stainless steel – the upper figure shows a 2B surface and the lower figure shows a grounded surface (Ciacotich et al., 2021).

2 HYGIENE FACTOR

To obtain a more adequate description of surfaces, FORCE Technology has been working to develop a hygiene factor (HF), which is a better measure of the hygiene quality of a surface. This measure also includes the number of peaks. The idea behind the hygiene factor is for the entire assessment to be carried out using an optical 3D microscope.

The formula for calculating the hygiene factor is shown above. R_a is the geometric mean distance from the mean line in a roughness profile, and Rpd is Peak Density (number of peaks per cm on the roughness profile). The parameters are defined below in Figure 2.

For the determination of the hygiene factor a modification is applied. The parameters are not measured on a fixed roughness profile, as originally defined in the ISO 4287 standard, which is the raw profile filtered through a high pass and a low pass filter with typical lengths of lc and ls, respectively. Instead of the standard values ls= 2.5 µm and lc= 25 µm are used.

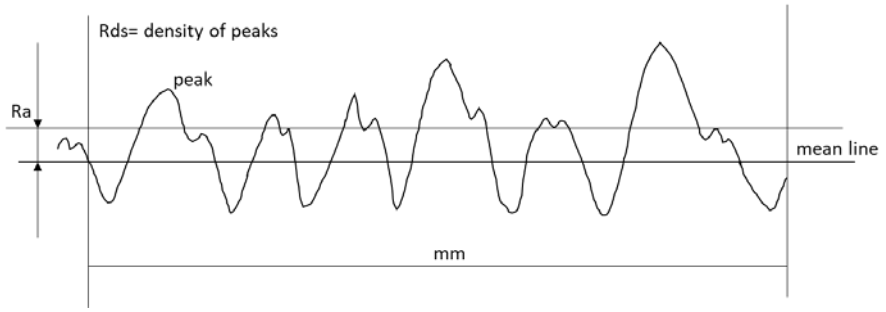

Figure 2. Measures roughness profile with indication of the relevant characteristics R_a and R_{ds} (Ciacotich et al., 2021).

Two roughness profiles with different R_{pd} for the can have the same R_a value if the mean distance between top and bottom in the profiles are the same. It is, however, evident that there a difference in the distance between the peaks greatly influence the topography and thereby likely also the cleanability in practice. This may be exemplified by a surface which has a soft and open shape with relatively few peaks, i.e., an electropolished surface, or one where there is multiple peaks whit a short distance between them, i.e., a grounded surface.

3 REQUIREMENTS FOR HYGIENIC STAINLESS STEEL SURFACES

Historically, a lot of work has been done to investigate the hygiene quality and cleanability of stainless steel, and a dogma has been established that for a hygiene surface the goal is for the R_a value to be below 0.8 µm. This is supported by recognised organisations such as European Hygienic Engineering and Design Group (EHEDG) and 3A Inc in the United States, and it is therefore the standard requirement made for stainless steel for food contact. There are examples of how, for example, the pharmaceutical industry has requirements for surfaces with a lower roughness, for example R_a values below 0.3 µm.

It is, however, important to know how the surface has been produced. As we saw in figure 1 there is a difference between a grounded surface and a 2B surface. Both surfaces are available in a hygienic quality and can easily be delivered with a surface roughness with R_a below 0.8 µm. The 2B surface is the direct product from the steelworks, which is cold-rolled and pickled while the ground surface is processed gradually (by grinding in steps with finer and finer grains) until the desired surface roughness is obtained, the origin for this is a surface that resembles 2B. Research has still not been able to conclude what the most hygienic surface is, but it is expected that it is possible to identify by creating a correlation between the hygiene factor and practical examinations of cleanability of different surfaces.

4 REQUIREMENTS FOR HYGIENIC SURFACES OF PLASTIC AND RUBBER

The same systematism has not been established for plastic and rubber as it has for stainless steel. In practice, a more subjective assessment is made as to whether a surface is smooth enough to be used for food contact. The reasons for this are that several products - such as packing made from rubber - must be more elastic and may therefore be more difficult to measure with the physical surface roughness gauge. The same applies to several plastic materials. Some plastic materials, for

example PEEK, may, however, be so firm that it is possible to measure roughness.

Microscopy is already used to assess whether plastic and rubber surfaces have unevenness and irregularities. It is therefore natural to consider using 3D microscopy to determine the surface roughness, which also provides data for determining the hygiene factor.

The work with characterization of surface roughness and hygiene factors on plastic and rubber surfaces is a new area which has not yet proven its value in relation to selection of material solutions with good hygienic quality.

5 PRELIMINARY RESULTS FOR STAINLESS STEEL

A study has been set up to compare determined hygiene factors to practical cleanability. The method developed by EHEDG is described in their guideline No. 2 was applied with some modifications. The method is designed to compare the cleanability of a test item to that of a straight pipe. Thus, the method is by design qualitative not quantitative as is desired for these evaluations. The method is modified and extended so that the number of remaining spores (the soling subject) can be determined through a two-step evaluation process.

The surfaces are slabs which are soiled and placed in a pipe which is cleaned in a pilot plant CIP setup. It is important to acknowledge that doing microbiological detachment studies in pilot plant scale will be subject to rather large experimental variations.

The validity of the hygiene factor has been evaluated and verified with both stainless steel and plastic plates. The tested stainless-steel surfaces had different finishing (grinding, polishing, bead blasting and ViwaTeq®), and the tested plastic surfaces were obtained by injection moulding using mould with different surface roughness.

The results show not surprisingly that polished surfaces as well as 2B and fine grinded surfaces show the best cleanability and this correlates well to the hygiene factor. The hygiene factor ranks the surfaces according to expectations and put the bead blasted in poor end due to the chaotic nature of the surfaces and large surface area. This is to be expected, however some of the bead blasted surfaces proved to be better cleanable than expected.

The ViwaTeq® which is blasted but in a different way than bead blasting. This surface proves advantageous in powder applications since the surface has features that allow powder to slide off easily. The first results of studies on this surface show that it may have an intermediate hygiene factor, but it is very difficult to clean. The bead blaster and ViwaTeq® will be subjected to further studies.

6 FURTHER DEVELOPMENT OF THE HYGIENE FACTOR

Good preliminary results show that the hygiene factor is directly correlated with cleanability of both stainless steel and selected plastic materials. The preliminary results and the further work with development of the hygiene factor are based on activities in "Competency centre for hygiene, health, and product safety" – a part of the result contract FORCE Technology has with the Danish Authorities.

The goal is to develop a tool which may be used in industry to characterise materials with respect to their hygienic quality solely applying the hygiene factor determined by 3D microscopy. In this way, the hygiene factor may be of practical relevance for industry in that it may be used for example for comparison between new surfaces and surfaces in use.

The current work will therefore include correlation of the hygiene factor with cleaning time and testing of residual microbiological material on surfaces. This will take place partly in pilot plants and partly through field trials on components in industrial plants. FORCE Technology would like to hear from companies interested in participating in case studies and practical testing.

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HOW DO YOU PREPARE FOR FUTURE SUSTAINABILITY CHALLENGES IN FOOD UNIT INVESTMENT PLANNING AND TECHNOLOGY CHOICES?

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1 INTRODUCTION

Food manufacturing is Europe's largest industry and under unprecedented pressure for change. In the climate change, consumption, population growth and sustainable food production are the biggest of our longer-term challenges. In addition, during the pandemic and geopolitical crisis, it has become clear how important the food industry is in maintaining a stable and functioning society and ensuring security of food supply both in Finland and globally. In response to climate change, we must quickly decrease the amounts of fossil fuel and food production greenhouse emissions, while simultaneously promoting the sequestration of carbon dioxide in ecosystems.

Globally, the greenhouse gas emissions of the food production systems of agriculture have increased by about a third over the last 20 years (SYKE, 2020). Emissions are primarily a result of plant and animal production increase, which in turn increases the use of fuels and fertilizers (nitrogen), the amounts of manure and pastures, and the production of gases from the digestive processes of ruminants (Wang et al., 2021).

