Gun Wirtanen & Raimo Pärssinen (eds.)

TURKU AMK
TURKU UNIVERSITY OF
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49th R³Nordic Symposium

Cleanroom Technology, Contamination Control and Cleaning

Proceedings

Naantali Spa, Naantali, Finland, May 22–23, 2018

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Program committee
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Preface

R^3Nordic, the Nordic Society of Cleanroom Technology, is a non-profit, independent association for the promotion of new technologies in cleanroom technology and contamination control in the Nordic countries. The aim of the annual R^3Nordic Symposium is to provide knowledge within the pharmaceutical and food industries as well as hospitals and hospital pharmacies. The sessions at the 49th R^3Nordic Symposium are Pharma & Hospital Pharmacy, Hospitals, Food & Biotech as well as General and the presentations deal with planning, design and construction of clean and controlled rooms, auditing cleanroom technology applications as well as protective clothing, contamination control, cleaning and disinfection and measuring techniques in clean processing areas. The venue of the annual symposium 2018 is Naantali Spa close to the city of Turku in south-western Finland.

The Programme Committee 2018 (PK18) is lead by Leila Kakko. Other persons involved in the PK18 are Jukka Vasara, Raimo Pärssinen, Kari Leonsaari, Antti Mikkola, Inga Mattila, Miko Stenman and Gun Wirtanen. The proceedings' editors, Gun Wirtanen and Leila Kakko, would like to express their gratitude to the speakers for preparing the full papers, extended abstracts or abstracts published in the electronic proceedings. We wish that this event will be fruitful in giving new ideas to both participants and exhibitors.

Contents

KEYNOTES

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Review of Key Comments on Draft Revision of EU GMP Annex 1 Prepared by a PHSS Annex 1 Focus Group

James L. Drinkwater

Franz Ziel & Chairman of Pharmaceutical & Healthcare Sciences Society (PHSS), UK

Abstract

The PHSS submitted (100) pages of comments on Annex 1 within the EMA consultation process. Two comment platform where created within the PHSS including 1) Pharma industry and supporting GMP consultants. 2) Pharma equipment/ supplies manufacturers and supporting consultants and academics.

Many common themes were identified from different comment contributors with a consolidated comment process prepared by the PHSS stakeholders submitted to the EMA EU Commission.

The PHSS also 'Bench marked' against other comment platforms from Not for profit societies/ associations. This presentation will share the key points from the PHSS consolidated comments on Annex 1 revision and discuss the potential impact to the Pharma industry.

Impact is considered in two ways; 1) a new requirement where preparation for implementation will be required. 2) Requirements that having lacking clarity so the impact cannot be fully assessed. 3) New requirements that the Industry do not believe is justified for all sites where either QRM should apply or a change in the Annex 1 draft is considered necessary.

There are aspects of the Annex 1 revision where guidance does not fully account for new product types and new technologies, although encouraged, where potent products may require Aseptic processing and Containment in combination and/ or with Cross contamination control.

The balance between prescriptive guidance and QRM that may be used to justify other methodologies where conventional GMP may be adapted for specific applications/ products will be an important balance to strike with continued consultation with regulatory authorities required to align regulatory expectation with written guidance as sometimes both are unclear. This presentation will provide current PHSS thinking on Annex 1 revision and the way forward.

Virtual Reality Models in Cleanroom Design

Tero Järvinen

Granlund Oy, Finland

Extended Abstract

The use of Virtual Reality (VR) possibilities has increased in recent years due to technology improvements. The driving force has been the gaming industry. The construction sector has been able to benefit from the technology leaps carried out by other industries. Building Information Models (BIMs) have been in use by architects and structural and mechanical designers since the early 2000's. In the Nordic countries, using BIMs is a normal way to design and the construction companies are able to utilize these models quite easily. By combining BIM processes and current VR technologies we are in the situation that the use of VR glasses can be a common means with which the design in construction projects can be promoted (Figure 1). When combining the VR glasses with models, the end users can obtain a better understanding of what architects and engineers are designing than based only on combined models on a computer screen. With VR glasses on, the users can walk inside the rooms and see objects in real scale. When the construction process goes further and we have a real environment built up, we can start using Augmented Reality (AR) possibilities. With AR, you can add objects to the camera view of tablets, phones or smart glasses. AR models can utilize the same BIMs as VR is using. Unfortunately, technology in AR systems and software still needs improvements. VR models are easy to set up but AR models need a lot more preparation to work in real-life use cases. Examples of possible use cases with VR models in the design and construction phases:

- Checking process functionalities inside a cleanroom, moving things in VR
- Checking service/maintenance possibilities
- Checking equipment/device locations in the design phase
- End user approvals/rejections to design team

- Visual inspection of different lighting environments
- Multi-user meetings inside a cleanroom (attendance from multiple locations)
- Training of people (device maintenance or processes etc.)

Examples of possible use cases with AR models:

- Seeing through walls/ceilings (using BIM)
- Locating equipment/devices (with indoor location or tags attached to devices)
- Serving additional information to end user for operating devices/to follow protocols (with preloaded material in the cloud)
- Seeing additional information on top of gauges etc. (using object recognition)
- Seeing and operating virtual user interfaces on top of QR code etc.
- Using voice commands for operating AR software (if you need both hands)

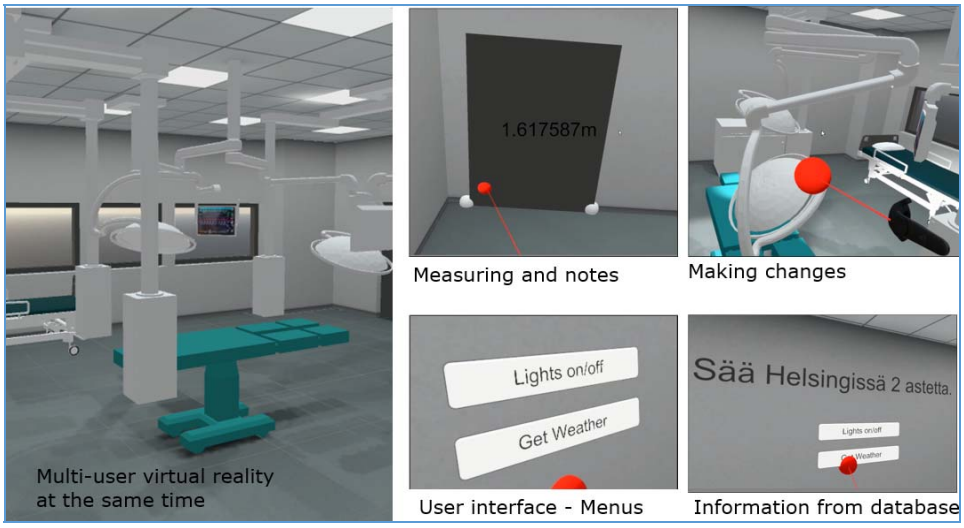

Figure 1. Examples of functionalities in VR models

Process

The construction process produces BIMs in multiple different formats. Efficient use of VR needs straightforward processes. Access to BIM information is available through an open BIM format called Industry Foundation Classes (IFC). All native BIM modeling software can export IFC-models and these models can be viewed through numerous other software. Using IFC models as the basis of a VR environment is the most powerful way to create and update VR information during a construction project. With IFC, different disciplines can combine each other's models and make their own VR models for other use cases from the same source and content (Figure 2). If the whole design team is using the same native BIM software, IFC is not needed in the process. But in Finland, that's not a normal case by any means.

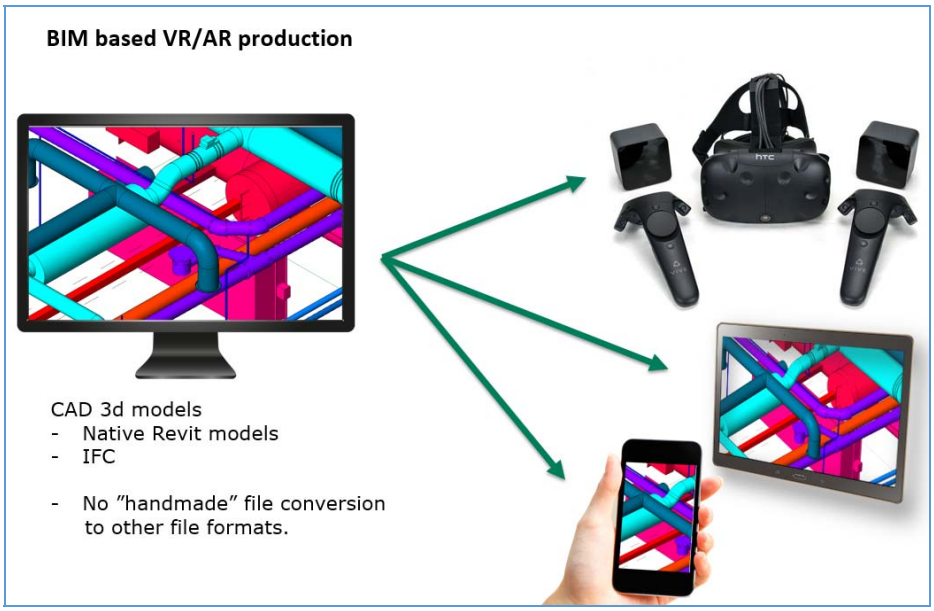

Figure 2. VR/AR models are created from a single source

Devices

VR/AR devices are developing rapidly nowadays. Oculus Rift and HTC Vive have been the best VR glasses for a couple of years. Microsoft launched its “Windows Mixed Reality” platform at the end of 2017 and the cost of VR headsets decreased dramatically. Now there are multiple hardware manufacturers in the market. In the AR sector, there are many different approaches to utilize models. The easiest way is to use your phone or tablet but in the cleanroom environment that’s not always possible. There needs to be a technology that brings the AR view to your visor or smart glasses. One working and tested solution is using smart glasses (Figures 3-5).

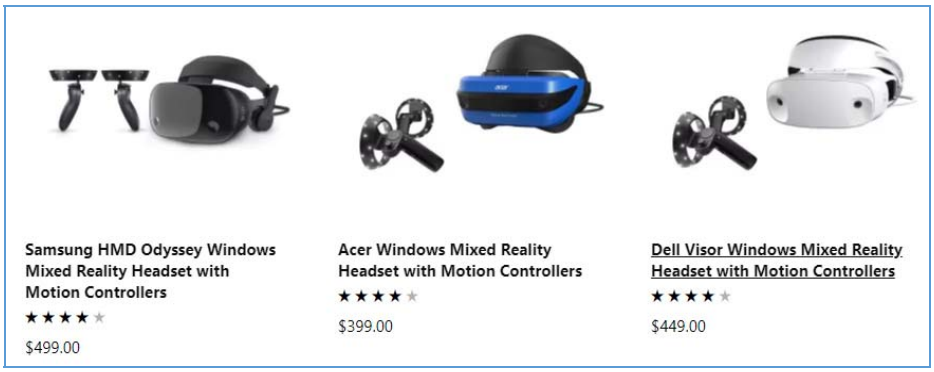

Figure 3. *Examples of Windows Mixed Reality Glasses*

Figure 4. Example of Smart Glasses, Vuzix M300 with Android operating system

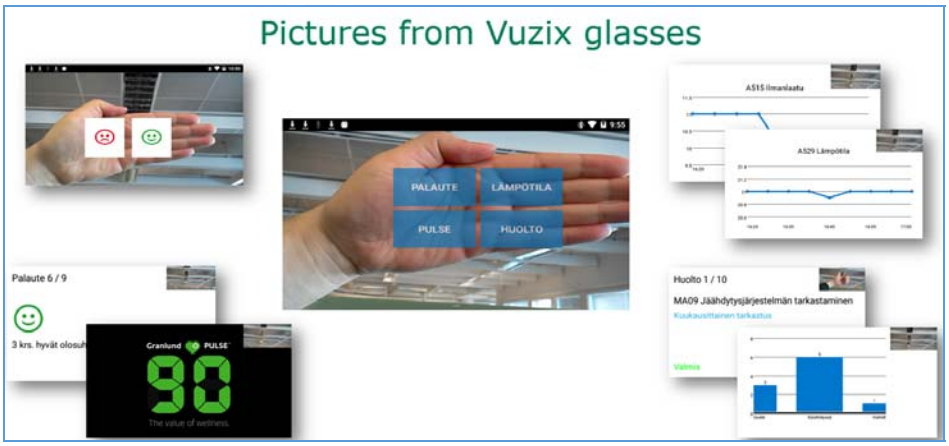

Figure 5. Screenshots from AR Smart Glasses

In Granlund, we made prototype software using smart glasses with a virtual dashboard. With that technology, the user can give a simple command using only hands to operate AR functionalities. Functionalities were made for Facility Management purposes, using cloud FM database information, but can also be made with any cloud information that has an interface to connecting data sources. The software recognizes the hand of the user and draws a virtual dashboard on top of the hand. The user can push the buttons on the virtual dashboard and see more information about the selected topic. The user can change pages by swiping a hand in the air or give “accepted/rejected” commands with a thumb up/down [1]. It is also possible to use voice recognition, but that was not tested in the Granlund prototype.

Information content

When using VR or AR models, the information inside BIMs is still very important. Therefore, access to BIM information is very important for use cases where the information of models is used. Using an open IFC format, information content is understandable to various software platforms. With IFC, you can build a BIM environment where you can see multiple discipline models in a single, coordinated model. This kind of environment is ideal for VR purposes. The downside of using the IFC format is that it contains static information. IFC is exported from designers' native BIMs and is therefore always "old" information, because designers are making updates to native BIMs. In the design and construction phases this is not a big problem, because these phases are used to having iterative information flow in their processes. The designer is publishing a new IFC model, for example, every week to the construction site. After the construction project – in the Facility Management phase – this kind of process is not possible. Updates to models must be done instantly when something has been changed. To achieve this, we need a Digital Twin of the building or cleanroom.

Digital Twin

Digital Twin is a representation of a real building, its components, systems, measurements and functionalities. Digital Twin can act as a user interface for AIM (Asset Information Model) [2]. With static asset information from BIMs and a dynamic IoT-sensor or system information from manufacturers' environments we can build up a system that can be monitored and updated through cloud services. Information from multiple different systems can be seen and operated through a single interface. With possibilities in cloud software, there is a possibility to update the information in the IFC model seamlessly, without the need of opening complex native BIM software. Native BIM software is needed only when there is a change in graphical objects – you need to move a wall etc. Using REST API technology, there is a possibility to connect multiple different systems and gather dynamic information from them. With Digital Twin, there are more VR and AR use cases in the future. The digital model comes alive when the user can see dynamic information of cleanroom in the visor or smart glasses (Figures 6-7).