Finland's greenhouse gas emissions have started to decrease in accordance with targets, although they vary a little from year to year. The food industry in Finland causes relatively few direct emissions, as

the biggest sources of emissions are made up of indirect sources – from primary production and energy production (Elintarviketeollisuusliitto, 2020). Thus, investments in renewable energy – solar, wind, biomass, and hydropower - play a key role in climate change primary prevention. Other new innovative technologies towards carbon-neutrality include e.g. development of more sustainable production of fertilizers, solutions for precision agriculture and improved feeding (Wang et al., 2021). Also, the development of biotechnology and bioengineering accelerate the transition to more sustainable food production (Timonen et al., 2020). When fields and livestock can be replaced with, for example, microbes and bioreactors where useful cultured and metabolic products are produced in aseptic or even sterile conditions.

2 REDUCING HARM FROM FARMING WITH NEW TECHNOLOGIES

Optimizing the use of fertilizers and water on arable land can significantly reduce the greenhouse gas emissions in crop farming systems with the help of digital, drone, and sensor technologies. In addition, new synthetic nitrogen fertilizers which release nutrients in a slow and controlled manner are being developed, as are new varieties which use nitrogen more effectively and have characteristics which inhibit emissions (Wang et al., 2021).

As one noteworthy solution, the disruptive food production technologies i.e., "food without fields" solutions can significantly contribute to achieving carbon neutrality goals while simultaneously promote biodiversity and carbon sequestration (Bioenergia, 2021). The disruptive food production solutions that are not dependent on agricultural land include 1) cellular agriculture, i.e., the utilization of microbes and plant cells to produce feed and food, 2) new vertical technologies for growing vegetables and proteins.

As an example, the vertical indoor cultivation systems can help to achieve very high productivity and low greenhouse gas emissions with small changes in land use when compared to traditional production

systems. Also, environmental impacts of operations can be minimized by using renewable energy to run the factory. The vertical plant factory enables continuous food production throughout the year regardless of the season or weather. All environmental parameters, such as lighting level, temperature, humidity, and air composition, are controlled in a smart, closed system. New testing facilities verify the viability of mass production, and full-scale factories have been built for the commercial production of fruits, vegetables, and medicinal plants. (Wang et al., 2021.)

3 WRITING INSTRUCTIONS

There is demand for feeding a growing population with the help of innovative and low-emission technologies. The development of biotechnology enables a novel food production that utilizes tissue engineering techniques to culture plant and muscle cells to make cultured meat, or microbes and fermenting to create proteins which can be processed to products similar to milk and egg white for example in a factory environment. This is cellular agriculture, where microbes and bioreactors replace fields and livestock. (Granath, 2021.)

Tempeh and tofu are traditional plant-based, meat-like proteins, which are made from soy, peas, and beans. During production, proteins are extracted and separated from the plants or fungus, which are then formulated and processed. The taste and structure of plant-based meat is improved through food additives and extrusion, as well as innovative technologies such as high-temperature shear cell technology and 3D printing. Another alternative source of protein is animal and crustacean cell-based protein products, which are produced by directly growing animal cells in a nutrient-rich solution in tanks- a technology most difficult to scale up.

According to the surveys of Boston Consulting Group (Witte et al., 2021), the transition to edible plant, microbe, and animal cell-based alternative protein products instead of traditional beef, pork, chicken, and egg alternatives will save more than one gigaton of CO_2 equivalent by 2035, which is roughly equal to the annual emissions of Japan.

In addition, there are potential savings in land use and water consumption: it is estimated that by 2035, they will equal the water consumption of London over a period of 40 years! This assumes that alternative proteins will represent an 11–22% share of the protein market in 2035, depending on the scenario.

4 PIONEERS: NUTRIENT PROTEIN CAN BE PRODUCED FROM AIR

Bacteria, yeasts, molds, and single-celled algae also produce edible microbe-based proteins, when proteins are fermented with cellular agriculture technology in a carbohydrate-rich solution. Depending on the method, the result is either a meat substitute – protein and biomass – or pure single-cell protein.

Quorn is one such microbe-based protein product, which was developed in England and has been commercially available since 1993. All in all, there is still plenty of development to be done with regards to these products. Their costs are three times that of traditional protein, particularly when it comes to the production of single-cell protein. Finding more cost-effective growth solutions and the development of separation technology are also highlighted in the further development of these protein products (Witte et al., 2021).

Despite the challenges, biotechnological pilot and demo facilities are already being built, where nutrient protein will be produced with the help of microbes and even the direct capture of carbon dioxide from the air. One of the most famous projects is SolarFoods' "Food without fields and food from thin air" project, which uses carbon dioxide as a raw material. The microbe is isolated from the sediment of Western Finland's seashore, which produces a soy protein-like powder for food products and nutrient supplements. All that is needed is electricity, carbon dioxide, and a source of nitrogen. According to the company, the pilot phase has shown that environmental impacts remain well under 10 per cent of that of traditionally produced plant or animal protein. (Granath, 2021.)

5 INVESTING IN ALTERNATIVE PROTEINS

Overall, alternative protein market has a huge potential – they are likely to account for 11% of the global protein market in 2035. Besides of regulative challenges related to EU Novel Food requirements and technological issues (e.g., scale up of capital-intensive technologies), cellular products might still have to overcome some additional challenges from markets, consumers and competing with conventionally produced food. However, it is estimated that nine out of ten of the world´s favorite dishes will have a realistic alternative by 2035. This means almost 30 million tons of bioreactor capacity, which in turn requires up to $30 billion in investment capital for building all these bioreactors plus necessary R&D spending or materials and operating costs of all these bioreactors and extruders. (Witte et al., 2021.)

Noteworthy is that the technology for growing cells in culture is not new – the pharmaceutical industry has been employing it for years. To reduce the cost of the growth process, however, the industry must shift from expensive, ultrapure pharmaceutical-grade ingredients and equipment to food-grade versions to produce large volumes of alternative products – quantities not previously seen.

6 CHALLENGES OF SCALING

Dealing with labile biological materials is challenging. Even more challenging is scaling them to industrial-scale production The labile biological materials make the fermentation and recovery processes a harder challenge than with chemical recovery. In these cases, the engineering is only an aid in regulating the biological processes and the micro-organisms command the centre of attention.

The target is maximal yield and homogenous quality for minimal costs and time – which is not an easy target. The secret of success in scale-up is stepwise development and testing of the processing concept in cooperation with technology providers and plant 3D-integrators. To properly manage a large-scale process, engineers must have experience of multiple materials, dimensioning of equipment and

utilities in addition to overall aseptic requirements in processing supported by a clear understanding of microbial growth kinetics.

Also, suitable scaled technological solutions to produce homogenous and uniform products must be found or taylor-made. Several trials are required in laboratory scale and then in the pilot scale before the industrial-level process and technology alternative is feasible and justified. Although several fermentations for metabolite production work well as processes at a laboratory scale, only a few processes have proved useful for practical application due to clearly fewer operational hours to be stable in a laboratory than in an industrial set up. Also, attention should be paid to maintaining hygienic conditions on an industrial scale over a long period of time. Variation of industrial composition of substrates must be anticipated as well.

7 HOW CAN ONE BE PREPARED?

Food companies now need crisis resilience and innovation both in terms of security of food supply and energy. Due to geopolitical situation, we face energy crisis which require new flexible energy supply solutions. E.g., most of domestic bakeries utilize natural gas ovens, which heating systems now need to be modified to liquefied petroleum gas (LPG), light fuel oil or even turned to electrical ovens. Greener transition further away from fossil fuel supplies should at the same time be investigated, however, as an investment, will require more planning, time, and money.

The investment planning, whether energy or process engineering related, should emphasize adequate techno-economic studies in the initial pre -engineering stages. Understanding fundamentals behind the desired process is a key factor to successful scale-up supported by project´s wider profitability and sustainability reviews. Experts and consultants should be competent in feasibility studies, capacity calculations and dimensioning of equipment as well as risk evaluations. Good relationship with several technology providers is also an asset. Clean room air condition and ventilation, clean utilities and instrumentation would also be great additions to this competence toolkit.