References

1. Demo how to use smart glasses with hand gestures (in Finnish): https://www.youtube.com/watch?v=EixdlYRRvAc&t=1s
2. PAS 1192-3, AIM; "Asset Information Model". Defined for guideline of using BIM models in operational phase of construction project by BSI, British Standards Institute. https://www.designingbuildings.co.uk/wiki/Asset_information_model_AIM

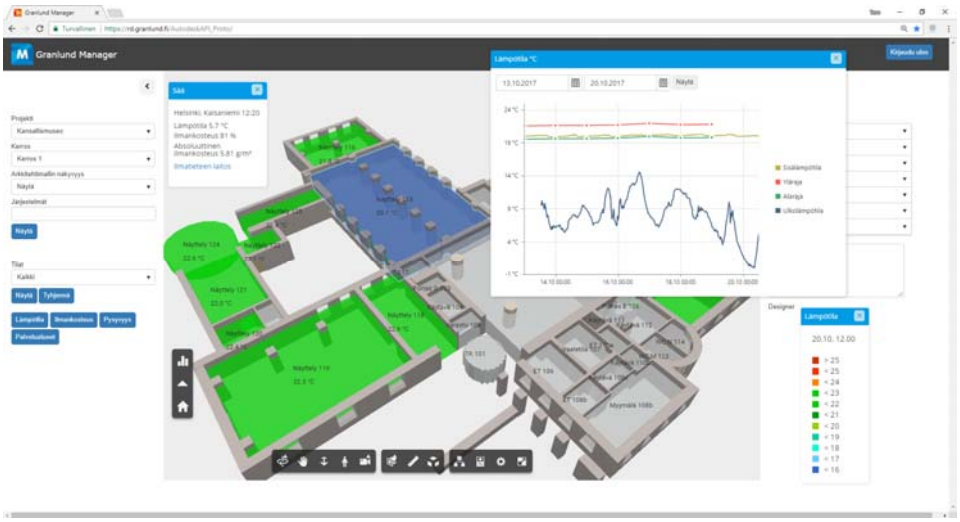

Figure 6. Example of Digital Twin user interface to monitor temperature, humidity and space performance, information available through REST API for VR/AR environment

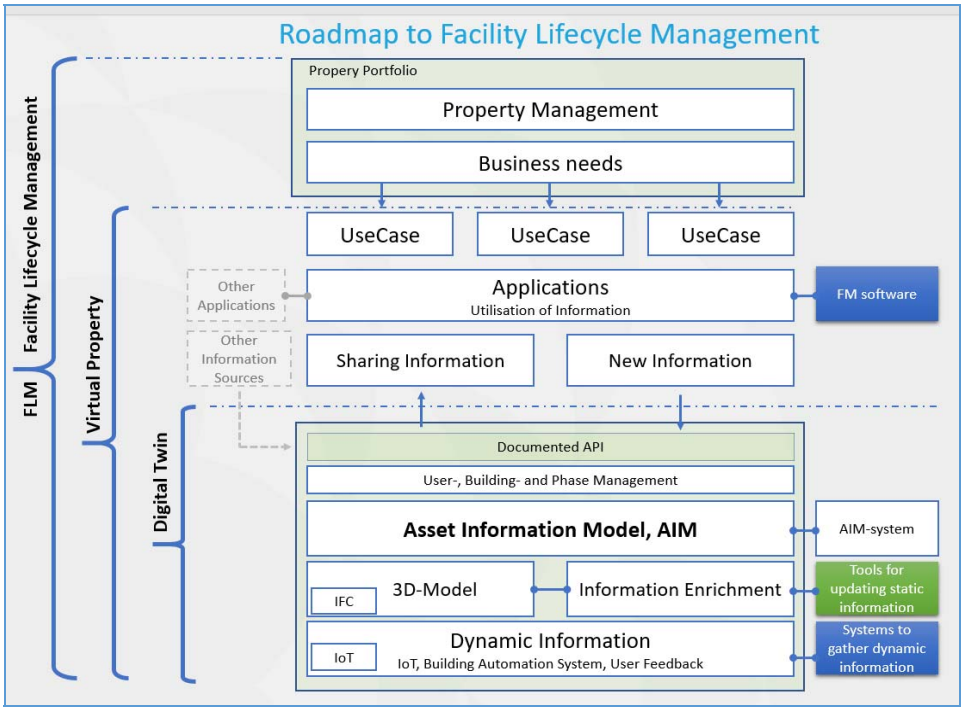

Figure 7. Concept of Digital Twin during facility lifetime

The Cleanroom Zoning, the Challenge of Pressure Differential and Flow. A Practical Implementation of Basic Physical Phenomena

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Abstract

Based on standards and guidelines such as EU GMP Vol 4 Annex 1 and the ISO 14644-3 and -4 the general understanding is that zoning requires a pressure difference. Because of that, the pharmaceutical and medical devices and healthcare industry puts a strong emphasis on controlling room pressure itself. As cleanroom construction becomes better and better, resulting in very limited leakage, active room pressure control becomes more and more complex. With a narrow focus on room pressure control and monitoring, the broader contamination control perspective and a useful different approach is overlooked. Room pressure control is only one aspect of the concept of segregation of zones of different classes. The broader view has many benefits. This approach is based on designing on airflow in stead of mere room pressure. While citing the named standards and guidelines it can be demonstrated that there is a basis for designing an overflow / pressure cascade. This cascade approach when compared to various other systems shows to have many benefits; increased protection of the controlled environment, less complexity, better stability, reduced energy-consumption and reduced costs.

Key words: Aerodynamic segregation, physical barrier segregation, room pressure, airflow/pressure cascade, stability, wind attack, reduced energy consumption, reduced costs of installation.

Introduction

Specifying an overpressure in cleanroom design is a common contamination control concept. Normally a standard pressure interval (commonly 10 – 15 Pa) per step is added upwards along with the increase in classification. Depending on the number of steps the "nominal" pressure of the various rooms can ad up to about 75 Pa. Such a design is illustrated as shown in Figure 1.

In order to achieve this segregation, the HVAC needs to be designed to control the room pressure by some means. Most commonly this is done by utilizing pressure controlled actuated dampers in the return ducting. These dampers have to be designed to modulate in a certain airflow range and with a specific accuracy and speed of reaction. As this requires adequate understanding and designing specific to the situation, in many cases this is not fully successful. Understanding the mechanism that will create a room pressure is essential as well as those that influence it.

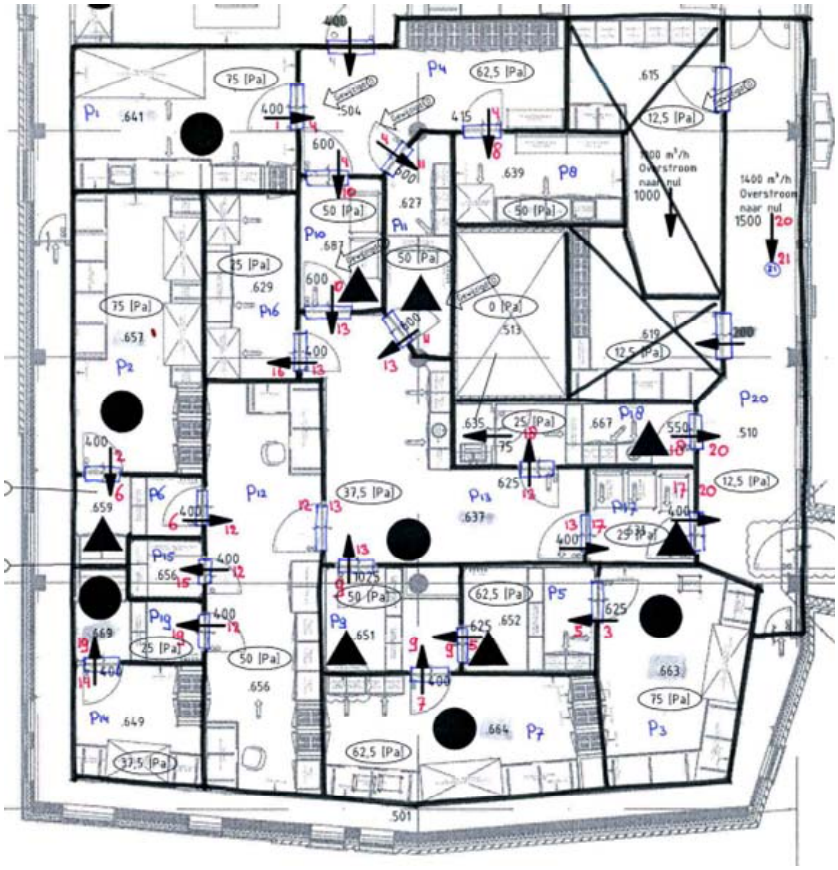

Figure 1. Room lay out showing pressure cascade and direct (●) or overflow (▲) air circulation.

Basic Understanding - Principles of Room Pressure Control

To understand the principles ruling room pressurization we consider at first an ordinary room within and surrounded by an enveloping general building. This room will have the same pressure as the surrounding environment as the construction is usually far from airtight. Large amounts of air will be able to flow to and fro without any significant resistance. In this case the pressure can be increased by two means: 1) increasing the amount of air leaking away or 2) improving on the leakage. For solution 1) vast amounts of air will be required to achieve a even the slightest pressurization. Solution 2) will be a more useful approach. This is based on the simple relation that airflow over a "resistance" will generate a pressure drop Δp [Pa], see also Figure 2. This can be formulated as:

$$\Delta p_1 = \frac{1}{2} \cdot \rho \left(\frac{Q_l}{A_1 \cdot \mu_1} \right)^n \qquad (1)$$

were:

Q_l	= Leakage air volume	[m^3/s]
ρ	= Specific density	[kg/m^3]
A_1	= Area of leakage	[m^3]
μ_1	= coefficient of contraction	[-]

For turbulent flow n = 2 for laminar flow n = 1; Common value for n=2 and μ≈0,75

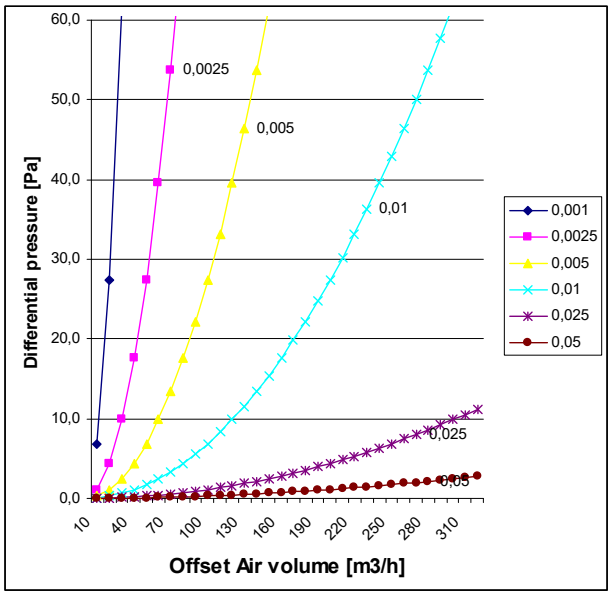

Figure 2. Differential pressure [Pa] in relation to the offset air volume [m^3/h] per area of leakage [m^2].

Furthermore, the dynamic reaction of the room tot pressure fluctuations can be considered as a capacity. According to Boyle Gay-Lussac law pressure, volume, temperature and the amount of gas molecules are related. At constant temperature Boyle's law can be applied. Applied for a given room volume here is a distinct relation to the (room-)pressure and the amount of gas in that given room volume. With Boyle's rule it can be clearly understood that when more air is supplied than exhausted, a large room will have a slower increase in pressure than a small room:

$$p_1 \cdot V_1 = C \qquad (2)$$

were:
P = absolute pressure [Pa}
V = *Volume* [m^3}
C = Constant (at given temperature) [Pa m^3]

For two statuses: $p_1 \cdot V_1 = p_2 \cdot V_2$ (3)

As V_2 could be considered as the room volume V_1 and the additional amount of air δQ added at pressure p_1 in a given time to the room.

$$p_1 \cdot (V_1 + \delta Q) = p_2 \cdot V_1 \quad (4)$$

Where δp is the increase in pressure: $p_2 = p_1 + \delta p$ (5)

This will result (Fig. 3) in: $\delta p = p_1 \cdot \left(\frac{(V_1 + \delta Q)}{V_1} - 1 \right)$ (6)

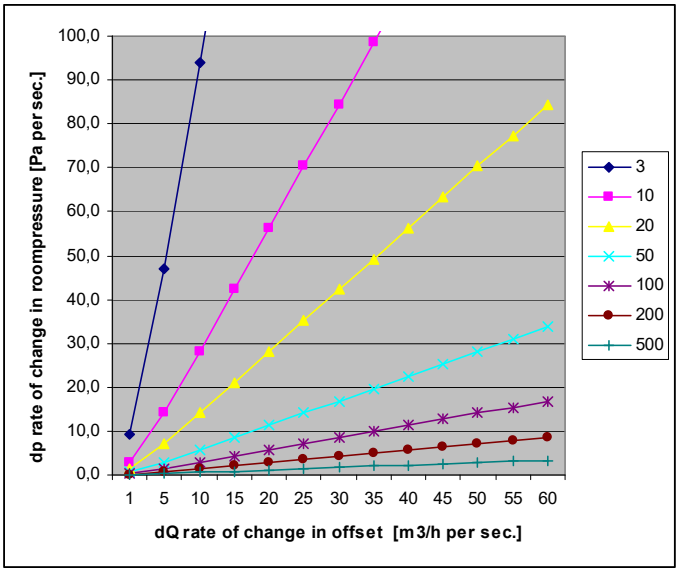

Figure 3. Rate of change δp in differential pressure [Pa] in relation to the rate of change δQ in offset air volume [m^3/h per sec.] per room volume [m^3].

As a large room has a larger absorption capacity for “off set” air than a small room, the latter will show more direct variations in room pressure with variations in “off set”. On the other hand, a small resistance to leakage will reduce the variation of the room pressure with variations in “off set” much more than a strong resistance to leakage. So over pressurization can be designed as the equilibrium of the differential pressure over the leaks of a room to the surroundings and the “offset” in the air handling, the difference between the supply and the return air volume. Heuristically speaking a small and very leak tight room is a very cruel one for stable control of the room pressure. (as shown by Van den Brink e.a.) This is illustrated in Figure 4. Unfortunately, in this respect, modern cleanroom constructions have succeeded in leakage reduction over the last decades. Also, the use of airlocks and separated small cleanrooms introduced an additional challenge for pressure control. Various cleanroom commissioning activities have been bothered by the results of this effect.

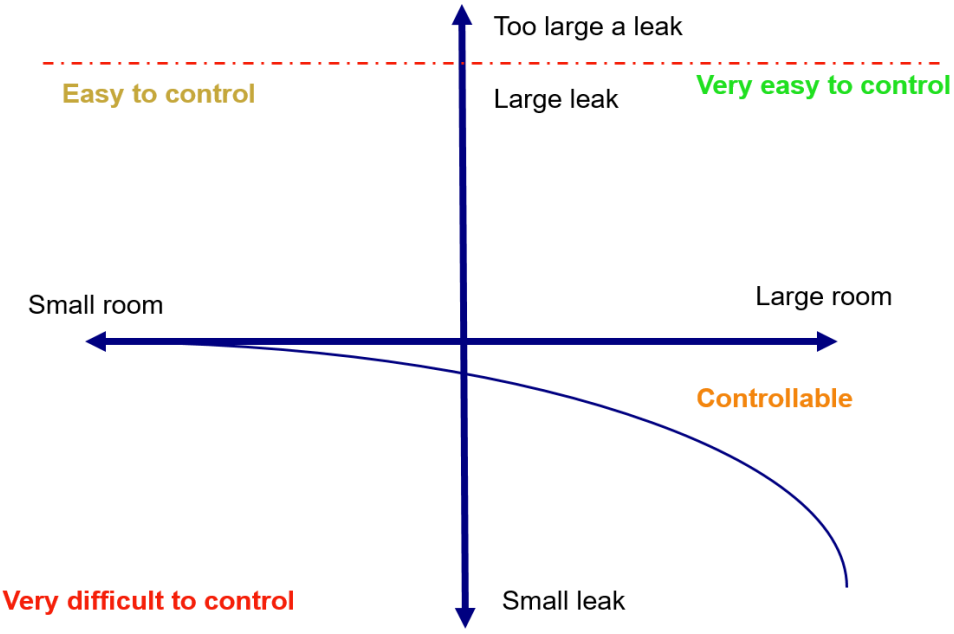

Figure 4. Diagramm showing the controllability of the room pressure with respect to the combination of room size and room leakage.

To overcome these problems diverse configurations and specific actuator/damper combinations have been engineered to improve speed and accuracy of the airflow control to achieving the required room pressure ranges. However, a variation around a set point in range of ± 4 Pa around a nominal value still is more common than exception.

Segregation by pressure or flow?

The approach based on pressure however, disregards that pressure itself does not protect a zone. Protecting a zone can be based on two principles and in practice those are in combination: a physical barrier and aerodynamic segregation. A physical barrier consists of an impervious surface that avoids the movement of contaminants from a cleaner to a less clean zone. Aerodynamic segregation consists of an airflow of such velocity and direction the contaminants in a zone of less cleanliness are prevented to move into the zone of higher cleanliness. Any contaminants in the cleaner zone are displaced to the less clean zone. As a physical barrier in practice of cleanroom construction never is 100% impermeable, a combination of both segregation concepts does co-exist. In analogue with ISO 14644-7, Seperative devices, this balance between aerodynamic and physical segregation can be called the 'segregation continuum'. Based on the permeability of the physical barrier and any discrete leakage path by design a certain flow/pressure drop relation will exist. This relation and the discrete leakage paths by design by 'overflow' devices will be explored further below.

Having designed and commissioned elaborated room pressure it appears to be possible to control a room pressure within certain margins of accuracy. To understand what is the intent of this effort Eudralex GMP, Vol 4 Annex 1 states: *"53. A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10 – 15 Pascal's (guidance values) …"*

This statement makes a combination between positive pressure and air flow direction! Indeed, these are related and yes, the significant one for contamination control is the air flow! This can be found in ISO14644-4-2001 Cleanrooms and associated controlled environments -Part 4 Design-construction and start-up: section A.5: "Concepts to achieve segregation of cleanrooms and clean zones" were 3 principles for segregation are presented:

A.5.2 Displacement concept (low pressure differential, high airflow)
A.5.3 Pressure differential concept (high pressure differential, low airflow)
A.5.4 Physical barrier concept

Note: here a comment can be placed that the ISO TC209-4 working group draft only identifies the said two principles: aerodynamic (combining A5.2 and A5.3) and the physical barrier concepts.

Considering the physical barrier concept as non-leaking, both the displacement concept as the pressure difference concept are based on air flow from one area, generally the cleaner one, area towards the other, generally the less clean one.

As we have seen that 1) airflow is the protecting effect when no physical barrier is there and 2) airflow over a leak or any form of "resistance" will result in an pressure drop, it is clear that this can be utilized when designed for. As the airflow will always be directed

from higher pressure towards lower pressure this can be called the pressure/flow cascade design.

The cascade design

Using the pressure/flow cascade in a design requires the following steps to be taken;

1. Identify on a lay-out the classification and preferred, allowed and prohibited air overflow directions.
2. Establish the supply air volume and the return air volume.
3. Define the overflow air volume and adjust the air balance accordingly.

Step 1 contains one aspect additional to a standard room pressure layout: the allowed overflow directions. In step 3 this comes to the final design. Here the beneficial effect of overflow can be exploited: Having higher classified rooms with a greater number of air changes and an allowed overflow to an adjacent room, makes it possible to increase the amount of overflow. So, depending on the size, class and use, the required supply air to that room can be significantly reduced or even avoided.

An overflow design thus reduces the required capacity of the HVAC system. Another benefit is gained as well: A cleanroom with all doors closed will normally be capable to provide the required protection against infiltration of contaminated air. When a door is opened in many a cleanroom a significant infiltration will take place. This requires a certain recovery time and a room/process lay out that manages this aspect. When an abundant airflow is designed towards the adjacent room with the door closed, the airflow will take the door opening when the door is opened. Thus, protecting against or at least limiting the exchanges and infiltration of contamination. For certain situations this can be designed such that an additional material airlock can be saved.

In the DIS 14644-3 Test methods (which unfortunately still is not been formalized), a ‘segregation test’ is introduced that provides the possibility to test the segregation effect. Challenging the segregation solution by a downstream concentration and testing the contamination found upstream, can be used to make sure the segregation is effective.

Wind attack challenge

To protect a controlled environment the relative pressure flow cascade as designed can be utilized. A challenge to be countered is the pressure around the building that envelops the cleanrooms. Depending on whether conditions, building height and configuration and relative position to surrounding structures, static wind pressures on the building façade can be in the range up to 600 Pa. A mere over pressurization in the normal order of magnitude of 50- 60 Pa will not provide protection. Even a very air tight construction will have an amount of infiltration at high external pressures, compromising the contamination control.

The only way to protect cleanrooms against a wind attack is isolating the cleanroom from the building façade. This not only requires a spaced construction but also requires

such an arrangement that the intermediate space can freely release air infiltrating through the façade. This configuration which can be referred to as box in box arrangement, is shown in Figure 5.

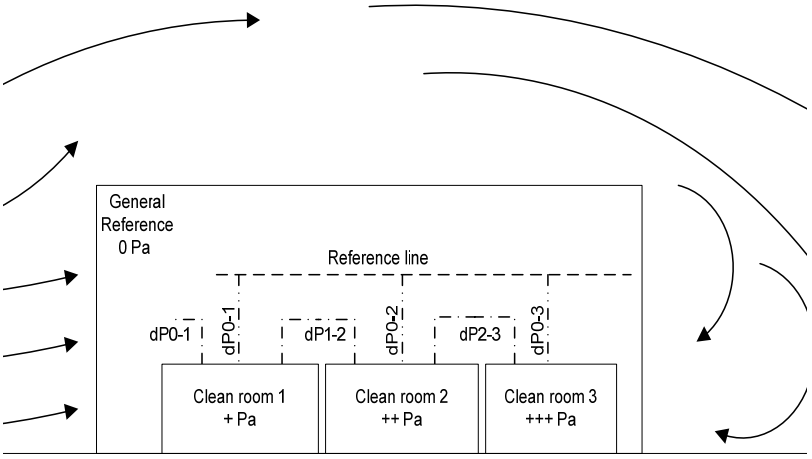

Figure 5. Box-in-box arrangement as well as differential pressure drop measurement and measurement against a reference line.

Monitoring the cascade design

As the concept of a cleanroom contains the element of protection against infiltration this is a genuine item to verify and monitor. However, flow being the basic mechanism of protection can not be directly measured as such. Pressure however can very easily be measured and monitored. So, designing for flow but sizing for pressure drop along overflow devices, provides the possibility to monitor the designed functionality.
This requires the measurement not to be on absolute pressure against a common reference line but to be a measurement relative to the surrounding area (Figure 5). The importance can be illustrated as shown in Figure 6 Here the pressure difference of a typical pharmaceutical cleanrooms against a central reference system is shown. The fluctuations are exceeding the established limits. The company got a deviation warning and had to put effort in a project to correct the situation.

At closer look, reviewing more pressure monitoring data is became clear that roughly all the rooms fluctuated in comparable direction and magnitude. Reviewing the data and comparing the room pressure values for adjacent rooms (Figure 6) it became clear that rooms with a higher classification and higher room pressure always demonstrated an overpressure of minimal 5 Pa despite all fluctuations (Figure 7).

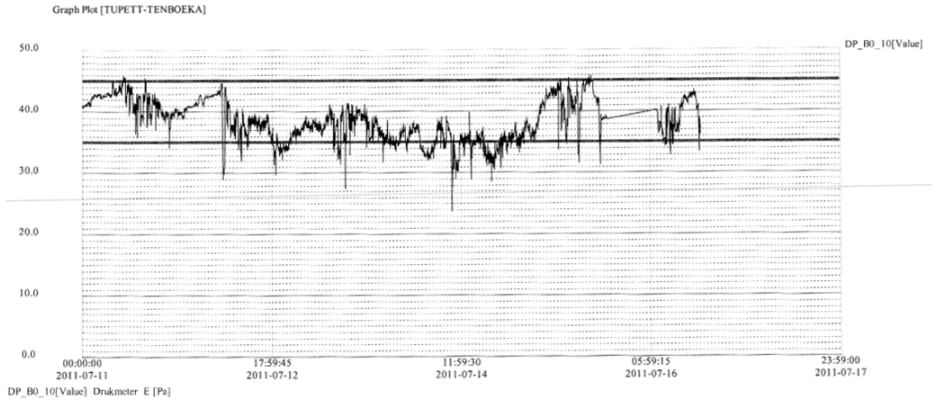

Figure 6. Individual room pressure against a reference line showing out of specification data.

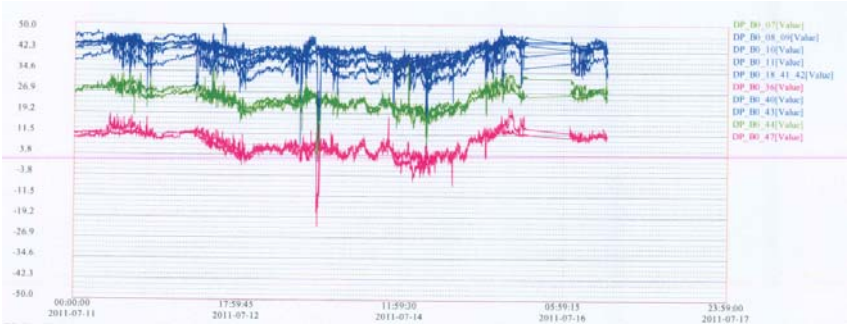

Figure 7. Individual room pressure against a reference compared to adjacent room pressure in the cascade showing >5 Pa difference.

So – although the documented pressures exceeded the formal established limits – from contamination control perspective there was not a serious problem. The only problem seemed to be the approach to monitoring the pressure regime and, as turned out later, the use of an unstable and erroneous central reference system.

The Pressure Reference issue

Defining a room pressure cascade requires the conceptual definition of a “zero” reference. This gives rise to a lot of confusion. One of the great errors is considering overpressure against a defined “zero” pressure reference to be enough to protect a cleanroom against infiltration. This might be the case but is depending of the total concept of the enveloping building. It should be noted that the pressure directly surrounding the cleanroom itself is the major factor to protect the inner conditions against the surrounding contamination. When the “zero” reference is not identical as the direct surrounding static

pressure, a false conclusion can be drawn that the cleanroom is in overpressure while it is not. In line with the resolution of the wind attack challenge, a greater building envelop containing the cleanrooms, will provide the optimal solution for the reference pressure. The reference pressure is all around within the building envelop. When a building is more confined and segregated an enveloping reference is more difficult to achieve. Various examples of reference pressure lines with non-zero reading compared to the surrounding envelop have been encountered in practice. Misreading in the order of magnitude of 10^{th} of Pascal's can be the result.

Cost and Efficiency Gain

Utilizing high quality supply air twice or thrice in a pressure cascade with overflow has various additional benefits. It reduces the amount of recirculating air. In the example of Figure 1 this added up to a 15% reduction in designed air volume. Based continues operation, this could save substantial amounts of energy and associated costs. As the air volume is reduced, the installation costs are reduced as well. Furthermore, a reduction in control equipment and software can be made as an overflow concept is self stabilizing by nature when designed and sized properly. These initial costs savings can ad up to at least to 5 – 10% of the installation costs. When using segregation, as in some projects has been designed, airlocks can be left out, also cleanroom construction and floor space can be saved.

Conclusions

Room pressurization of modern leak tight cleanrooms, especially small ones becomes a significant design and commissioning challenge as the required accuracy, resolution and reaction time of utilized controls need to increase significantly. The pressure/flow cascade concept offers a stable energy and cost-efficient alternative that offers the additional benefit to have a better protection when doors are open. A box in box approach is useful to counter wind attack and as a relevant pressure reference.

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PHARMA & HOSPITAL PHARMACY SESSION

A Practical Approach to GMP Cleanroom and Cleanroom HVAC Projects

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Abstract

This text describes how a GMP cleanroom project is started, develops and goes over to the construction phase to finally be commissioned. The description focuses mainly on the design and construction of GMP cleanrooms and cleanroom HVAC.

Introduction

The work of the GMP cleanroom project team (further in the text “project team”) is in all parts guided by the current legislation, following company`s quality system as well as Good Engineering Practice, GEP, which lays a foundation for Good Manufacturing Practice, GMP. The cornerstone of the project team work is a good control and understanding of EU GMP Volume 4, FDA cGMP, PIC/S GMP and WHO GMP. There are also other GMP regulations, which the project team may follow, depending on the customer’s need. The project team will base their design solutions on scientifically proven and traceable methods and procedures. At the beginning of the project, the project team will utilise well-tried assumptions and rules of thumb, such as air change rates and equipment-specific heat release, in order to be able to produce concrete plans and preliminary dimensioning, which will be more accurate specified during the project. The project team will follow the pharma industry standard V-model according to Figure 1, or the ASTM E2500-13 standard to ensure GEP and GMP quality.

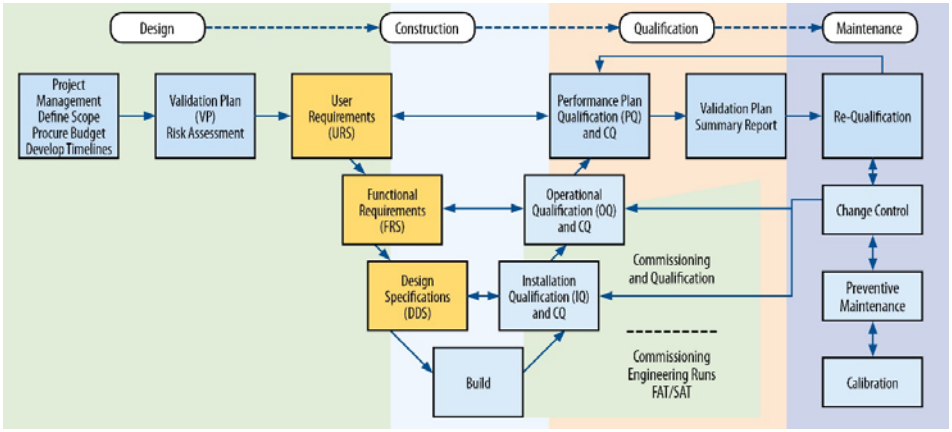

Figure 1. The Industry Standard V-model

The primary data source for the project team is literature produced by the International Society for Pharmaceutical Engineering (ISPE), but also relevant standards such as ISO 14644, BS, VDI among others can be applied in design solutions. The project team will utilise the newest literature and research in order for the suggested solutions to be applicable as far ahead in the future as possible. The members of the project team make sure that they have the latest information by continuously participating in trainings provided by the operators and organisations in the industry. A GMP cleanroom project usually starts, when a customer contacts the project team and a first meeting is arranged, where the customer presents his preliminary thoughts on what he expects from the project team.

The customer can be company that is starting up a pilot production or production plant. The customer could also be a bigger pharmaceutical company with established procedures and methods for the procurement of design and construction management services. A company that is only starting production, is usually more demanding for the project team, as the responsibility of the experts in the project team is wider, and very often because a start-up company does not have equal financial resources as bigger pharma actors. The project team has to make right-sized decisions that are as good as possible right from the beginning of the project.

Usually the customer has already determined the demands, but also this can be included in the project team's tasks, if requested. This could also be called an audit, where the customer determines and weighs the capabilities of the project team to deliver the services or possibly a completely new GMP production or renovated facility that the customer is planning to invest in. Usually it is agreed during the first meeting that a quotation is done, for instance as Conceptual Design, Basic Design or Detail Design packages. It is completely possible that the customer requests a quotation for all of the afore-mentioned design phases, support for permit application, tender materials, contractor selections, site supervision, commissioning and validation, i.e. a so called EPCM delivery. Naturally, there are also other procurement types.

The quoted scope can include as separate tasks or all together the design and construction of the building, GMP cleanrooms, plant utilities, clean utilities, ventilation and cleanroom ventilation. When the customer has received the quotation, he will select a designer or EPCM contractor and offer to sign an assignment contract with the project team. When the contract has been signed, the design phase of the project starts.

Conceptual Design CD

The customer has ordered a Conceptual Design package from the project team. This package may include, with a preliminary status, e.g.: plant layout, cleanroom layout, layout for cleanroom pressure differentials, operating areas for the cleanroom HVAC AHUs, implementation time schedule, risk assessment, cost estimate with a ±30% accuracy and a CD report describing all factors that can have an essential effect on the project. The CD package can be more detailed or have a wider scope than the afore-mentioned, depending on what the customer wants.

The most important outcome from the CD is to answer the customer's question regarding the commercial and technical perspectives that should be observed when implementing the project. The project could end after this stage, if the customer's objectives are not fulfilled. The project can also continue with a new CD, if the customer finds that it would be useful. A CD package can be done with an investment of approximately 100–200h, depending on the size of the project.