As a recommendation, during different designing phases, agile plant design and simulation tools should be used. With 3D software´s visual modelling and process simulation, the desired change or expansion can be tested cost-efficiently and proactively. The virtual 3D model and process simulation also allows you to test the functionality and usability of your new equipment and identify bottlenecks in the production setup on a real scale without expensive trials. Finally, proper data acquisition and analysis are essential for calculating the effects of process variables on the outcome in every development step. Those who take advantage of new innovations originated from the food value chain with sustainability aspects and the opportunities brought by the digitalization platforms and more carbon-neutral energy solutions will continue to thrive.

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CORRECT STRUCTURES IN HYGIENIC FOOD FACILITIES ARE IMPORTANT

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1 INTRODUCTION

It is important that the production facilities and equipment are suitable for the process, i.e., that they are designed, manufactured, built, and installed in accordance with hygienic design principles (EHEDG, 2014). In the planning principles consider both external and internal risks should be considered (EC Regulation no. 852/2004). In 2021, the EU Regulation no. 2021/382 was launched on 3 March 2021. It amends the Annexes in 852/2004 on foodstuff hygiene regarding the food allergen management, the redistribution of food and the food safety culture. The hygiene principles exist to meet the requirements set by the law and the customer (EC Regulation no. 852/2004; EHEDG, 2014; EU Regulation no. 2021/382). These instructions should be applied, when building completely new food plants as well as in renovation of already existing facility. This applies also when existing facilities are converted into production facility for food production.

There are many different surfaces and structures in the food production facility, which must be hygienically designed to prevent both microbial growth and presence of allergen residues. The renovated food facility Frami Food Lab at Seinäjoki University of Applied Sciences (SeAMK) served as a case in the final thesis of Jenni Peltomaa. More information is available in her thesis (Peltomaa, 2022). Solutions for production facilities will be discussed in more detail in the presentation.

2 IMPORTANT POINTS IN PLANNING FOOD FACILITIES

Horizontal surfaces that collect dirt and dust should be avoided. All corners must be rounded to enable easy cleaning. The materials used in food facilities must also be non-toxic, free of odours and compounds affecting the taste. The materials must also withstand prevailing production conditions e.g., both low or high temperatures, cleaning chemicals e.g., acids, alkalis, and disinfectants, process liquids e.g., oils, fats and other process raw materials, humid conditions as well as mechanical and chemical stress. Foreign objects must not be transferred from the process equipment to the product. Lamps must be splinter proof.

Paintings and coatings must not flake, because flaking will enable space for the microbes to multiply. The spoilage and/or pathogenic microbes can hide from both mechanical cleaning and disinfection in porous material e.g., concrete. Furthermore, there must be no holes in the flooring or wall surfaces because dirt will accumulate in these mini pits. The seams must be tight, not allowing liquids to penetrate the upper floor and wall surfaces (Wirtanen, 2002; Korkeala, 2007; EHEDG, 2014).

2.1 Floors

The floors in the food production facilities form the basis for safe and hygienic food production. The food and beverage industry has many different production environments that can be very challenging for floors. The floor design and installations on them are important in maintaining a required hygiene level in the food production. Poor floor hygiene can be caused by failure of floor installation, defective floor interface and material. If the floor cannot withstand the operating conditions, it will be damaged, weakened or broken. A good floor structure and material choices are functional and durable. It must be remembered that repairing a failed flooring often results in high costs and therefore a proper designing phase should be carried out (EHEDG, 2014).

On floors with cracks pathogenic microbes e.g., *Listeria monocytogenes* is likely to persist despite rigid cleaning and disinfection procedures. The occupational safety must also be considered so that the floors are not slippery. The flooring must withstand wear and tear. In the food industry many where small hard wheels are common. All joints between e.g., floor and wall and edges or equipment and fasteners connected to the floor must be sealed. The floors must also stand internal traffic with forklifts etc. The flooring must be smooth and easy to clean with an inclination of the floors supporting the drainability. The rinsing and cleaning liquids should flow towards the drains. Standing water on the floor must be avoided, because the floors become unhygienic and possibly also slippery (Wirtanen, 2002; EHEDG, 2014).

According to the EC regulation 852/2004 the floor surfaces "are to be maintained in a sound condition and be easy to clean and, where necessary, to disinfect. This will require the use of impervious, non-absorbent, washable and non-toxic materials unless food business operators can satisfy the competent authority that other materials used are appropriate. Where appropriate, floors are to allow adequate surface drainage".

2.1.1 Inclinations

The required inclination depends on the food processing activities in the room i.e., whether the floor is permanently wet or dry, the frequency and nature of leaks, the frequency and methods of cleaning. Floors in dry production areas should generally be level, and in wet areas there should be no more than a 2% (<20 mm/m) inclination. Generally, a slope of 1.5% (15 mm/m) towards the drain is sufficient to dry the floor.

Extreme inclination should be avoided. In general, more textured floors require steeper slopes to drain freely. No accumulation of water should remain on the floor and the area should be completely free of water in an hour after the cleaning has been carried out (EHEDG, 2014).

2.1.2 Seams and joints

Flooring seams can often cause maintenance procedures, the seams are normally one of the weakest points. The width and depth of the joint depends on the expected movement and the flexibility of the joint seal. Seams must be designed in such a way that they respond to movements in the floor. Some flooring materials require joints at certain intervals, while some materials do not require joints e.g., seamless concrete. All joints should be inspected regularly. If the joint sealant cracks, the sealant should be removed and the joint refilled with fresh sealant. When choosing the flooring material, reactions caused by chemical spillage of e.g., lubricants and cleaning chemicals, must be known. The concentration and temperature of spillage help to determine the suitability of the flooring (EHEDG, 2014).

2.1.3 Connecting points, curbs, and protection posts

Connection points, curbs protection posts, etc. are used to keep the walls and doors, which must be protected from collisions caused by pump carts, forklifts, and transported containers, in hygienic condition. The volume of the internal traffic must be analyzed to determine the right protection level of the hygiene in the food facility. Furthermore, the connection points of the walls and the floor, i.e., the corners, must be rounded to enable easy cleaning. If the floor or wall surfaces are damaged, liquids can penetrate. This enables giving microbial growth in the structures.

The purpose of curb coating is to improve cleanability and hygiene and to prevent liquid penetration into the structures. The curb surfaces must be easy to clean. The material should thus not be porous. The curb stone, where it connects the wall and the floor, is a critical zone in hygiene. They must fulfill several tasks i.e., prevent the accumulation of dirt, promote easy cleaning, prevent water from penetrating the building structures, protect the walls from damage and separate the treatment areas at floor level (EHEDG, 2014).

Posts of stainless steel must be tightly fixed into the floor structure. The connection of the crash bars in the floor must be sealed (and rounded)

with a food-safe sealant. Note that galvanized steel bars with or without coating should not be used in food preparation areas, because this material corrodes very quickly (EHEDG, 2014).

2.1.4 Drains

Drainage of the wastewater generated in the food production area is important. Drying must be holistic to maintain hygienic conditions. To enable easy cleaning and inspection of drains, they should not be placed under the process equipment. The type of drainage (gully or canal) depends on the requirements of the operation. Channels are easier to use for sloped floors. Water splashing from the equipment can be minimized by using pipes in/above the drains when there is an air gap, which is twice the pipe's diameter, between the drain and the water outlet pipe of the equipment. The air gap is essential for two reasons i.e., to avoid: backflow and cross-contamination. Contaminated water should preferably be transported in a closed pipe system. In the CIP system, the water should be directed to the sewer with a pipe; here air gaps are also needed both to avoid backflow of the wastewater and to protect the hygiene of the line. In dry production facilities with wet cleaning, ducts and wells should have grids of a high level of hygiene (EHEDG, 2014).

The direction of the sewage flow should be from the higher hygiene area towards lower hygiene areas. If possible, the drain of the high hygiene area should run in a separate system up to the external drain connection. An ideal system enables cleaning from a point outside the high hygiene area. Furthermore, the sewer pipes must be designed so that they can be cleaned through the entire drainage system. Clogged pipes pose a hygiene risk, because contaminated water can flood onto the floor (EHEDG, 2014).