Basic Design BD

The customer has been satisfied with the CD package produced by the project team and decides to order the next phase, i.e. the basic design package, from either the same project team or another team. This phase is more in-depth and has a wider scope, and it requires a significantly larger investment from the customer. Usually, the BD phase means an investment of several thousand hours, if its purpose is to produce commercial and technical documents and plans intended to purchase and build GMP cleanrooms and connected HVAC systems.

The target of the BD phase is to produce detailed information on administrative, commercial and technical details related to the project implementation, such that all relevant GEP and GMP requirements are fulfilled. In general, the accuracy of the cost estimate after the BD phase is ±10%, which in the Nordic construction environment requires that the contractors and equipment suppliers give binding quotations for contracts and equipment deliveries. This, in turn, puts great accuracy requirements on the design.

The most important documents in the BD phase are the Validation Master Plan (VMP) and the subsequent user requirements specifications, URSs, for GMP Cleanrooms and connected HVAC systems. User requirements can be issued separately for all systems and equipment. The user requirements specification defines the Direct Impact and Indi-

rect Impact factors that can affect the final product quality. The concepts GEP and GMP can be used to support the selection of applying commissioning or qualification to the testing and documentation requirements. The fulfilment of numbered URS requirements is systematically verified and documented as the project proceeds.

Nowadays, the design in the BD phase is usually conducted by means of a Building Information Modelling, BIM, data model. BIM means a design, where all rooms, equipment and utility systems are placed in a common Master File model with a commonly agreed level of detail, Basis of Design, BOD-300/350 or BOD-400. The design programmes used for modelling are compatible with the IFC file format. The model gives a 3D geometry model, 4D time schedule follow-up as the construction work proceeds and 5D cost follow-up to determine committed and predicted costs. The strength of BIM modelling is that all information included in the model corresponds to the constructed reality. BIM modelling can be utilised when creating a virtual reality, review usability and for CFD or other technical computations. When the construction work is ready, the “as built” BIM model serves the operation and maintenance of the building and its utility systems. BIM is the standard of today and 2D design is history, even if it can be used, if the customer so wishes.

Layout and section drawings of the cleanrooms and connected HVAC systems will be taken out from the BIM model that was created during the BD phase for contract offer calculations, work descriptions will be issued, as well as functional and circuit diagrams and equipment lists. All documents for the building management system, BMS, will be written in the BD phase. These documents constitute together with the VMP and URS the contract tender documents.

The contract tender documents are in the Nordic construction culture divided into commercial and technical documents. Commercial documents are according to the Finnish General conditions for building contracts, YSE 98, e.g., request for quotation, contract programme and contract boundary annex. Technical documents are, e.g., VMP, URS, work descriptions, layout drawings, section drawings, functional and circuit diagrams and equipment lists. The VMP and URSs can also be regarded as commercial documents. The commercial documents have priority over the technical documents.

Detail Design DD

BIM modelling is utilised maximally in the detail design, DD. The data that was inserted into the BIM model in the previous BD phase, can be updated with equipment and component data agreed upon with the contractor, if they differ from the ones used during the BD. BIM modelling changes the traditional interface between the BD and DD phases such that design solutions that were previously selected in the DD phase are now selected already in the BD phase. The information from the DD phase constitutes the foundation for the design reviews, DR. If needed, work shop drawings are drawn in the DD phase. A correctly done BIM model enables this.

In the DD phase, all functional and circuit diagrams related to the BMS system are

also complemented and updated, as well as the equipment lists with the contractor's equipment and component data, if they differ from the information in the BD phase. All detailed drawings needed for construction are issued in the DD phase. Such drawings are related to, e.g., cleanroom constructions, such as walls, doors and ceilings.

Selection of Contractor and Equipment Supplier

The project team will together with the customer select the contractors and equipment suppliers that will be requested to provide contract or equipment delivery quotations based on the documents issued in the BD phase. In GMP construction only known contractors and equipment suppliers should be used, but this is easier said than done. It is always a matter of persons and their GMP competence, not companies. Companies may have strong references from previous and corresponding GMP level contracts or equipment deliveries, but the persons who handled these projects may not be employed by the companies anymore. The project team and the customer should carefully re-audit contractor and equipment supplier candidates, when the afore-mentioned situation is the case. The project team shall prepare to provide the selected contractors and equipment suppliers with sufficient GMP training and instructions. If GMP training and instructions are given, the biggest misunderstandings can be eliminated.

The selection should be based on the total points for quality and price, and not only price. Contract negotiations are conducted with the selected candidates before the final selection. Matters should be handled very thoroughly in the contract negotiations and documented in protocols that are attached to the contract agreement documents. A thorough review means, e.g., that all URS requirements and complementing work descriptions are discussed in such a manner that the parties have a common understanding of the contents and scope of the contract or equipment delivery after the review.

In this phase the customer makes his final decision, whether to build the GMP cleanrooms and the connected HVAC systems. The conditionality of the implementation decision should be written down in the protocols from the contract negotiations. Usually the customer's own organisation will separately go through and make an investment decision. It could also be negative. This conditionality should also be clearly indicated in the building contract programme.

Design Review DR and Design Qualification DQ

The project team will together with the customer's representatives convene and lead design review, DR, meetings with the selected cleanroom contractor and supporting ventilation system contractors, when all contract and equipment delivery contracts have been signed. In these meetings all URS requirements and complementing work descriptions will be handled thoroughly and to the extent that the afore-mentioned requirements can be verified based on the design. The documents and equipment data that are discussed in these meeting, make up an entity consisting of plans issued by the project team, the

contractor and the equipment suppliers.

All parties should prepare themselves well before the design reviews. Only drawings and documents that have been commonly approved in the design reviews can be used as a basis for implementation. Enough time should be allocated for the design reviews in the project time schedule. The contractors and equipment suppliers will need time to issue plans and documents and procure the needed equipment. This is something that takes time.

The design reviews will be documented in protocols or memos, with a clear and easily readable structure. Based on the DR protocols or memos, a design qualification, DQ, report will be issued. The documents, protocols, memos and reports that have been handled in the DR meetings will be assembled into common DQ binders, that are signed by all parties as a confirmation that the DQ phase has been approved and completed and that construction can begin.

Construction phase

During the construction phase all those plans that have been approved in DQ will be implemented. The construction work is supervised closely and systematically. Construction and supervision work is documented. The most important cooperation forms during the construction phase are the contractor meetings and site meetings.

Commissioning C

The commissioning phase includes supervised GEP tests according to the URS, to the extent they are included in the concerned contract or equipment delivery. The results, protocols and other related measurement data from all C tests are assembled into one file or binder.

Installation Qualification IQ

The installation qualification, IQ, is a controlled procedure for conducting all GMP tests according to the URS, to the extent they belong to the concerned contract or equipment delivery. The results, protocols and other related measurement data from all IQ tests are assembled into one file or binder.

Operational Qualification OQ

In the operational qualification, OQ, all the GMP tests that are included in the contract or equipment delivery according to the URS will be conducted under supervision. The results, protocols and other related measurement data from all OQ tests are assembled into one file or binder.

Handover

When all liabilities related to contracts and equipment deliveries have been approved, there will be a common handover inspection, which is documented in a handover protocol. Financial matters can also be agreed upon in these meetings, or there could be separate meetings for so-called final financial statements

Conclusion

An important conclusion is that all GMP cleanroom and cleanroom HVAC project phases should be executed according to well-proven models. The model can be the industry standard V-model or the ASTM E2500-13 model. A GMP cleanroom and cleanroom HVAC project differs in numerous aspects from so-called normal building projects. The most significant difference is that it requires right and competent persons with the right attitude. Equally important is to understand the importance of documentation. People with right competence and attitude is a guarantee for quality. This applies to the entire and unbroken chain of designers and constructors. GMP cleanrooms and cleanroom HVAC can be successfully designed and constructed when the pharmaceutical company knows what they want, choose the right project team for design and site supervision, without forgetting the importance of engaging a constructor who is familiar with GMP demands. The entire chain is kept together by means of a systematic and documented approach to defining, reviewing and finally verifying the relevant requirements throughout the project.

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GMP-grade Clinical Cell Production with an Isolator System - Key Considerations

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Introduction

The Finnish Red Cross Blood Service (FRCBS) is a non-profit organization responsible for collecting blood and supplying blood products to all Finnish hospitals in a centralized manner. The FRCBS has been involved in stem cell and novel cell therapy research since 2002 and the Advanced Cell Therapy Centre (Solutuotantokeskus) with its GMP facilities for the development and manufacturing of novel cell therapy products has been operational since 2012. Parenteral cell therapy products intended for clinical use should always be produced in a controlled cleanroom environment according to a quality system and must comply with current legislation and good manufacturing practices (GMP principles).

Background and regulation of ATMP

Advanced Therapy Medicinal Products (ATMP) are medical products for human use based on genes or cells that offer potentially ground-breaking opportunities for the treatment of injury and disease, particularly in cases of severe, untreatable or chronic diseases which do not respond adequately to conventional treatments. The European Commission has adopted the Guidelines on Good Manufacturing Practice (GMP) specific to ATMP (adoption by EU 22.11.2017).[1]

The new Guidelines take a risk-based approach, allowing manufacturers some flexibility in their processes and control systems, depending on the level of risk. According to GMP for ATMP aseptic manufacturing should take place in clean areas of appropriate environmental cleanliness level. Specifically production in a closed system, in an isolator, or positive pressure isolators: a background clean area of grade D is acceptable.

Aseptic Cell Isolator System

The definition of Isolator: *An isolator is sealed or is supplied with air through a microbially retentive filtration system (HEPA minimum) and may be reproducibly decontaminated. When closed it uses only decontaminated (when necessary) interfaces or Rapid Transfer Ports (RTPs) for material transfer. When open it allows for the ingress and/or egress of materials through defined openings ("mouse holes") that have been designed and validated to preclude the transfer of contamination. Isolators can be used for aseptic processing activities, containment of potent compounds, or simultaneously for both asepsis and containment*.[2]

Key factors for FRCBS isolator design included an understanding of the process, risk assessment and ergonomics. Multiple chamber arrangements provide defined barriers between process steps, enhancing aseptic performance. The core of the FRCBS GMP facility is an aseptic cell isolator system of class A in a class D background. The isolator consists of a six chamber arrangement providing defined barriers. All needed accessory devices such as cell culture incubators, centrifuge, fridge, microscope and a decontamination system has been integrated within the isolator system (Figure 1).

The aseptic isolator operate under positive pressure air delivered through HEPA filters. In this particular application this pressure is 75 Pa in the chamber A and B and 50 Pa in the airlock, incubator chamber A and B as well as centrifuge chamber. Isolator need to be periodically leak tested to ensure its integrity and prevent escape of the decontamination agent. In addition a Grade II Microbiological Safety Cabinet is installed next to airlock so that materials can be transferred through a safety cabinet with laminar air flow to the airlock and after cleaning/disinfection/unpacking procedure further transferred to the main processing chamber A/B.

Six (6) units of CO_2 incubators for cell incubation integrated to the isolator: 4 incubators are installed inside incubator chamber A (behind the chamber A and separated by sealable doors) and 2 incubators are installed inside incubator chamber B (behind the chamber B and separated by sealable doors).

The centrifuge is integrated to the centrifuge chamber, which is located below the processing chamber B and the cover plate is separating chambers from each other. The microscope is located in the processing chamber B and is connected by a CCD camera to an outside computer. All isolator system doors are interlocked doors with delay time. Open phases are carried out in the main processing chamber A and B.

There is independent integrated VHP decontamination system (VHP generator) and inside the isolator there is its own pipeline for VHP distribution and circulation.

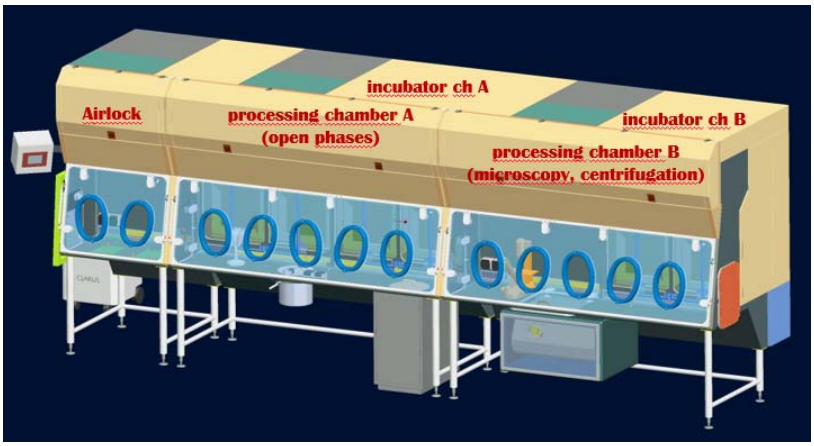

Figure 1. The FRCBS aseptic cell isolator system.

Validation activities

Isolator validation procedure consisted of individual stages that evidence of regulatory compliance and required performance includes reviews of: documentation, instruments calibrations, isolator function and performance testing, together with environmental testing and operator training. All validation activities were performed according to previously agreed protocols. Details of the specific tests and methodology were found in the validation protocols for each item. The validation was composed of the following sub-categories:

- User requirement specifications (URS)
- Validation Master Plan (VMP)
- Design Qualification (DQ) including
  - ✓ Functional design specifications (FDS)
  - ✓ Software design specifications (SDS)
  - ✓ General Assembly (GA)
  - ✓ Mock-up study
- Factory acceptance tests (FAT) with customer FAT (cFAT)
- Calibration certificates
- Documentation
- Commissioning/SAT
- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)
  - ✓ includes aseptic validation
- Validation studies of Vaporized Hydrogen Peroxide Decontamination

Especially the mock-up study was one of the most important efforts during the planning phase of the isolator project. User friendliness and ergonomic aspects are crucial part. This requires a very close co-operation between the client, the isolator manufacturer and possible other subcontractors (manufacturers of accessory equipment).

Milestones of the FRCBS Advanced Cell Therapy Centre

Currently, the isolator system is utilized for the manufacture of mesenchymal stromal cells (MSC) for the experimental treatment of refractory graft versus host disease (GVHD), a severe complication of hematopoietic stem cell transplant patients. Project initiated in autumn 2009 and GMP facilities with novel cleanroom solution were ready summer 2011. GMP inspection by Finnish authorities were organized in February 2012. First developed ATMP is a bone marrow-derived mesenchymal stromal cell product and national production permit based on the ATMP hospital exemption received in May 2012 for drug-resistant graft-versus-host disease (GvHD). Patient treatments initiated in January 2013. Now there are 22 GvHD patients treated (6/2017).

The Aseptic of MSC production

The validation of LY-MSC manufacturing aseptic validated by a process simulation test as part of the isolator PQ validation. The validations showed that the aseptic production process fulfills the quality requirements and that the process is in a validated state. Process simulation is used for large preparation and for several subcutaneous delivery medicinal products, as well as for regular re-validation. Because the manufacturing process of LY-MSC is so long and multi-stage that it’s totally real simulation is virtually impossible: 25-30 days. The LY-MSC manufacturing process uses blood and tissue materials and the process is long-lasting and multi-stage. Process simulation using simple microbial substances does not necessarily reveal all the risk factors of production.

LY-MSC's production process has stabilized over these years and the process of aseptic monitoring is monitored continuously during production and the quality requirements are met for each sample of each batch. Aseptic is a critical quality attribute (CQA). The strategy for securing this critical feature in LY-MSC manufacturing covers the following areas:

- sterility of starting material, raw materials and other production materials
- conformity of production environmental conditions
- asepticity of the finished product, intermediate products and breeding conditions

The microbiological purity of the isolator is also monitored regularly by monthly sampling of air and surface samples. Sampling samples for the incubator humidification waters are sampled for aerobic BactAlert cultivation. The purity of the D background mode is monitored regularly once a month by air and surface samples taken.

A facility monitoring system (FMS) is used in the ACTC cleanrooms and isolator as a process monitoring tool that collects data from sensors as optical particle counters,

differential pressure sensors, and temperature probes in real-time. Real-time alarms notify facility operators of alert limits to enable an immediate response to an unwanted event or excursion. Reports and trend graphs can be produced.

Bio-decontamination of the isolator by H_2O_2 vapour

Vaporized Hydrogen Peroxide (VHP) bio-decontamination is used to achieve surface sterilization of the exposed, clean and dry surfaces of components, containers and working areas of isolator. VHP is bactericidal, fungicidal, sporicidal and virucidal and produces hydroxyl radicals, which rapidly cause cell death. VHP is supplied by a generator that delivers the vapour phase agent to an isolator chambers.

In the first phase of the validation were checked critical parameters of the gassing process: airflows and temperatures of nozzles were balanced. The objective of nozzle airflow and temperature balancing was to ensure that during gassing process HPV gas is divided to each isolator chamber evenly and the desired temperature. In the gas cycle development (GCD) studies there were used Geobacillus stearothermophilus spores as indicator organisms for the decontamination challenge for each validated cycles (4 cycles): airlock with load, chamber A, chamber B and full isolator system with six chambers.

Before to set final disinfection cycle parameters for HPV gassing processes there were studied with BIs/CIs fractional study method to determine the time point at which no further growth was observed. Finally, an arbitrarily chosen safety margin (say 20% additional time) was added to the cycle before performance qualification. There observed in the PQ studies of each validated cycles 100% inactivation of log 6 spore population biological indicators. In addition there were studied the required aeration time for each final disinfection cycles.

In the validation of the HPV decontamination system was verified that de-contamination system works reliably. By using validated HPV cycles the decontamination process can eliminate all microbes in the isolator system and after that cell production can be performed safely in the isolator system gassing point of view. The re-validation procedures of the hydrogen peroxide decontamination system have been performed every 3 years according to the PIC/S guide for isolators.[3]

Summary

The project of a new GMP facilities and isolator for parenteral cell therapy products was a great entity, and through the progress and learning of the project revealed the scale and the complexity of the project. The success of the project was also influenced by the motivated project team, the management's positive attitude towards the project and the management / steering group.

GMP and pharmaceuticals bring great costs and take resources. For cleanroom solutions, you should think about the system's technicality: is it too technical? How much

does internal technical know-how? Is it technically possible to create a big production risk?

The utilization of isolator technology and integration of proprietary devices to minimize human interventions in processing areas resulted in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. The manufacture of cell therapy medicinal products is different from conventional medicine manufacturing, and expertise especially in cell biology, microbiology and process technology is critical.

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Usage of Contamination Recovery Rates as Control Indicator for Aseptic Environment

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Abstract

Contamination Recovery Rates (CRRs) were introduced in USP <1116> a few years ago as a tool for monitoring aseptic processing environments in mainly cleanrooms grade A and B. However, the additional benefit of this new quality indicator has not been very obvious from the start, which led to a hesitant implementation at manufacturing sites. Gaining experience after implementation of CRRs at manufacturing sites, this new way of looking on data has been proven to be an excellent monitoring tool for the evaluation of both, processes within cleanrooms, and cleanroom-designs. Compared to only focusing on action limit excursions (OOLs), CRRs give more accurate data on the cleanroom status and also allow easy comparison of data in between manufacturing sites. In this presentation the influence of cleanroom-processes and cleanroom-design changes on CRRs are shown for a case example of a sterility testing suite grade B area. CRRs will be shown to be an effective tool for cleanroom monitoring, but also providing an excellent way to verify effectiveness of improvement actions implemented.

Introduction

The term “Contamination Recovery Rates” (CRRs) was introduced in the non-enforceable USP guidance chapter <1116> “Microbiological Control and Monitoring of Aseptic Processing Environment” during 2012. It is defined as the rate at which environmental samples are found to contain any level of contamination, calculated as:

Number of samples with any growth / Total number of samples

CRRs have a statistical focus on growth incidents for detecting an adverse drift in the environment rather than only relying on single excursion data. The term is independent of action limits (as e.g. given in EU GMP Annex 1) and should support potential loss of control detection. Limits for "suggested initial CRRs" are given for cleanrooms from ISO 5 (differentiated between areas inside isolators/closed Restricted Access Barrier Systems [RABS] and grade A areas other than those) to ISO 8. There are many aspects that need to be defined by manufacturers before utilizing CRRs, as for instance:

- What is the timeframe for the calculation to look at (e.g. weekly, monthly)?
- What is the sample type to look at or should different sample types be combined?
- How to define the cleanroom area size (e.g. merging areas with common entrance areas and multiple filling lines)?
- What sample number do we need, to get statistical value in the calculations?

Since the implementation of CRRs does not mandate to stop the usage of action limits and investigations to be performed upon exceeding those, it is seen an additional indicator for cleanroom quality, giving additional efforts as reporting and statistics to be compiled. Based on that the benefit of using CRRs has not been very obvious and questions arose whether this additional indicator is worth the effort. Based on a real life example this presentation shows the benefits of using CRRs in a case study.

Results

Initial Assessment

Until May 2015 "classical" environmental monitoring with alert and action level excursions for cleanrooms was used at most sterile manufacturing plants. CRRs were not actively used as a quality indicator/parameter on neither local nor global level. A global key performance monitoring (KPI) tool was available and certain quality parameters, as e.g. the number of action limit excursions, were collected from sterile manufacturing plants.

An increased number of sterility test failures were observed at one of the sterile manufacturing plants microbiology QC laboratory. During six test occasions failures occurred during sterility testing within a 2 year period (with more than 2650 individual tests performed). Mostly growth was observed in the negative control during the same test occasion. Investigations showed that all of those sterility test failures were related to laboratory error. Certain OOLs were reported in the sterility test laboratory environment grade A/B area during that timeframe. Question arose whether the laboratory was in a "state of control" and, if not, how far from a controlled state was it? Furthermore, could we have seen an environmental trend in the laboratory before sterility test failures occurred?

CRRs were calculated retrospectively for the month of May 2015 for manufacturing areas and the sterility testing laboratory to get an understanding of the current status. All data confirmed to the USP recommendation limits, except the sterility testing facility. Specifically, the CRRs for the grade B sterility test background area showed a combined

CRR for all sample types of about 30%, a significant difference to the USP expectation of less than 5%.

Immediate actions and effects on CRRs

Upon discovery of the high recovery rates for the laboratory an extensive investigational sampling was performed, followed by a well-defined multi-step “deep clean” to reset the baseline for the sterility testing facility. Routine cleaning practices and frequencies were assessed and revised, as well as sample disinfection and material transfer procedures (e.g. sporicidal disinfection usage for all transfer activities was implemented). Focus was given to cleanroom practices and multiple training activities for analysts and laboratory managers, and effectiveness checks for correct aseptic behavior throughout the whole testing procedure were implemented. Beside procedural changes a significant awareness increase was also accomplished. An immediate improvement of the CRRs could be achieved from the previous 30% to around 7% in the month of June, as seen in Figure 1.

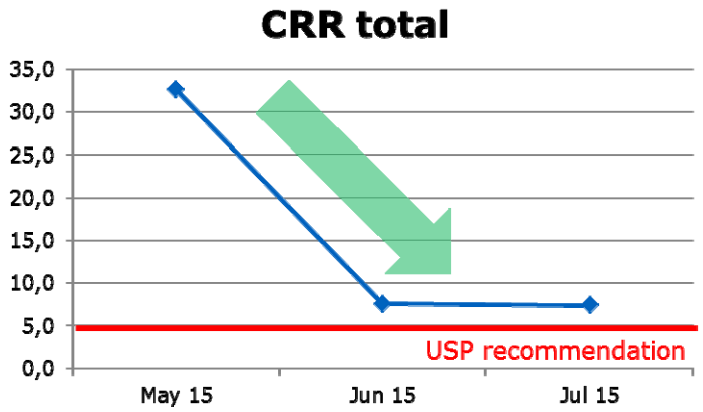

Figure 1. Initial (May 2015) combined CRR for the sterility testing grade B background environment and the improvements achieved with the immediate actions.

However, despite continuous efforts to further improve awareness and procedures, the USP limits of less than 5% could also not be reached for the following months. There were no sterility test failures, hardly any recoveries within the grade A testing area (closed RABS) and very few OOL in the grade B background area. The “classical” environmental indicators were all fine, but still, looking on the CRRs no full state of control was reached for the sterility testing facility. For the months to follow the CRR was relative constant always within a corridor of 5 to 15%, as shown in Figure 2 below.

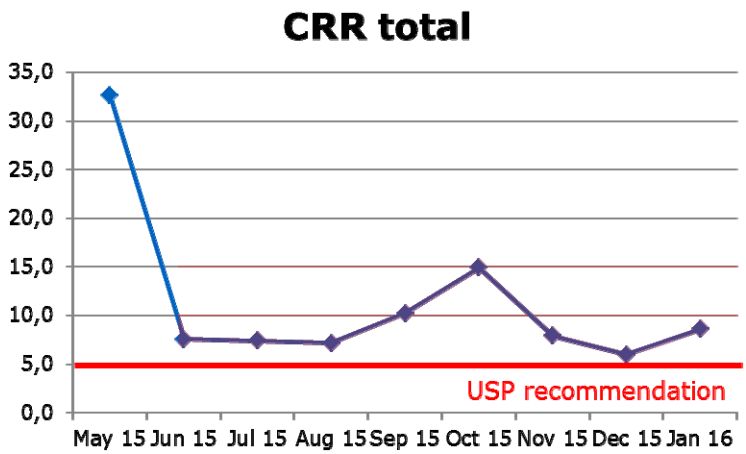

Figure 2. Combined CRR for the sterility testing grade B background environment from May 2015 to January 2016.

Design Actions and Effect on CRRs

Already shortly after the implementation of the immediate actions a comprehensive design assessment of the sterility testing facility was performed. Following main deficiencies were identified:

- Shared gowning (upon entrance) and de-gowning (upon exit) areas for grade B
- Shared gowning rooms in between grade B sterility testing and adjacent laboratory grade C areas
- Test samples were transferred from not classified areas directly into grade C and then further into the grade B testing suite, “jumping over grade D”
- Passive air pass-boxes were used for certain transfer activities

Positive aspects were seen, beside others, in the double door autoclave that connects media preparation into the grade B testing suite and the closed RABS system with transfer box, which is utilized as grade A testing environment. A general layout of the previous design of the area is presented in Figure 3.

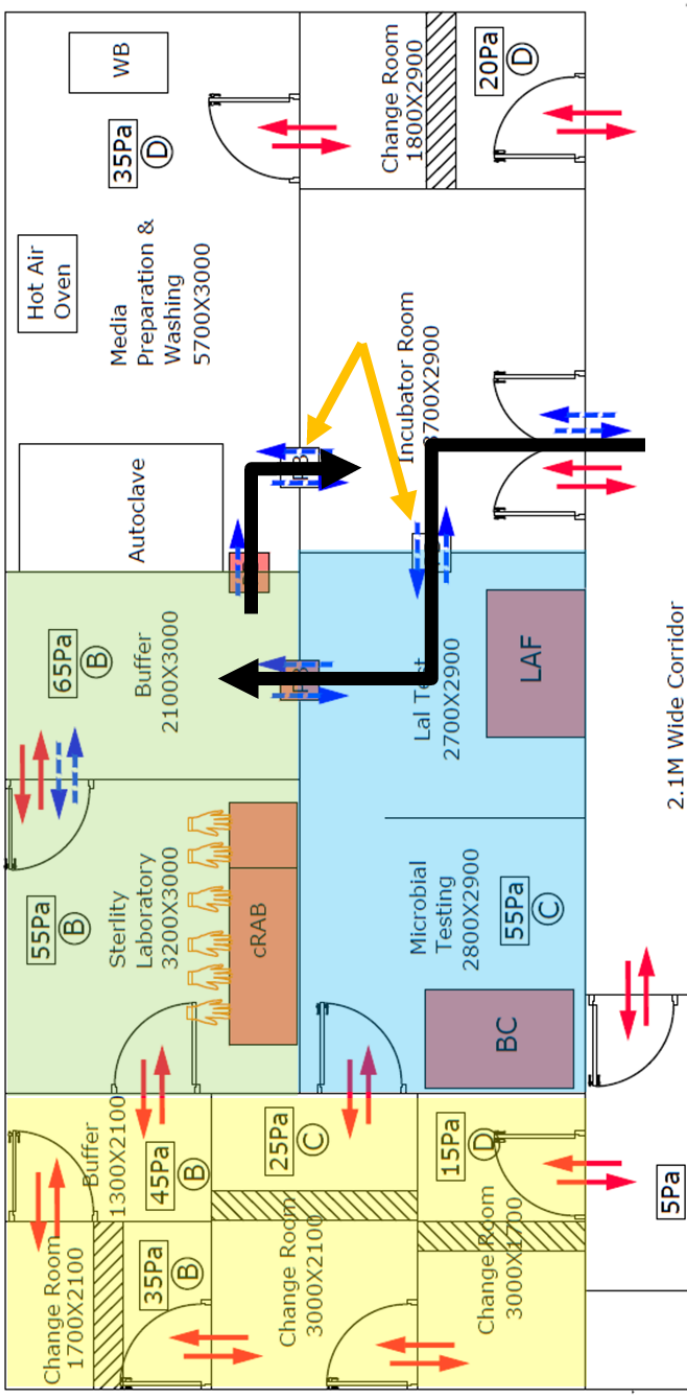

Figure 3. Schematic layout of the sterility testing facility (and adjacent microbiological laboratory area) before the design changes.

Based on the design assessment a project plan for a re-construction of the microbiological laboratory was prepared and a 12-week shutdown period scheduled from middle of January to middle of April 2016 for re-built and qualification activities. Significant design changes were made during the re-built (Figure 4) as e.g.:

- Complete separation of gowning (upon entrance) and de-gowning (upon exit) activities for grade B area (3+2 concept)
- Complete separation of gowning rooms for entrance into grade B and grade C areas
- Three active air pass-boxes for sequential sample transfer and disinfection from not classified → grade D → grade C → grade B (3 step)
- A complete physical separation between the classified areas and the open cell culture handling & media disposal areas via the laboratory corridor
- Installation of a new double door autoclave in between the grade C and grade B area

In addition, a vaporized hydrogen peroxide (VHP) system was installed for the sterility testing cRABS and the surrounding grade B sterility testing suite (allowing regularly scheduled disinfection) and a new gowning system was implemented (pre-sterilized single use gowns). Compared to a new “greenfield” construction a few compromises needed to be made during the planning phase due to space constraints (e.g. some space from the adjacent chemical laboratory was converted), but a “state of the art” design fulfilling current expectations could be established.