Mounting of the drain in the floor is important, as leaks between the floor and the drain element are common causing moisture problem around the drain. The drain frame must be mounted under the upper floor layer. Proper sealing is important, this enables the floor surface to be separated from the substructure. The gullies should have a round body with slopes towards the water lock. It must be possible to empty

it completely. The floor drain must have a removable sediment basked. The water locks should be easy to access for cleaning purposes. The water level of the water locks must be maintained to prevent odors entry of pests. (EHEDG, 2014)

2.2 Ceiling

All process areas must be covered with a roof. In the EC Regulation 852/2004 it is stated " ceilings (or, where there are no ceilings, the interior surface of the roof) and overhead fixtures are to be constructed and finished to prevent the accumulation of dirt and to reduce condensation, the growth of undesirable mould and the shedding of particles;". The ceiling should be at a height of at least 3 m to prevent condensation. According to EHEDG guideline No. 44 (2014), ceilings must be: light-colored with desirable light-reflecting properties. They must be cleanable, dense, hard, resistant to impact, durable, rust- and dust-proof. Furthermore, properties e.g., impermeable, washable, water-repellent, and non-toxic are desirable properties. The surfaces must be smooth and crack-free, and all joints sealed with impermeable sealant. The materials must be repellent to grease or food particles as well as pests and insects. They should also be resistant to microbial growth and stand cleaning chemicals and methods.

The ceiling is usually made of sandwich panels with smooth, impermeable, and easy-to-clean surfaces. It must isolate all structural elements from the production area; all utilities should run inside the roof structure to avoid horizontal piping in the production area. The joints between the wall and the ceiling should be rounded, sealed and easy to clean. Double roof structures should not be used because they collect dust and create hollow spaces. Lowered ceilings must be sufficiently supported, and the seams must be sealed. Adequate access to the empty space, which should be outside the production area, must be ensured. Roofs should be built enabling maintenance and inspection. Perforated or porous materials should not be used in noise reduction, as these materials collect dust. All penetrations in the ceilings, including pipes, must be well sealed with a gasket or collar and they should be vertical. A ceiling consisting of small panels should not be used in production areas, as they are difficult to seal and clean

effectively. Ceilings of gypsum should not be used in wet environments due to their porosity. And corrugated metal should not be used as they because they can cause condensation problems (EHEDG, 2014).

2.3 Walls, doors, and windows

In the EC regulation 852/2004 it is stated that "wall surfaces are to be maintained in a sound condition and be easy to clean and, where necessary, to disinfect. This will require the use of impervious, non-absorbent, washable and non-toxic materials and require a smooth surface up to a height appropriate for the operations unless food business operators can satisfy the competent authority that other materials used are appropriate."

2.3.1 Exterior walls

The exterior walls should also be well insulated. They must protect from weather, water, insects, and rodents. Rats can get through a hole as small as 12.7 mm in diameter. Correspondingly mice through a hole with the diameter of 6.4 mm. The walls' exterior surfaces should not have horizontal parts. The surfaces must be smooth. These walls are usually built of concrete, brick, steel coatings or sandwich panels (EHEDG, 2014).

Ready-made wall elements are large structural parts that are manufactured in factories or workshops. These wall elements are designed to be used either outdoors or indoors, the quality is specified in the order. The double walls are prefabricated elements consisting of two thin concrete slabs, which have been connected to each other by pouring infill e.g., concrete after installation (EHEDG, 2014).

2.3.2 Interior walls

Brickwork, concrete, sandwich panels, metal sheets etc. can be used in interior walls. All interior walls separating hygiene zones must be installed up to ceiling height to prevent cross-contamination. The wall surfaces must be easy to clean up to a height of three meters.

They must be: light, dense, impact resistant, rust- and dustproof, and resistant to cleaning chemicals, cleanable, waterproof and made of non-toxic materials. The surfaces must also be smooth and free of cracks. The joints must be sealed with impermeable sealant, which is not absorbing grease or food particles, and which prevents the entry of microbes, insects, and vermin into the room. The joints or "corners" between the wall and floor / ceiling / a second wall must be rounded and the edges must be sealed, waterproof and without cracks. It must be possible to close the gaps/openings in high hygiene zones and the insulation must be mounted on the lower hygiene wall. Furthermore, horizontal wall projections and thresholds must be avoided.

2.3.3 Doors

Doors are important in the design of buildings, they separate production areas from each other and prevent the spread of contaminants e.g., dirt particles, microbes, insects, and other pests. However, the food products can get contaminated with dirt on the door surfaces when they pass through the doors. For this reason, the doors must be designed hygienically. The surface material used should be light, non-toxic, impermeable as well as rust- and dustproof. They should not absorb oils and grease as well as be resistant to both mechanical and thermal impact. They should be resistant to cleaning chemicals and disinfectants. The door structure must be open or easily to open because all surfaces must be easy to clean and, if necessary, disinfect. All surfaces must be totally dry after the cleaning. All horizontal surfaces must be sloped at least 3 degrees (EHEDG, 2014).

All doors in hygienic zones must be made of metal, stainless steel, or aluminum. The doors must be self-closing and equipped with kick and push plates. There should be no hollow spaces in the doors. Doors must be high and wide enough to allow vehicles with raw material or products to move without touching the door. Vertically opening roller shutter doors are not acceptable from a hygienic point of view. Correct seals must be used in sliding doors. The door structure should not include a thermal bridge, because we should be able to prevent "warm side" condensation on screws, door locks and hinges (EHEDG, 2014).

2.3.4 Windows

Windows, which can be opened, should be avoided in food facilities, because these windows can contaminate the area. If the windows can be opened, they should open outwards to enable easy cleaning from the outside. The windows must remain closed both before and during production. Windows that can be opened to the outside must be equipped with easy-to-clean insect screens. Double-glazed windows prevent condensation. Windows in both exterior and interior walls, in doors etc., must be designed and constructed to prevent dirt accumulation. The window frames should be light and the windows easy to clean. The windows must be made of toughened glass or unbreakable plastic with e.g., a protective film. Window frames must not be made of wood. Windows must be mounted at least 1.2 m above floor level and equipped with frames that are dense, smooth, durable, non-toxic, dust- and rustproof, impermeable, non-absorbent, cleanable, waterproof, free of cracks, and resistant to cleaning and disinfection chemicals. Windowsills or horizontal edges should be avoided. The slope of the edges of the exterior windows must prevent birds from nesting. The windows must be installed tightly and flat with the walls. Skylights must be non-opening as well as cleanable and non-condensing (EHEDG, 2014).

2.4 Stairways, elevators, walkways, and platforms

Stairs, walkways, and platforms are built from steel. Gaps, protrusions, and cavities, where product residues, dirt and insects can accumulate, must be avoided. In designing support and frame structures as many projections as possible must be removed to minimize dirt and dust accumulations. This is best achieved by choosing square, rectangular, or circular tube shapes whenever this is practical. The orientation must be considered when other structural forms are used. Open profiles should be used in the frame for the vertical parts. All hollow structures should be avoided. If closed profiles are used, they should frequently be inspected for cracks to prevent contamination risks. If the railings are made of round pipes, they should be welded and all pipe joints should be smoothed after the welding. All open ends of the pipes must be closed with a plate through welding (EHEDG, 2014).

2.4.1 Stairway

In high hygiene zones, a gridded metal plate should be used in the stairway. The stairs must be self-drying after cleaning. Stairs with a single support pillar attached to a base plate or preferably embedded in concrete are acceptable in production areas. There is no need to coat the stairs or install a solid handrail if the stairs of concrete are not in a high hygiene zone. Uniform stairways limit the dripping of rubbish. Stairways above a process line should have pick plates to protect dripping of dirt and trash into the product processed. (EHEDG 2014).