After re-opening of the sterility testing facility in April 2016, for the first time, we were able to comply to the USP recommendation limit and also following the months after, showing a clear shift in CRR trend from before and after the design changes, while other “classical” indicators remained more or less unchanged. Already shortly after the implementation of the immediate actions a comprehensive design assessment of the sterility testing facility was performed. Following main deficiencies were identified:

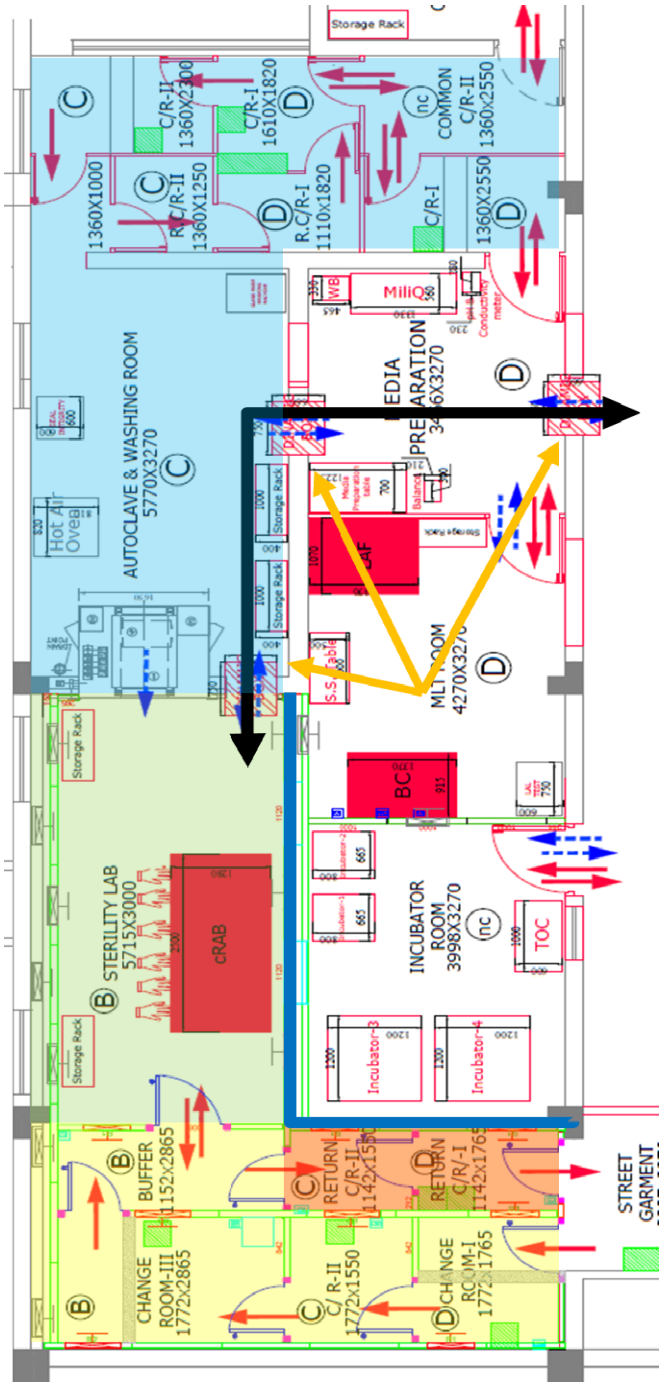

Figure 4. Schematic layout of the sterility testing facility (and adjacent microbiological laboratory area) after the design changes.

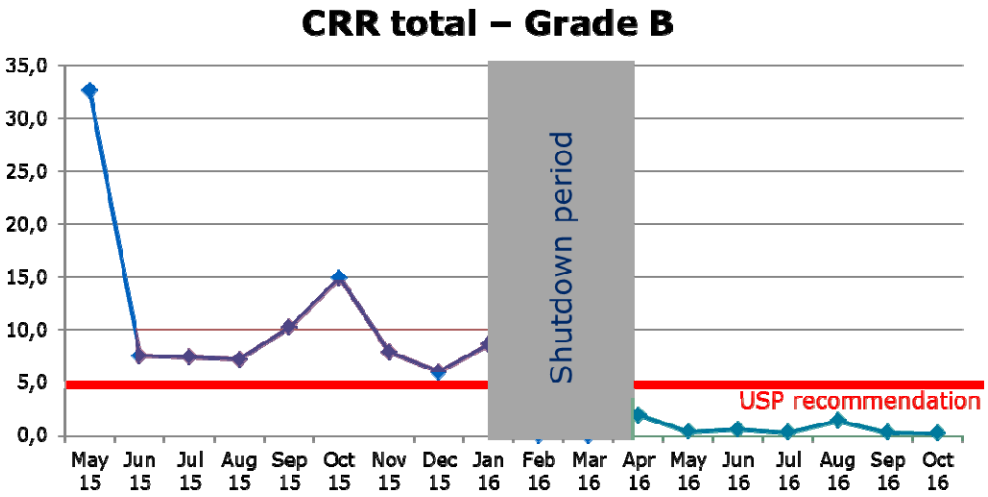

Figure 5. Combined CRR for the sterility testing grade B background environment from May 2015 to October 2016.

Discussion / Conclusions

Contamination Recovery Rates (CRRs) were shown to be a very useful tool to monitor the state of control in grade A and especially grade B manufacturing and laboratory areas. CRRs are to be used on top of the “classical” action limits applied but give an easy and quick statistical evaluation whether a cleanroom environment is within a state of control. It can be used as reliable assessment tool on plant and global level for collecting and comparing data (Figure 5).

Even if CRR limits are also given for ISO 8 (grade C) areas in USP <1116> we see a conflict in the definition of the CRR as such, since CRRs require that “all operators are aseptically gowned”, which is only given for grade A/B environments. Working with CRRs in grade C areas did not proof to be as helpful and the classical evaluation and trending with alert and action limits being sufficient for those areas.

References

USP <1161> ‘Microbiological Control and Monitoring of Aseptic Processing Environment’

Risk based Environmental Control and Monitoring - PHSS Case Study Guidance Initiative

James L. Drinkwater

Franz Ziel & Chairman of Pharmaceutical & Healthcare Sciences Society (PHSS), UK

Abstract

To provide more applied guidance on environmental control and monitoring the PHSS Aseptic processing & Bio-contamination special interest group are preparing GMP supportive guidance based on six cases studies that range from Aseptic process filling of Sterile non-hazardous and toxic products, filling pre-sterilised containers with combined RABS-Isolator filling lines, Aseptic processing of ATMPs, Sterility testing in Isolators and Pharmacy Aseptic preparations in Isolators.

With the release of the draft Annex 1 revision it is clear such supportive guidance is really important because although Annex has increased to 50 pages there are still many aspects of GMP guidance that cannot be prescriptive for different applications.

Some of the case studies include new methodologies and technologies plus new requirements for Aseptic processing containment where OEB containment levels now include OEB6 for highly potent products e.g. ADCs (Anti body drug conjugates) where the toxic linkers are at Nano gram levels. For each case study (12) twelve data sets of case study guidance have been identified including:

- Contamination and Cross contamination control strategy and where applicable Containment strategy.
- Environmental classification of cleanroom and controlled areas (Isolators/ RABS).
- Manual disinfection agent selection, qualification and rationale of application.
- Gowning and Garbing rationale for selection and use in Cleanrooms and associated Separation barrier technology: Isolators and RABS.

- Rationale for Barrier technology and process machine bio-decontamination and surface sterilisation and application of VHP/vH202.
- Environmental control risk assessment of CPPs/ technical control measures based on HACCP methodology.
- Environmental monitoring sample location and sample type risk assessments for Cleanrooms and Barrier technology: Isolators and RABS.
- Environmental isolates characterisation establishing baselines and the environmental control state via ‘Go Clean’ process.
- Environmental qualification of Barrier system environments through Media Fills/ Process simulation trials (PSTs).
- EM programs for routine monitoring program (frequencies) in production operations a critical surface end of batch surface sampling.
- Rationale for EM sample incubation regimes and associated targeted monitoring characterisation studies.
- Barrier technology Glove management strategy considering the Life cycle: Selection, Change frequency, in-process integrity testing/ inspections, risk assessment in response to post batch pin hole detection.

Development of a Harmonized Method for Cleanroom Hard Surface Disinfectant Efficacy Evaluations

James Tucker

Ecolab Contamination Control, UK

Abstract

This presentation explores the development of a test method which overcomes the shortfalls in existing methods and guidance documentation. It also explores the validation behind the method which covers, parameters and repeatability as highlighted below. It will explore equivalence testing considerations and method design to harmonize common variables in the test method e.g. surface, chemistry and microorganism. It will also explore development the variability seen within biological test systems and methods developed to understand these parameters and define this into the final method. This presentation also details factors that should be considered prior to any testing to minimize the potential for validation failures or retests. The use of the harmonized method and consideration of the factors discussed will aid in the creation of a robust disinfectant efficacy study that will stand up to regulatory scrutiny across the globe. The learning outcome will be understanding the development allowing for implementation of a strategy and rationale for disinfectant validation testing that is in line with this global harmonized approach. This universal method developed by Ecolab Life Sciences enables end users to select a validated efficacy testing method, which can be adapted for their own facility cleanroom surfaces and isolates. Use of the harmonized method can also give companies a transferable platform to achieve replicable results between laboratories and countries.

Risk Management for Development of Safe Pre-Use Post-Sterilization Integrity Testing (PUPSIT) Strategies

Alain Vanhecke

Pall Life Sciences, Belgium

Abstract

The pre-use post-sterilization integrity testing (PUPSIT) on the final sterilizing grade filter before filling is a EU GMP requirement in Annex 1 since 2007. This test will remain in the revised version of Annex 1 that is expected to go for public consultation early 2018. While this test is allowing for the detection of marginal filter defects before running the filtration, a significant part of the industry is considering it as a higher risk for contamination of the filtered product. Starting with the current regulatory specifications and the justification for this test, the speaker will present the risk-based strategies that have been successfully developed by a filter manufacturer for an easier implementation of PUPSIT in single-use systems and the mitigation of the risks associated with this test.

Design of GMP Premises

Jukka Vasara

Granlund Oy, Finland

The GMP Guide for Cleanroom Design of Hospital Pharmacies

The EU Commission has adopted regulation No. 1252/2014 and directives 2003/94/EC and 91/412/EEC. These directives lay down principles and guidelines for good manufacturing practice of medicinal products for human and veterinary use. The “Guide to good Manufacturing Practice” (GMP), offers guidance to archive the requirements set out in these directives. In Finland, the “Finnish Medicines Agency” (Fimea) gave an order in May 2012, requiring compliance with GMP, for medicinal production and operations related to it. GMP in turn often refers to the widely used cleanroom standard ISO 14644.

The most important parts in GMP are in Chapter 3 and Annex 1. Chapter 3 covers the cleanroom design, placement within premises, equipment and maintainability. Annex 1 covers manufacture of sterile medicinal products, classification of air cleanliness with regard to particle concentration and microbial contamination. Ref. Tables 1 and 2.

Table 1. Air cleanliness classification based on particle count

	At Rest		In Operation	
Grade	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size.			
	0,5 µm	5 µm	0,5 µm	5 µm
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	-	-

Table 2. Cleanliness classification based on microbial contamination

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

BASIS OF DESIGN

The first stage for hospital and pharmacy cleanroom designs begins with the drafting a “basis of design document”. This document describes the operations that will take place in the facility. There are also covered the volume of production, personnel and material flows, large machinery requirements and preliminary options for structural and technical solutions. This document is written together with the pharmacy personnel and designers. The document gives a good and firm foundation for continuing the designing process.

CLEANROOMS IN A HOSPITAL PHARMACY

Premises and Structures

A “cleanroom” is a working space with a tightly controlled environment within a secondary shell. In a typical hospital pharmacy cleanroom, the height in the working space is about 2600 mm. A space usually in the range of 1800...2100mm is reserved above the cleanroom for technical equipment and maintenance. Ductwork for ventilation and other technical installations are placed in this space. The equipment room for air handling units is commonly situated above the cleanroom floor.

It is crucial for a successful layout design that the design group is experienced in cleanroom technology and operations in hospital pharmacies. Placement of airlocks and gowning rooms within a facility are define by the routes of personnel, materials and finished products. Space and service areas for special equipment within production areas must also be taken into account at this stage.

Structures in hospital pharmacies are primarily designed by using sandwich elements. The boundary wall elements are made by using polyurethane elements which are coated with powder painted galvanized steel. Thickness of the element is usually 65…100 mm. Neither the cleanroom standards nor the GMP defines a specific material or method of construction that should be used for the manufacture of the elements. The designer should consider carefully therefore which options to present to the customer and users.

The structure is however required to meet the following criteria:

- Air-tight shell
- Internal surfaces to be smooth and easy to clean
- Resistance to wear and staining
- Resistance to chemicals
- Staticity or antistaticity

Technical systems

Ventilation in hospital pharmacy cleanrooms is usually archived using a dedicated air handling unit (AHU) and ventilation system, which serves only the cleanroom. Contaminated or hazardous air such as the extract from laminar airflow cabinets is led outside using separate ductwork and a roof fan. If necessary, according to a risk analysis, the AHU can be duplicated. Most of the air supplied has been re-circulated and treated though the AHU, then supplemented with fresh air as required. Indoor air is usually conditioned to a relative humidity of 45% ±10% and temperature of 21°C ±1°C. The operating indoor conditions are decided upon with the user. Air exchange rates in air cleanliness classes D-B are 15...50 1/h. Supply air is normally brought into the room through ceiling diffusers which are equipped with HEPA filters. Extract air is normally removed by floor level extract grilles set within the walls.

One of the basic principles of cleanroom design is to archive the required air cleanliness classification within the specific work spaces. The GMP guideline for pressure between different classes is 10-15Pa. Almost all recently built hospital pharmacy cleanrooms have a control system for regulating pressure differences. The system consists of VAV-dampers and controls for single rooms and a central overall control. VAV-dampers regulate the airflow so that the room pressure remains in its set point.

Cleanroom doors are often interlocked to ensure that only one door at a time can be opened from a single room. When a door is opened the pressure difference control is frozen for a specified period of time. Cleanroom compliance with its given requirements must be demonstrated by regular measurements and documentation. Recently it has become customary to produce documentation of compliance with a validated enviromental monitoring system. The monitoring system collects data of pressure differences, particle counts, temperature and humidity. The system consists of room sensors and particle counters usually situated in the service space above the cleanroom.

Validation

Validation is testing and assurance with a goal of proving that the premises meet the requirements set in standards and guidelines and that the facility can be used to manufacture medicinal products of specified quality. A cleanroom, which is used to manufacture or in any way interacts with medicinal products, has to comply with GMP and EU regulations. GMP requires process validation in chapter 5, Annex 15, “Qualification and validation”. Validation is done by measurements, tests, and experiments. Documentation is a vital part of validation. It could be said that what hasn't been documented has not been validated. Validation is divided into four parts, design, installation, operational and

performance qualification. Validation in hospital pharmacies covers the cleanroom, its technical systems and the process to be carried out in it. All validation is based on a validation plan, which includes testing, measuring, simulating and above all documentation.

Continuous Monitoring of Environmental Conditions Keeps Data and Assets Safe

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Vaisala Oyj, Finland

Extended Abstract

Monitoring environmental conditions in pharmaceutical and healthcare facilities is still often performed manually or mechanically with chart recorders. Building management systems (BMS) or building automation systems (BAS) are also used to monitor conditions, most often environmental parameters like temperature and humidity. However, how companies monitor their controlled environments is changing. As the number of technological solutions grow, operations become more global, and the cost of bringing new products to market increase, many companies choose an automated, continuous monitoring system (CMS) to help them with their challenges. Based on these factors many companies are turning to automated monitoring systems that are secure, easy to validate and expand, and independent of control systems like BMS or BAS.

Automated monitoring systems are computerized systems often used in life science environments such as pharmaceutical and biopharmaceutical cleanrooms, laboratories, warehouses and distribution centers, hospital operating/procedure rooms, as well as in tissue culture laboratories and blood banks. These systems are also used for monitoring high-value assets and processes in museums and archives, semi-conductor and aerospace manufacturing, and IT-server rooms.

The main difference between continuous monitoring and building automation systems is that BMS/BAS are used both to control and monitor, whereas a CMS is used primarily for monitoring. Using two systems to redundantly monitor controlled environments guarantees that the same sensor is not used for two separate activities, controlling and monitoring. This is an important form of insurance against device and communication failures.

The use of parallel sensors also allows for comparison of the parameter values, which can reveal sensor performance issues, thereby reducing false alarms, wasted energy in the control system, and time spent in troubleshooting efforts. In addition, BMS/BAS typically include less expensive sensors that are not as accurate as the high quality, well calibrated sensors used in continuous monitoring systems. Ideally, a CMS will include remote alarming capabilities, which allow the system to communicate directly with personnel. Another valuable CMS feature is its reporting function that allows users to generate data that are unalterable and compliant with GxP regulations.

When choosing a monitoring system for life science facilities and processes, the system should be specified, designed, implemented and tested according to relevant standards and guidelines. For example, the ISPE's guide "GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems" is a useful reference for GxP-regulated companies seeking to adhere to current good practices. In addition to GAMP 5, the ISPE has published several other guidance books, e.g. "GAMP Guide: Records & Data Integrity." These guides contain valuable information on how to manage environments according to current regulatory expectations.