2.4.2 Elevators

An elevator is a convenient way to move both materials and people from one level in a building to another. Separate elevators must be used for incoming and outgoing raw materials as well as intermediate and finished products to avoid cross-contamination. The elevator floor should not be double-layered, because it prevents effective cleaning. Process residues and garbage must be transported in different elevators except when the transport is in the same hygiene zone and the materials are tightly packed i.e., both dry raw materials and finished products. Elevators must not be placed in a high hygiene zone, because there are areas above and below the elevator that cannot be accessed and thus not cleaned frequently. The area below the lift should be regularly inspected and kept clean of debris. In the design the drainage and ventilation of the elevator shaft must be considered to affect the hygiene. The elevator is not sealed, which means that dust, insects, and vermin can enter it. In addition, the air draft creates movements of dust in the air, which is a pollution source. The regular inspection points should be easily accessible. Elevators should never be used to connect different hygiene zones.

2.4.3 Walkways and working platforms

Walkways and platforms should be easily accessible for inspections, maintenance, and cleaning. Horizontal surfaces and protrusions must be avoided, as dust can accumulate on them. There must be a rubber seal between the floor and the frame to ensure a tight fit that minimizes

microbial growth. The body of the walkway should be built from an open profile, but all hollow structures, should be avoided.

Above the production lines, intermediate platforms, stairs, walkways, etc. must have plates, which are at least 15 mm high, to prevent contamination of the area below. Kick plates and steps in the stairs must be designed as one part. Metal mesh should be avoided as dirt drips through the holes. Stair steps must be closed. Elevated walkways and platforms over open processes expose the product to the environment should be avoided to limit the cross-contamination.

2.4.4 Transportation and personnel airlocks

Transportation locks are used to move material and tools between the different hygiene zones to minimize the contamination. The number of transportation locks depends of the activity. They consists of two doors, one toward the lower hygiene zone and the other in the higher hygiene zone. These doors cannot be opened at the same time. These transport locks are hygienic compromises especially if the air in the area between the doors is not exchanged during the time the doors are locked. These transport airlocks are used to bring in e.g., packaging material and cleaned tools to the high hygiene zone and take out used tools and process material residues. Similar structures but more spacious airlocks are used for personnel when they move between the hygiene zones. In these airlocks the personnel are changing protective clothes according to what is used in the different hygiene zones. The personnel is also washing as well as disinfecting their hands in this area and possibly also putting on gloves and other protection needed e.g. correct caps. Note that there should be enough space for the personnel to change shoes or put on shoe covers in the airlock for personnel (EHEDG, 2014).

3 CASE FRAMI FOOD LAB

The case-object was the Frami Food Lab at the Seinäjoki University of Applied Sciences. The Frami Food Lab was completed in 2019 and it serves as a teaching area for students studying food technology. The food facilities were placed in an already built area, which was not

originally planned for food processing. This is challenging especially in plumbing and for electrical work, as there will be surface installation. There are some hygienic shortcomings:

- The space between the wall and the devices next to the wall is very narrow. Dust and dirt get into the narrow gap, and it is difficult to clean.
- There are devices too close to the wall. They should be moved further away from the wall to make it easy to clean the space between the wall and the device. Alternatively, the device should be tightly fixed to the wall and the seams tightly sealed.
- In the flooring there were crystals formed, these crystals have broken the flooring creating cavities, which provide good growth conditions for microbes.
- Gas bubbles were created when the floor was moulded. The bubbles in the flooring are harmful to the food hygiene. They create favorable growth grounds for biofilms. When the coating breaks, the flooring is impossible to clean. The floor should be resurfaced to achieve good hygienic conditions.
- The silicone seam between the wall and the floor has been painted. The paint is not suitable on the silicone seam. The paint has started to crack. Cracked paint flakes off easily and poses a hygiene risk. The seams should be renewed.
- The floor drains should be merged evenly with the flooring, so that the liquid gets into the drain easily.
- The flooring around the gully is not evenly laid. The flooring rises in the immediate vicinity of the gully making it difficult for the water to drain freely into the gully. The flooring is uneven around the gully. The joint between the flooring and the gully should be smooth.
- The top surface of the electrical casing collects dust and dirt. The top surface should be inclined to prevent dust to be collected on it. Horizontal surfaces should be avoided in production areas. Dirt and dust do not accumulate as much on the beveled surface.
- Horizontal pipeline installations should also be avoided because they collect dust and dirt. The pipe installations could be done with an inclination. Another possibility would be that the pipes were inside the wall. In the FFL-case this is not possible because the food facility was designed in an existing area made for another purpose.

4 IN CONCLUSION

The food safety requirements continuously growing, which lead to new design and renovation requirements. The factory construction work has often exact budgets and schedules, but hygiene requirements should still not be neglected, because the construction must not cause chemical, physical, and microbial hazards to the foodstuffs. Horizontal and multidimensional surfaces that collect dust and dirt should not be placed in the food production area. Maintaining good hygiene is an important part in the food production. A well-planned production area helps to ensure high hygiene level in the production and to create a proper basis for hygienic working circumstances. The food factories must minimize pests, insects, microbes, and physical particles in production. Inclination of surfaces must be considered during the construction phase.

There should be separate storage rooms for dry, chilled, and frozen products. Ingredients of animals, e.g., meat and milk, must be stored separately from each other. Vegetables should also be stored separately. Allergens, genetically modified and other organic ingredients such as raw material containing gluten as well as religious ingredients must also be kept separate from each other. In addition, various contaminants must be monitored, so that agents being dangerous do not transfer from one hygiene area to another.

This requires effective planning for packaging material, raw material, product, people, waste, and air flows. The above can lead to various foods being processed in different buildings or at least in different rooms to enable the control of contaminants. The hygienic factory design thus promotes production of safe and healthy food. It also helps to ensure that product labelling claims are supported.

No production space is the same, and the facilities are designed according to the production conditions. Basic hygiene requirements apply to all types of facilities. In this case, all the hygiene requirements of the food production facility were not considered. In food safety, it is important that the construction instructions are available in the national language.

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OWN-CHECKING GUIDELINES FOR SURFACE SAMPLING IN RESTAURANTS INCLUDING SOME TEST RESULTS

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1 INTRODUCTION

The aims of the thesis were: 1) to update the own-checking guidelines for registered food operators based on the amendments in the Food Act (297/2021) and the Food Hygiene Decree (318/2021), 2) to guide the food operators in surface cleanliness sampling (in accordance with the new recommendations) and 3) to harmonize the control of the surface cleanliness. In the thesis, the restaurants' hygiene measures were investigated based on a survey and the cleanliness level based on surface sampling.

The background for the work was similar requirements for operators and harmonization of guidelines and supervision. In the summer 2021, the health inspector surveyed 32 restaurants in Ilmajoki and Kurikka regarding self-monitoring, surface cleanliness and hygiene practices. In the fall 2021, surface in 30 restaurants were sampled for cleanliness. At the same time, operators were instructed about requirements in self-monitoring. A total of 268 food contact surfaces - both direct and indirect - were sampled. (Tietäväinen, 2022).

2 FOOD CONTROL OF RESTAURANTS IN FINLAND

There are a total of 16,500 registered grills, cafés, and restaurants in Finland. Food service places are inspected twice a year at most and at least every three years. Food control is carried out according to the Oiva system, which also provides consumers with information on the results of the food control in form of an Oiva report, which must be visible both in the restaurant and on the restaurant's homepage (Finnish Food Authority, 2021).

3 GUIDELINES FOR SURFACE HYGIENE SAMPLING

Premises and operations must meet the requirements set in food legislation (European Union, 2005; Food Act, 2021; Food Hygiene Decree, 2021; European Hygienic Engineering and Design Group, 2014; Finnish Food Authority, 2022).

In the restaurant, the microbiological compliance of food is ensured by taking care of sales and serving times and storage conditions as well as temperatures (Koskinen et al., 2021; Lundén, 2007ab; Välikylä, 2021). When the restaurant's activities involve the handling and cooking of raw food of animal origin, surface cleanliness samples should be examined.