Especially relevant to continuous monitoring systems in GxP-regulated operations, GAMP 5 classifies software systems into separate categories that can indicate how to validate and manage the systems. In the context of a CMS, categories 3, 4 and 5 are most important. Category 3 systems are commercial-off-the-shelf (COTS) systems that are commercially available and commonly used in industry. Category 4 systems enable some user-specific configuration. Category 5 systems are specifically designed and configured for a particular purpose and special use within a company's automation environment. It's self-evident that the validation effort and risks related to automated systems increase from category three to four and five, with the latter necessitating a greater amount of validation resources.

According to GAMP5, requirements for a new automated system should be listed in a User Requirement Specification (URS) document before starting the buying process for a system. Other useful documents include: Traceability Matrix (TM), Functional Specification (FS), Coding Specification (CS) and Design Specification (DS). The need for these separate documents will depend on the category of the monitoring system. For a simple category 3 system, less documentation is required than for a specifically designed category 5 system. The software categories, associated documentation and validation steps are described in detail in the following figure. This graphic outlines GAMP 5 recommendations on validating the software component of a continuous monitoring system.

Regulatory requirements for computerized systems are specified in FDA's Title 21 CFR Part 11 and the EU's GMP EudraLex Volume 4, Chapter 4 and Annex 11. Also, latest EU Good Distribution Practice regulations (2013/C 343/01 and 2015/C 95/01) require monitoring activities when medicinal products or active substances for medicinal products, for human use are stored or transported before administration. Obviously, all monitoring systems should be designed to be compliant with regulatory requirements when used in GxP-regulated operations such as manufacturing medicines for humans

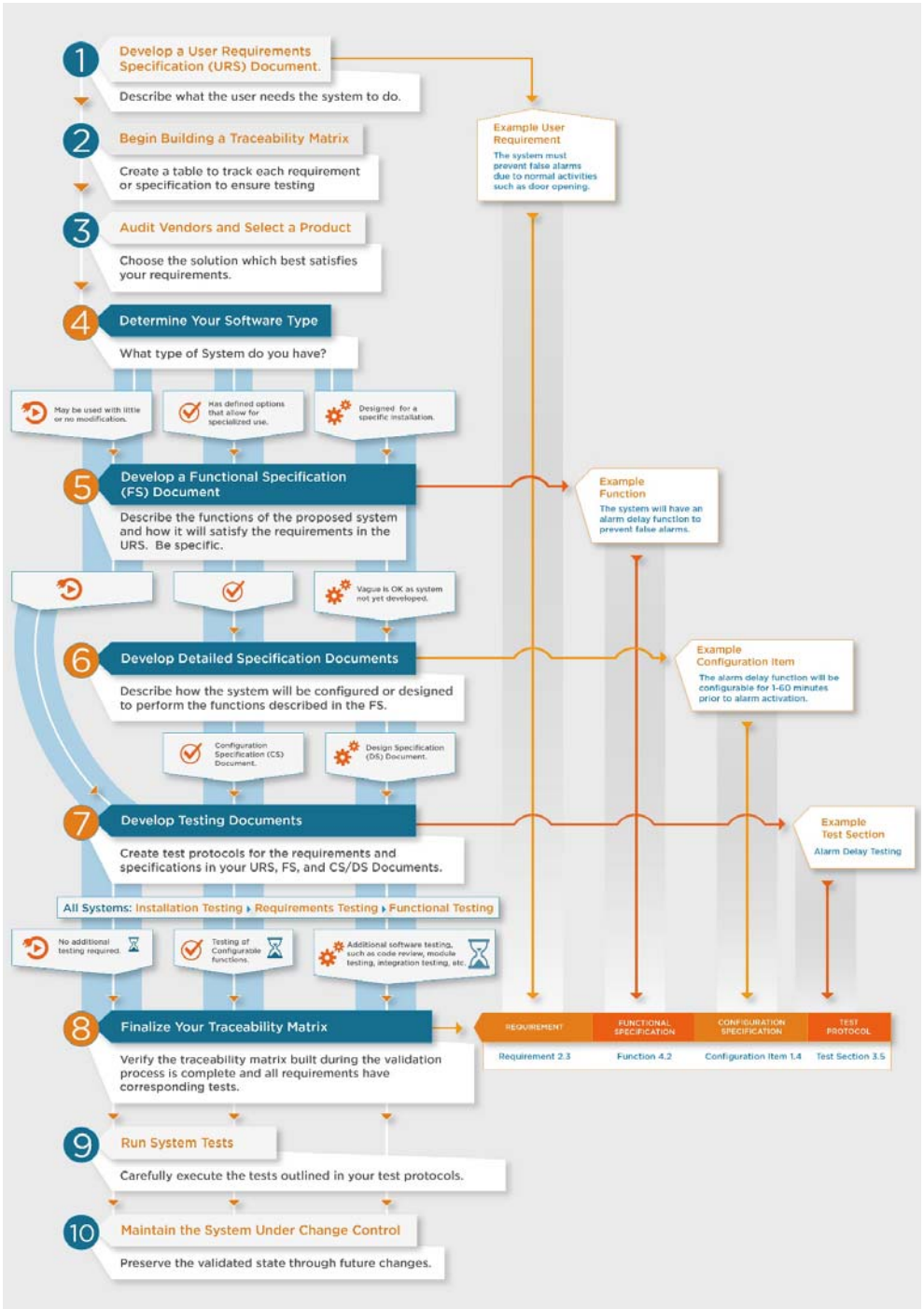
and animals (GMP), transporting finalized medicines from manufacturing site to warehouses or pharmacies (GDP) or while performing human clinical trials with medicine candidates (GCP).

Most continuous monitoring systems used in life science environments seek to help firms comply with regulatory guidance. However, the best continuous monitoring systems have some key additional features. Ideally, the system should be able to monitor many different activities and parameters simultaneously. Typical monitored parameters are temperature, humidity, different gas concentrations like CO2 concentration, differential pressure, door contacts (signals door closures and openings), particles, flow, fluid level, pH and electrical properties. The selected system should also be able to integrate analog hardware that outputs 4...20 mA, 0...5 V or 0...10 V for monitoring any additional parameters.

For global operations in different manufacturing and distribution locations, an enterprise-wide monitoring system can provide several benefits. Enterprise systems make validation and life cycle management activities in global operations significantly less cumbersome. Finally, a vendor that is experienced in GxP-regulated applications can increase a firm's knowledge and help with risk assessments, fast system deployment and validation, change management and system retirement activities.

Throughout the life science industries — from pharmaceutical research, manufacturing, medical devices to biotechnology — guidance and regulatory enforcement strategies have been recently re-evaluated with a focus on data integrity. This trend continues with the March 2018 MHRA publication of "GXP Data Integrity Guidance and Definitions." Data integrity considerations apply to manual, paper-based as well as electronic systems. When paper-based systems are used for monitoring, typical data integrity problems are easy to predict: users forget to collect data, write down wrong data by mistake, or even deliberately select to report falsified data. With automated systems data integrity issues become more complex and require an understanding of software and network connectivity basics. In terms of managing risks to data integrity, the most important considerations for using automated continuous monitoring systems are:

- Access to the system must be controlled by individual login IDs, user names and passwords.
- Specific software features (like user-specific rights and access control permissions) should be used to create different authority levels in the system, fulfilling the regulatory requirement for segregation of duties.
- Software should include "device check" functionality that guarantees the origin of the data, and "validation alarms" to guarantee the validity of collected data.
- Only software, not users, can create data records, and these are non-editable and inerasable.
- Additions, changes, modifications, and deletion of data are recorded by an audit trail.
- Ideally calibration data is stored in each device, as well as in the software, ensuring accuracy specifications of devices are also tracked.


1
Develop a User Requirements Specification (URS) Document.
Describe what the user needs the system to do.
Example User Requirement
The system must prevent false alarms due to normal activities such as door opening.
2
Begin Building a Traceability Matrix
Create a table to track each requirement or specification to ensure testing
3
Audit Vendors and Select a Product
Choose the solution which best satisfies your requirements.
4
Determine Your Software Type
What type of System do you have?
May be used with little or no modification.
Has defined options that allow for specialized use.
Designed for a specific installation.
5
Develop a Functional Specification (FS) Document
Describe the functions of the proposed system and how it will satisfy the requirements in the URS. Be specific.
Example Function
The system will have an alarm delay function to prevent false alarms.
Vague is OK as system not yet developed.
6
Develop Detailed Specification Documents
Describe how the system will be configured or designed to perform the functions described in the FS.
Example Configuration Item
The alarm delay function will be configurable for 1-60 minutes prior to alarm activation.
Configuration Specification (CS) Document.
Design Specification (DS) Document.
7
Develop Testing Documents
Create test protocols for the requirements and specifications in your URS, FS, and CS/DS Documents.
Example Test Section
Alarm Delay Testing
All Systems: Installation Testing ▸ Requirements Testing ▸ Functional Testing
No additional testing required.
Testing of Configurable functions.
Additional software testing, such as code review, module testing, integration testing, etc.
8
Finalize Your Traceability Matrix
Verify the traceability matrix built during the validation process is complete and all requirements have corresponding tests.
REQUIREMENT
FUNCTIONAL SPECIFICATION
CONFIGURATION SPECIFICATION
TEST PROTOCOL
Requirement 2.3
Function 4.2
Configuration Item 1.4
Test Section 3.5
9
Run System Tests
Carefully execute the tests outlined in your test protocols.
10
Maintain the System Under Change Control
Preserve the validated state through future changes.

- All graphs, system reports and environmental reports should be easy to read, fulfilling the requirement of human readable data.
- All measurements should be synchronized against the system's server clock for an easy comparison of data sets.
- Software should be able to preserve data integrity and manage multiple time zones automatically.
- Thorough system documentation should be available to help with qualification, validation and future usage of the system: User requirement specification, Functional specification, Traceability matrix, Risk assessment, Validation documentation and reports.
- Metadata should be easy to access and provide contextual information on all data.

Conclusion

Maintaining environmental conditions within product and process specifications is a critical part of GxP operations. To protect their products and processes, many firms now use a continuous monitoring system in parallel to their control systems to provide more accurate sensing, real-time and remote alarming, and reports that can be used to show compliance and data integrity under an audit. A parallel system devoted to monitoring and alarming functions, without control elements, is also much simpler to validate, expand and change. For a fully compliant software validation, we recommend the GAMP5 methodology to ensure monitoring system software performs throughout its life cycle. The categories defined by GAMP 5 show how the effort level required in validation is related to system complexity. A GAMP approach to system deployment, validation, and maintenance will increase the lifespan, usability, and compliance of CMS software.

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Reconstitution Robotics in Cleanroom

Marja Jaurakkajärvi

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Backgroud

Many times commercially available medications require to be prepared to a ready-to-use dose prior the parental administration. Often, these medications are available in vials that consist the drug(s) in dry powder or concentrated liquid which has significantly longer shelf lives than they would otherwise have in their ready-to-use form. Preparing these drugs is consisted of following steps: i) adding the correct solvent and dissolving the powder (reconstitution) and ii) withdrawing the correct dose of the liquid to syringe or infusion bag (compounding). These phases are very prone to mistakes and, the prevalence of errors is high. An observatory study in wards on UK hospital revealed there was at least one error in preparation or administration in 49 percent of the doses. Most of the preparation errors occurred in so-called multiple step preparations and, one percent of these errors were classified to be severe to the patient. In addition, there are numerous studies which showcases the exposure of hospital personnel to drug substances during the compounding or their daily routines. Positive samples have been found from skin, clothes and urine. The compounding itself is strenuous and upper limb disorders (ULD) have been reported. Kuopio University Hospital evaluated ergonomics and skin and respiratory track reactions associated with parental antibiotic reconstitution among nurses and ward pharmacists. All problems were found to be common and, the use of laminar flow cabinet was suspected to increase the prevalence of musculoskeletal problems.

One way to tackle these problems in compounding is to implement detailed guidelines. A cross-sectional study on exposure to cyclophosphamide in The Netherlands reveals that surface and glove contamination have been decreased 3-4 fold between 1997 and 2000 amongst nurses working at outpatient clinics or oncology wards, likely because of better practises. Another way to interfere to these problems is to implement

centralised intravenous admixture services (CIVAS). In Finland, there are 24 hospital pharmacies and they are obligated to follow Good Manufacturing Practises (GMP) to ensure identity, strength, quality, and purity of the drugs they compound. But in a global scale, that is not always the case.

In 2012, there was 7.500 compounding pharmacies in US that were under the authority of Board of Pharmacy and underwent FDA inspections rarely. They did not have any obligation to follow GMP regulations and only two percent of them participate participated industry's voluntary accreditation program. However, in 2012, there was a nationwide meningitis outbreak that sickened 778 patients, including 76 deaths after receiving contaminated steroids prepared in New England Compounding Center. The pharmacy owner was charged with second-degree murder and in 2013, US Congress passed the Drug Quality and Security Act to bring more compounding pharmacies under the authority of FDA. A new category of outsourcing pharmacies was created and today 70 firms has been registered.

Many times the centralisation is started on hazardous drugs but the trend is slowly expanding the antimicrobials, anaesthetics and analgesics. Unfortunately, no regulation can prevent a human error and, the third way to work around the problems is to automate. So far, roughly one hundred automation systems have been implement for improving IV compounding and over ten different kind of robotic systems are on the market, some of them available only locally. Slowly, automation is spreading around the world.

Content

In this presentation, a piece of the history, a bits of here and there, NewIcon's IV robots and a brief literature review on safety, accuracy and cost in comparison of manual and automatic compounding are presented. Outcomes of the studies are likely to vary depending on the system in use, however, they will imply what could be expected.

In 2008, a German study revealed that 53 percent of the manually prepared solutions and 16 percent of the machine-made solutions deviated more than ± 5 percent. This study was conducted with one of the first systems in the market. Another study in Brigham and Women's Hospital in US came to conclusion that robotic device improved staff safety and accuracy significantly. In this study, staff safety events were decreased to 2.9 percent and dose deviations to 0.9 percent. Material costs were decreased 56 percent. However, there was 47 percent increase in drug preparation time. University in Arizona had a different approach and they simulated 1000 compounding cases. Based on the simulations they estimated that utilisation of robotics could prevent 4.520 medication errors and bring $288.350 savings annually.

University hospital in Brussels measured in 2015 environmental contamination, product contamination and staffs exposure following the preparation of IV bags with a robot. Contamination was mainly observed inside the robot, also after cleaning. Manually prereconstituted vials entering the robot were contaminated but powder vials were not. Also all of the outer parts of the gloves were contaminated but no contamination was found on

inner parts of the gloves, stationary, personal air samples or urine samples. Therefore, a low level of environmental and product contamination was observed but no measurable exposure of the staff.

The suitability of the CIVAS is highly depended on the shelf life of the drug; how long it can be safely in store prior the administration. Unfortunately, the information about this is a bit limited. Rigge and Jones published a study on piperacillin / tazobactam and reported that drug is stable in seven degrees temperature in buffered sodium chloride formulation in non-PVC bags for 58 days and in sodium chloride formulation for 17 days. Also Cefaxolin and cefuroxime sodium have been reported to be stable enough to be prepared in advance by a centralised intravenous admixture services. In many of the countries, it is still enough to refer to stability studies and not to conduct one.

Conclusion

Globally, there is evident need to improve the patient and occupational safety in reconstitution and compounding by implementing guidelines and shifting to centralised processes. The quality of centralised intravenous admixture services may be significantly improved by utilisation of automation, nevertheless the country is following the GMP or not. Fortunately, Finland is one of the tightest countries in the world what comes to GMP. Therefore, Finland is likely be the best development ground in the world robotics and it pushes the robotic solutions to reach even higher level of performance than ever.