Finnish Food Authority recommended sampling frequencies are 4-12 times a year. In the food control units of Southern Ostrobothnia, the recommended sampling frequencies are 2-6 times a year since the supervisors know the restaurants and the scale of the activity. Sampling frequency is affected by the daily dose.

The operator is responsible for taking self-monitoring samples. Samples are taken from surfaces in direct contact with foodstuffs: equipment, worktops, cutting boards, knives, storage and serving utensils (Rahkio et al., 2013).

4 WHAT INFORMATION DID THE SURVEY PROVIDE

According to the survey, just over half of restaurants have previously taken surface cleanliness samples. During the project, information was provided on surface cleanliness sample requirements for restaurants. Based on the responses, restaurant operators attach great importance to sanitation. In restaurants, food contact surfaces are cleaned several times a day after use. Due to the coronavirus situation, all restaurants have increased sanitation, the use of disinfectants and in addition, customers are offered hand sanitizer.

Based on the responses, there is still room for improvement in the hygiene of disposable gloves. According to the recommendations, hands should be washed before putting on gloves and between changing gloves. More than half of the restaurants use disposable cleaning cloths. In small restaurants, cleaning cloths are also transported home for washing. At home, it should be noted that cleaning supplies are washed separately from other laundry. Only 27% of restaurants had cleaning equipment marked on different surfaces. Cleaning equipment should be marked when there are several employees in the kitchen.

As a rule, the level of equipment and cleanliness of the cleaning closets was good. The cleaning closet should have shelf space so that there is space for all the goods. The storage on the floor is not recommended. This affects the cleaning, because free floor surfaces are decreased. Food and cleaning equipment must be stored separately. Less than half of the restaurants disinfect their cleaning supplies. It can be stated that the food contact surfaces in the restaurants were well cleaned, but all restaurants did not expose the surfaces to detergents for a sufficient period. Based on surface cleanliness samples, food contact surfaces were cleaner than the surfaces in indirect contact with food. According to the performed survey, most restaurants clean the door handles daily.

Half the responding restaurant operators neither disinfect their cleaning tools nor wash the floor drains before washing the floors as it is recommended. Based on the answers, improvements in the hand hygiene

and used disposable, protective gloves are needed. The hands must be washed before putting on and when changing the protective gloves.

5 SURFACE SAMPLE RESULTS

Based on the surface cleanliness samples (Figure 1), the food contact surfaces were cleaner than the indirect surfaces (Figures 2 and 3). Poor or contaminated results were obtained on 47% of the surfaces. 53% of the samples showed better hygiene. The cleanest results were obtained from machine-washed knives and serving dishes.

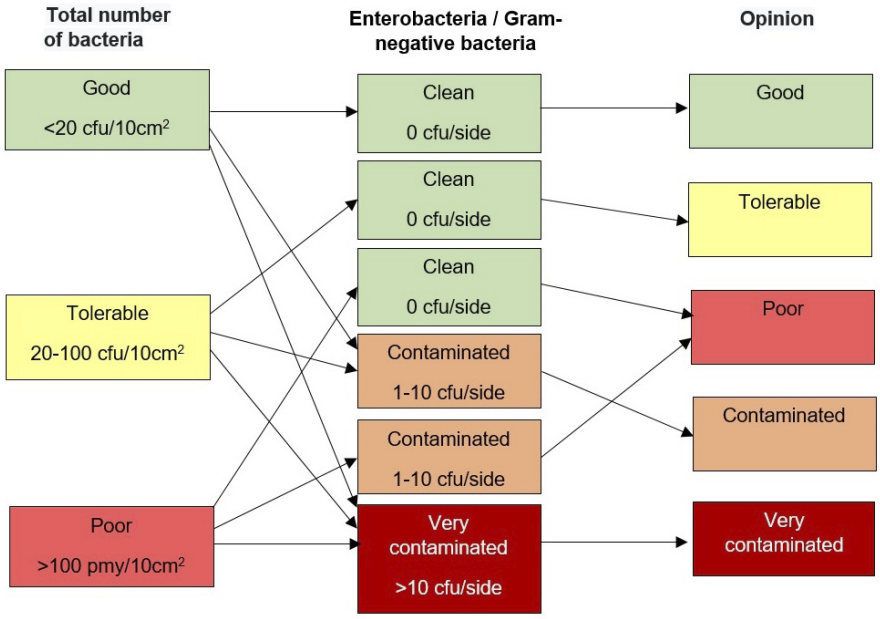
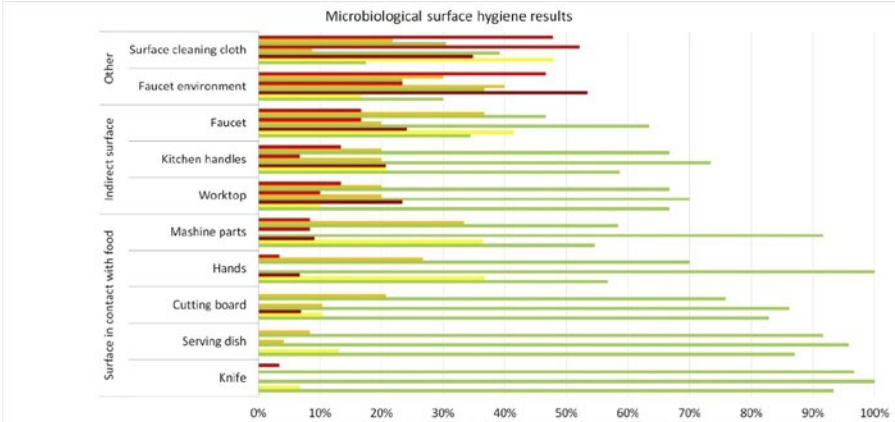


Figure 1. Based on the total number of bacteria, the results of enterobacteria and Gram-positive bacteria, the statement on surface cleanliness was determined.

Enterobacteria or high levels of microbes were found on cutting boards (23%), on washed hands (33%) and in hand-washed cutters (41%) (Figure 3). On indirect surfaces, enterobacteria or high levels of microbes were commonly detected on kitchen handles (38%), on worktops (47%) and on faucets i.e., taps (59%). The faucet environment is often very dirty, only 23% showed clean results.

In addition, the surface around the faucet was often damp, thus the growth condition for microbes is very good. Most restaurants have a standard faucet. Only 20% of restaurants had automatic faucets installed. Due to the poor results, the operators were instructed to check the cleaning results repeatedly, which should be a part of the own checking system.

The results also showed the importance of washing and cleanliness of cleaning cloths. The disinfectant exposure must also be checked as well as the use of paper towels or clean cloths, when drying the surfaces. The drying should preferably be carried out with disposable cloths. In the survey, Enterobacteria were found on chopping boards, kitchen handles, worktops, faucets, and sink rims. Site-specific guidance and counseling can be provided to the restaurant operators to improve the hygiene level in their restaurants based on the hygiene results and the responses in the questionnaire.



	Surface in contact with food					Indirect surface			Other	
	Knife	Serving dish	Cutting board	Hands	Mashine parts	Worktop	Kitchen handles	Faucet	Faucet environment	Surface cleaning cloth
Gram- negative bacteria Very contaminated	3 %			3 %	8 %	13 %	13 %	17 %	47 %	48 %
Gram- negative bacteria Contaminated		8 %	21 %	27 %	33 %	20 %	20 %	37 %	30 %	22 %
Gram- negative bacteria Clean	97 %	92 %	76 %	70 %	58 %	67 %	67 %	47 %	23 %	30 %
Enterobakteria Very contaminated					8 %	10 %	7 %	17 %	23 %	52 %
Enterobakteria Contaminated		4 %	10 %			20 %	20 %	20 %	40 %	9 %
Enterobakteria Clean	100 %	96 %	86 %	100 %	92 %	70 %	73 %	63 %	37 %	39 %
Total number of bacteria Poor			7 %	7 %	9 %	23 %	21 %	24 %	53 %	35 %
Total number of bacteria Tolerable	7 %	13 %	10 %	37 %	36 %	10 %	21 %	41 %	17 %	48 %
Total number of bacteria Good	93 %	87 %	83 %	57 %	55 %	67 %	59 %	34 %	30 %	17 %

Figure 2. Microbiological surface hygiene results. Food contact surfaces, indirect surfaces, and other surfaces: total bacteria, enterobacteria and Gram-negative bacteria. Surfaces in contact with food were cleaner than those in indirect contact.

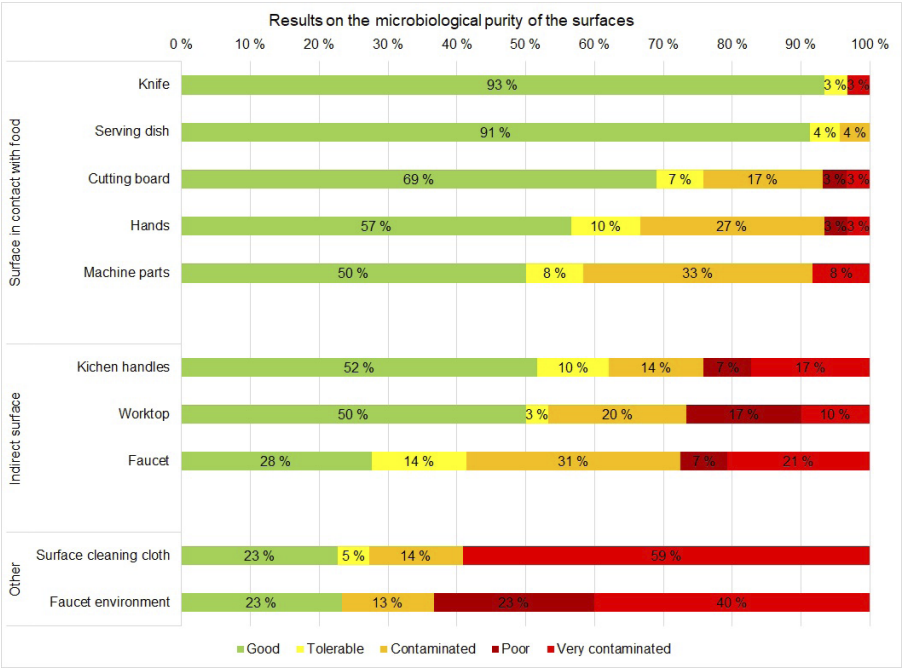


Figure 3. An overall statement of the microbiological cleanliness of the surfaces in the restaurants. The worst result in the overall evaluation is determined using total bacteria and enterobacteria. The presence of Enterobacteria on the surfaces lead to a description as either contaminated (1-10 cells) or highly contaminated (> 10 cells). A high total number of bacteria describes a poorly cleaned surface.

6 CONCLUSIONS

Based on the surface sample results and questionnaire responses, restaurant-specific guidance and counseling was provided to improve the hygiene level. Alcohol-based substances should preferably be used for disinfection in kitchens. It must be stated that sensory evaluation is not sufficient for monitoring the cleanliness of surfaces. Based on the results, restaurants should continue to consider: 1) cleanliness of cleaning cloths, 2) the duration of the active agents in the cleaning chemicals / disinfectants used, and 3) drying the surfaces with paper towels (preferably) or other type of disposable or clean cloths.

Worn cutting boards must be replaced and all food contact surfaces should be cleaned several times a day. Attention should be paid to machines and equipment, especially those that are manually cleaned. Machine laundered microfiber cloths for cleaning in kitchen are recommended. In case, disposable cleaning cloths are used they should be used only once.

It is also good that the instructions for disinfecting cleaning equipment are available in the restaurant. Kitchen hygiene can be improved by cleaning the floor drains before washing the floor.

Hand washing worked well against the coronavirus. Thus, it would be advisable to install several hand washing points in the serving area. This advice is especially worthwhile when setting up a new restaurant. The hand hygiene of restaurant workers can be further improved by using antiseptic hand rub after washing hands. Care should be taken to keep the faucets clean, and the faucet should be closed with a paper towel. In very small sites there can be only one water point, which means that all operations are performed in the same basin. In such cases, it is important that the water point is thoroughly washed and disinfected between the various operations. It is recommended that there are at least three washing points in a restaurant: one for hand washing, one for rinsing food and one for rinsing dishes. A separate water point should be reserved for cleaning of the cleaning equipment. This should be placed in the cleaning closet or maintenance room for cleaning equipment.

Disposable protective gloves should often be changed, and care should be taken to wash the hands between the changes. The health inspectors will continue to pay more attention to both hand hygiene and implementation of sanitation procedures at the restaurant inspections. In the own checking, the catering establishments must take surface samples at certain intervals. The restaurant owner is obliged to check that the samples have been taken according to the own checking plan. The personnel at the restaurant can themselves take the samples or purchase the service.

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CONTAMINATION CONTROL – MAKE CLEANROOM CLEANING REUSABLE AND MINIMIZE WASTE

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1 INTRODUCTION

Based on the EU GMP guidelines and the IEST method recommendations, we build up sustainable cleaning systems for Sterile and Non-Sterile cleanroom environments. The ground rules are to create an ergonomically and sustainable cleaning regime to be able to maximize cleaning abilities in all cleanrooms. To minimize waste and use of single use products, the cleaning material is designed to be reused again and again. This is demanding a cleanroom validated laundry and due to this, partnership with world leading laundries has been established across the world.

To minimize creating waste by using disposable cleaning utensils and high amount of water and chemicals, a unique cleaning method has been developed (Figure 1). This special designed pre-dosing system is the heart of the cleaning regime which enable the operators to avoid any wringing or dipping into a buckets. Each mop is exactly dosed via a special designed sieve system for use in the facility, according to the cleanroom challenge the company have. Doing this, time is saved same time less liquid is spread into the cleanroom and many operators will perform same way of cleaning/disinfecting. This will leave the cleanroom in compliance with the EU GMP and reduce or even avoid buildup of biofilm and/or residues on the surfaces.

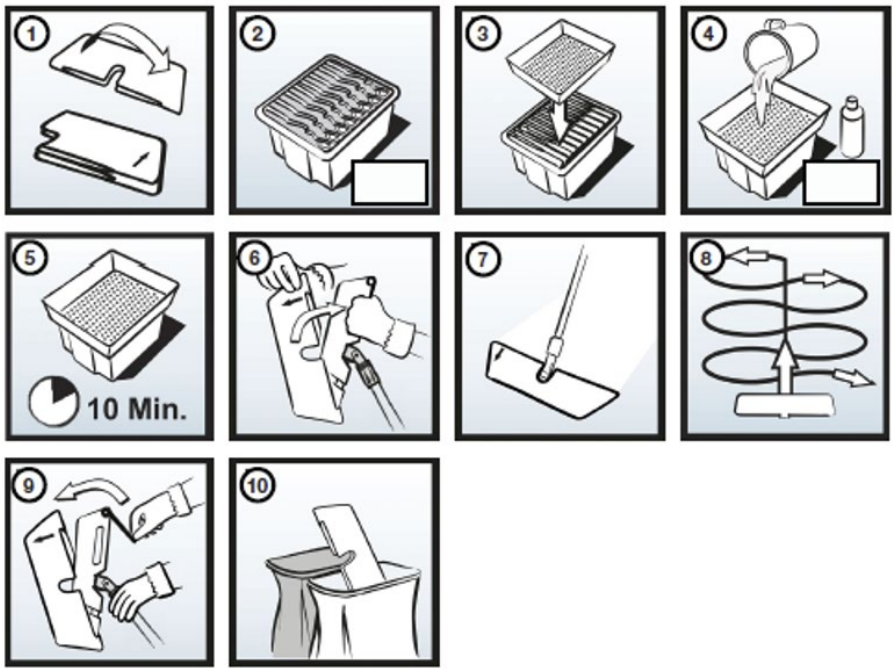
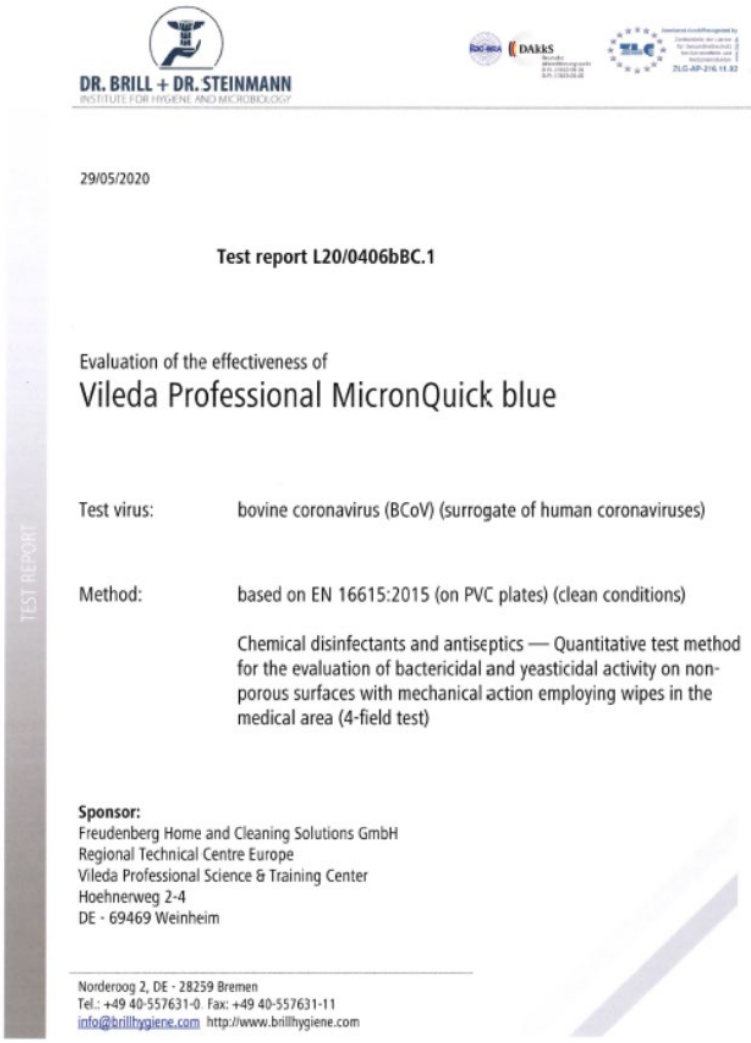


Figure 1. Example of dousing recommendation.

2 FABRIC AND EFFICACY

The special made microfiber fabrics, giving perfect fit into the different Grades of cleanrooms focused on the potential contamination to be removed, will ensure a very high pickup performance, and leave the surfaces clean without the use of too much liquid – which will minimizing humidity in the cleanrooms. This fine combination of microfiber capillary effect together with exact dosing of liquid is making it easy to build up a cleanroom cleaning system which are easy to replicate and will ensure that even a large group of operators will perform same result. Hard data proving the claims of high particle removal and how the right use is minimizing traditional issues in cleanroom, the system can be implemented without any change of chemicals (Figure 2). New validations can also be avoided.



DR. BRILL + DR. STEINMANN
INSTITUTE FOR HYGIENE AND MICROBIOLOGY

29/05/2020

Test report L20/0406bBC.1

Evaluation of the effectiveness of
Vileda Professional MicronQuick blue

Test virus: bovine coronavirus (BCoV) (surrogate of human coronaviruses)

Method: based on EN 16615:2015 (on PVC plates) (clean conditions)

Chemical disinfectants and antiseptics — Quantitative test method for the evaluation of bactericidal and yeasticidal activity on non-porous surfaces with mechanical action employing wipes in the medical area (4-field test)

TEST REPORT

Sponsor:
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Regional Technical Centre Europe
Vileda Professional Science & Training Center
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Norderoog 2, DE - 28259 Bremen
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info@brillhygiene.com http://www.brillhygiene.com

Figure 2. Example of data report.

On top of this, the offer to go 100% reusable both with mop heads for large surfaces, hard to reach areas and wiping for dedicated and smaller surfaces even into the Grade A areas – will leave a much smaller carbon footprint for the company compared to the use of disposable and bucket/wringer methods.

3 LONG LASTING TEXTILE - PRODUCTION

The key utensils are produced in Europe at own manufacturing plants in Finland and France and which are certified according to ISO 14001, 9001, OHSAS 18001. Some of the utensils are even certified with the Nordic Swan label. Working with cleanroom laundries around the world for many years clearly showing that the quality and design is suitable both to be used in highest Grade Cleanrooms with a long-life circulation, allowing the utensil to be used again and again.

4 RESPONSIBLE MANUFACTURING

FHCS Vileda Professional is working on minimizing the carbon footprint in all plants (Figure 3), e.g., the plant in Salo, Finland is powered solely by solar energy.

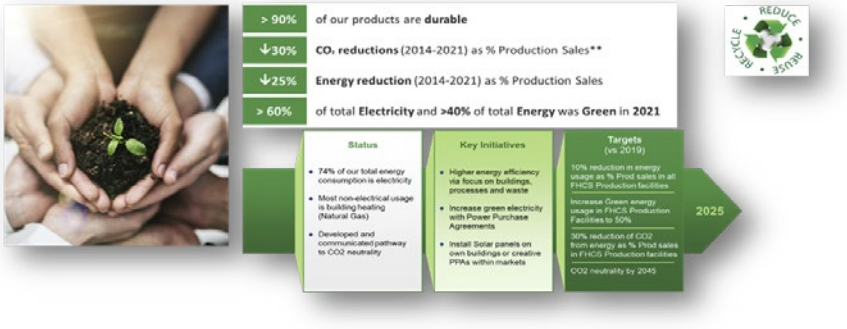

Figure 3. Freudenberg Group has set the goal to be CO2 neutral by 2045.

5 CLEANING TECHNIQUES

Giving clear recommendations how to use and clean with the equipment is part of the success (Figure 4). High focus on hygiene and looking careful into how to avoid Cross Contamination with a clear focus on the flow of contamination which potentially is getting into the Controlled Environment and Cleanroom, the cleaning system is easy to use for all operators.

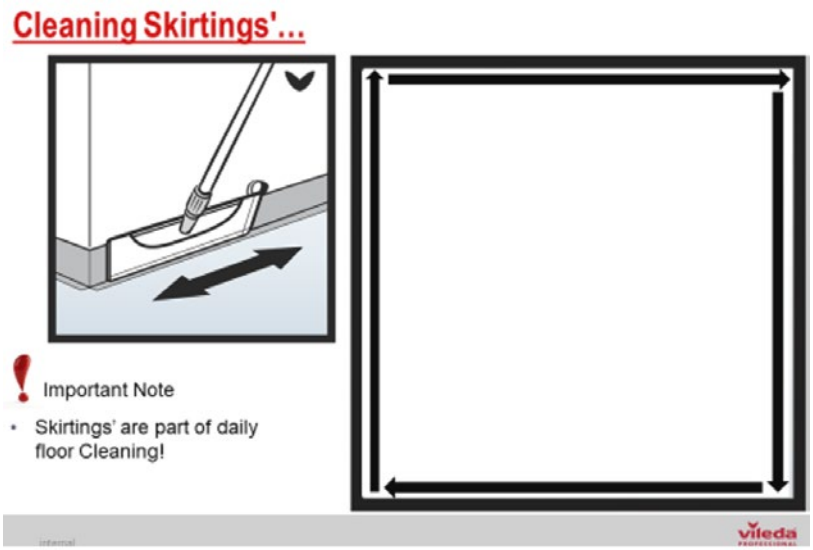

Figure 4. Example of cleaning recommendation.

6 IN CONCLUSION

With hundreds of implementations across the world, the Vileda Professional® cleaning system clearly show evidence for a perfect match for both EU GMP and ISO cleanrooms. Even most of the industry is not willing to share data before and after implementation, experience is share in between the same Company and therefore giving a good spread of best practice within sister companies. As the industry is constantly giving new challenges in cleaning and disinfecting, our development department together with our consultants try to develop new equipment nonstop, to be ahead of the development and demands.

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