General Requirements for Good Projecting of Facilities through GMP

Esa Högel

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Abstract

There are different alternatives in cleanroom constructions for flooring, walls, doors, windows and ceiling. The customer preparation for coming project is needed and should be agreed: customer room card, technical parameters of cleanrooms and medias for process equipment, the room parameters of clean-rooms (T, H, Pa), summary of medias for process equipment (Equipment Utility Matrix), supplier quota-tion, clear definition of interfaces and time schedule. The customer control practice about suitable supplier for the project includes: similar references from same customer field and from last two years, enough sufficient technical and financial resources, competitive prices and purchasing procedures, own QA-department and is able to show about own qualification procedures some, references, knowledge about local and global requirements of authorities, quality certificate ISO 9001, audited suppliers, competence and common understanding about customer process etc.

HOSPITAL SESSION

HOSPITAL SESSION

Protective Supply Air Distribution in Hospital Isolation Rooms

Petri Kalliomäki & Hannu Koskela

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Abstract

This study examines healthcare worker (HCW) exposure to patient exhaled airborne pathogens in hospital isolation rooms. Typically, negative pressure is applied to isolation rooms to prevent airborne infections escaping the room. However, negative pressure does not control the airflows inside the isolation room. This study investigates the effect of two different supply air distribution modes on HCW exposure to patient exhaled air: overhead mixing ventilation and local downward air supply. The experiments were carried out in an isolation room model built to a ventilation laboratory. Breathing thermal manikins were used to simulate the HCW and the patient. Smoke visualizations and tracer gas measurements were used to qualitatively and quantitatively assess the HCW exposure. The results show that supply air distribution notably affects the exposure and should be designed carefully in order to decrease the possible exposure. Especially the local downward ventilation showed potential to reduce the HCW exposure throughout the room compared to typical overhead mixing ventilation.

Introduction

Typically, patients with airborne infections are placed into negative pressure isolation rooms in hospitals. The negative pressure directs the airflow towards the isolation room thus preventing containment failures from happening. Inside the isolation the room the air flow patterns govern the dispersion of airborne pathogens. Typically mixing ventilation is recommended for isolation room ventilation (ASHRAE 2013). However, this does not

always guarantee efficient mixing and quick dilution of airborne contaminants especially close to source. On the other hand, local supply air distribution mode can provide fresh air to breathing zone directly and hence yield more effective solution in reducing high contaminant concentrations already close to source. Thus proper supply air distribution can provide additional protection to healthcare workers (HCW) (complementary to personal protective equipment) and decrease the exposure risk to patient released airborne pathogens. In this study, the effect of two different supply air distribution modes on HCW exposure to airborne infections were tested: local downward and overhead mixing ventilation. The local downward air distribution mode provides fresh air to the occupied zone locally downward from the ceiling and mixing ventilation distributes the fresh air along the ceiling evenly over the room.

Methods

Isolation room model

The experiments were carried out in a simplified full-scale isolation room model. Figure 1 shows a schematic of the model layout and a picture inside the isolation room model. The model room was 4 m wide, 4.7 m long and 2.6 m high. Two different supply air distribution modes were examined in this study: overhead mixing ventilation and local downward ventilation. Three different supply air diffuser locations were tested: far away from the patient (A, See Figure 1), in the middle of the ceiling (B) and over the patient bed (C). There were two extracts in the model: the main extract was located in the ceiling level and a smaller one on the floor level simulating toilet extract. Constant supply air flow rate (169 L/s) and exhaust air flow rate (186 L/s) was used in the experiments (corresponding to 12 air changes per hour). The supply air temperature was 19 °C and the room air temperature 22.5 °C. The room had 800 W heat load (HCW 90 W, patient 90 W, lighting 110 W and solar load and equipment 510 W). In the experiments the HCW and the patient were simulated with breathing thermal manikins. The HCW manikin was simulated with a realistic manikin and the patient with a simplified heated dummy. HCW exposure was assessed in four different location inside the isolation room model: far away from the patient (1, see Figure 1), at the end of the patient bed (2), next to patient (3) and leaning over the patient (4). The patient manikin was lying on the bed with backrest tilted 20° upwards from the horizontal plane throughout the experiments. The nose and mouth of the manikins were attached to pumps enabling the simulation of breathing. The tidal volume of the breathing was set to 10 L/min and the frequency to 14 1/min. The exhalation temperature was set to 34 °C. These values corresponded to typical adult breathing parameters (Gupta et al. 2010, Höppe 1981).

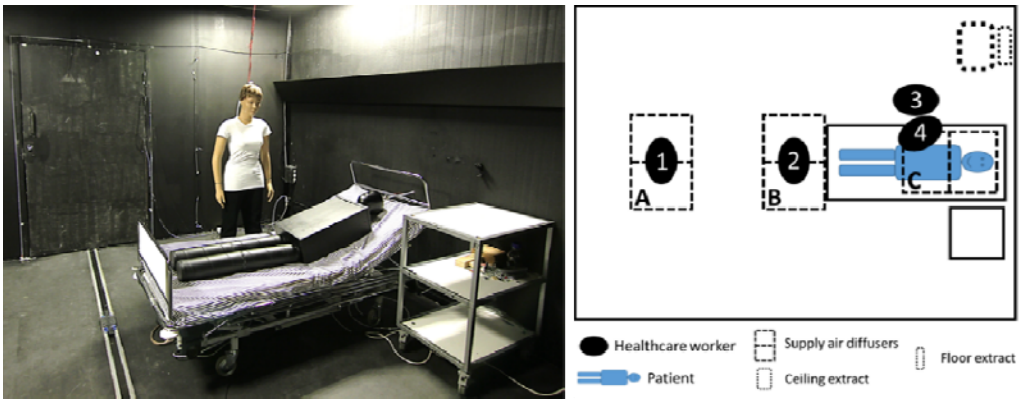

Figure 1. Picture of the isolation room model (on left) and a schematic of the layout (on right) showing the different HCW manikin (1-4) and supply diffuser (A-C) locations.

Experimental methods

Smoke visualizations and tracer gas experiments were carried out to assess the performance of the two supply air distribution modes and HCW exposure to patient exhaled airborne tracers. Smoke visualizations were carried out in order to visualize the supply air distribution and the dispersion of the patient exhaled air. In the experiments the smoke was generated with a smoke machine and dosed to exhalation of the patient or to supply duct. Additional lights were used inside the isolation room model to illuminate a sheet where the smoke flow was examined. The smoke movements were recorded with a digital camera (Canon 7D, Canon Inc., Japan). Still images of the recorded videos are shown in this paper.

Tracer gas measurements were carried out in order to quantitatively assess the local average HCW exposure to the patient exhaled airborne contaminants. A tracer gas (SF6, Sulphur hexafluoride) was used as a tracer to mark the patient exhaled air and to simulate airborne infections. A tracer gas analyzer (Brüel&Kjær type 1302, Brüel&Kjær A/S, Denmark) was used to measure the tracer concentrations from different points inside the isolation room model. The sampling interval of the analyzer was c. 40 s. The tracer gas was dosed with a mass flow meter to the patient exhalation. Prior to dosing, the tracer gas was mixed with air and the mixture supplied to the isolation room with the patient manikin exhalation through nose. The tracer concentration in the isolation room model was allowed to reach steady state before actual measurements from the extracts and from the inhalation of the HCW began. Tracer concentration in the HCW inhalation was monitored for an hour to increase statistical significance (sample size) (Kierat et al. 2018). The exposure of the HCW manikin was assessed with so called susceptible exposure index (Qian and Li, 2010). The index is defined as:

$$s = \frac{C_i - C_s}{C_e - C_s},$$

where C_i is the tracer concentration in the inhalation of the HCW manikin, C_s the tracer concentration in the supply air and C_e the tracer concentration in the exhaust. In steady state conditions average concentrations can be used in the equation. If the tracer concentration in the supply air is close to zero, the equation above reduces to:

$$s = \frac{C_i}{C_e}.$$

Basically, the index scales the locally inhaled tracer concentration with exhaust concentration and the higher the value the higher the local relative exposure.

Results

Still images of the recorded smoke visualizations are shown in Figure 2. Only the visualizations with the supply air diffusers above the patient are shown. The dispersion of the patient exhaled air with the local downward ventilation is shown on left and with the overhead mixing ventilation on right. The visualizations illustrate that the downward air supply directed the exhaled air away from the HCW's breathing zone more efficiently than the overhead mixing ventilation. Hence the HCW exposure close to patient (source) is expected to be smaller with the local downward ventilation in the illustrated case.

Figure 2. Smoke visualizations of the dispersion of the patient exhaled air. The case with local downward supply is shown on left and with overhead mixing on right. The diffusers were placed in the ceiling above the patient in both cases.

Tracer gas measurement results are shown in Figure 3. As with the smoke visualizations, only the results when the supply diffusers were above the patient are shown. Tracer gas measurements showed notable difference in the exposure index values when the HCW was leaning over the patient where the local downward air supply mode produced substantially smaller exposure than the overhead mixing ventilation. Further away from the patient the differences in susceptible exposure index values between the two supply air

distribution modes were found to be smaller. Similar trend with differences were found with other supply air diffuser locations as well.

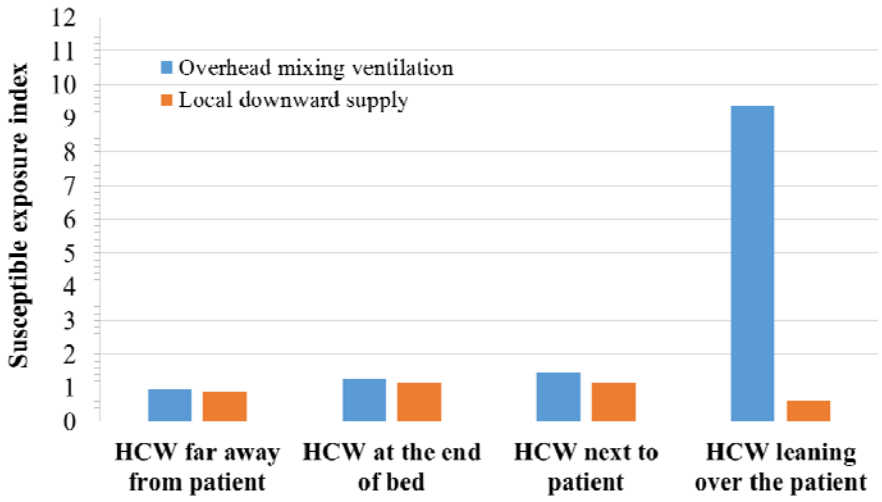

Figure 3. Tracer gas measurement results when the supply air diffusers were located in the ceiling above the patient.

Conclusions

Both the smoke visualizations and the tracer gas measurements showed that supply air distribution affects highly the patient exhalation dispersion and the HCW exposure to it especially close to the source. Local downward air supply was found to have the potential to reduce the exposure of the HCW to patient exhaled airborne contaminants. However, the performance of this and other local air distribution methods in isolation rooms should be studied in more detail in the future. For instance, thermal comfort of the patient and HCW should be examined carefully in order to maintain comfortable thermal environment together with low exposure values.

Acknowledgements

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New Standard for Ventilation in Hospital - Isolation Units

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Abstract

The CEN working group for “Ventilation in Hospitals” is currently working with part 3 “Ventilation in isolation units”. The background for this part is the lack of common European guidelines for ventilation in isolation units. There are some existing national and international guidelines, which are slightly different from each other. This lecture will explain the strategy for the new CEN-standard, where the most important issues are: source strength, recovery and air tightness.

The most common strategy in the Nordic countries (as well as in Europe) has until now been to rely on pressure difference between corridor, airlock and patient room. This is now turning into the fact that the only way to control contaminants is to have enough air changes, combined with the right airflow direction. To prove this, the main tests will be recovery time and air tightness of the construction around the unit. There will also be some examples of how this principle can be solved by different technical solutions.

Operating Room Ventilation: CFU Concentration Measurements

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Abstract

Operating room air quality has a great influence on patient safety. Microbes are often carried to the surgical wound via operating room indoor air. Currently in Finland there is no valid standard for design and implementation of operating room ventilation. Additionally, the air quality is not required to be monitored or verified after commissioning. However, European Committee for Standardization (CEN) is working on European-wide standard "CEN/TC156 WG 18" which focuses on hospital air quality and ventilation design. In the standard the indoor air quality is determined based on the microbial concentration, and according to it, operating rooms are divided into two purity classes.

In this study, the microbial concentration of indoor air in Finnish operating rooms was examined during actual surgeries. Samples were taken in ten hospitals in a total of 32 operating rooms. The results were compared to the limits set by the standard to determine how well the operating rooms meet the requirements. Based on the results, the operating rooms meet the limits of the standard well. Most of the samples were inside the Ultra Clean Air limit. Clean Air limit proved out to be so high that all the samples met the value distinctly.

Introduction

Operating room air quality has a great influence on patient safety. Microbes are often carried to the surgical wound via operating room indoor air. (Wang et al. 2010) The basis for designing operating room ventilation is to protect the patient from contaminants from

other people. Properly functioning ventilation also protects personnel and the surrounding environment from microbes of the surgical wound. (Dascalaki et al. 2008)

Currently in Finland there is no valid standard for design and implementation of operating room ventilation. Additionally, the air quality is not required to be monitored or verified after commissioning. The National Building Code of Finland D2 (2012) determines the minimum requirements for ventilation and indoor climate. However, it does not define specific limits for operating rooms. Instead it states that operating room ventilation must be designed individually. Also Finnish Indoor Air Classification (2008) instructs and defines classes for the indoor climate but there are no separate criteria for the ventilation of operating rooms.

However, European Committee for Standardization (CEN) is working on a European-wide standard “CEN/TC156 WG 18” (2017). Its objective is to create common practice for the hospital and healthcare indoor climate in Europe and to set minimum requirements for it. In the standard, the quality of operating room indoor air is determined on the basis of the microbial concentration both operational and at rest. In addition, the standard defines acceptable recovery times during which the microbial concentration level must revert back to the rest mode level after the contamination spike of an operation. CFU (Colony forming unit) concentration has been chosen to represent the operating room air quality. A CFU is considered to be a microbe or other particle emitted from a person (excluding the surgery patient).

Operating room air quality has been studied mostly during At Rest mode or simulated surgery. Operational CFU concentration has been measured very little. It raises a question how well Finnish operating rooms align with the limits of the standard. In this study, the microbial concentration of indoor air in Finnish operating rooms was examined during actual surgeries. The objective was to measure various rooms extensively throughout Finland and compare the results with the limits of the standard. The results would possibly provide more information to the CEN draft standard project group.

Draft Standard CEN/TC156 WG 18

“CEN/TC156 WG 18” (2017) is a draft standard whose purpose is to create European-wide standards and regulations for healthcare indoor air. Part 2 of the standard examines the specialties of operating rooms and can be further divided into two parts based on the content. The first part defines common performance requirements for operating rooms. It defines the design criteria for the ventilation and the purity criteria for the rooms. The second part aims to unify the verification and testing methods of the operating room ventilation. Thus, it orders hospitals to monitor, test and maintain the whole operating suite system often enough in order to ensure that everything functions correctly.

“CEN/TC156 WG 18” classifies operating rooms into two levels according to the microbe concentration of the indoor air. Those levels are normal risk of infection level “Clean Air” and high risk of infection “Ultra Clean”. The health care personnel, often a

surgeon, decides which level of purity is required. The maximum CFU concentration limits during operation are set for both levels. Those levels are:

- Clean Air < 100 CFU/m3
- Ultra Clean Air < 10 CFU/m3

The standard also defines operational microbe concentration as the factor for designing the ventilation of the operating room. When the ventilation is functioning properly and as designed, people are the only source of contamination in the surgery. Thus the number of personnel and the quality and type of clothing have a huge effect on the supply air flow rate.

Methods

Air quality was measured in 32 operating rooms in ten hospitals throughout Finland. The measurements were performed in 2017¬ – 2018. The primary measuring parameter was operational CFU concentration but in addition other supportive surveys were performed. The purpose of the support surveys was to ensure that the ventilation is working as planned.

The hospitals allowed only one sampling person to enter the operating room during surgeries. This person was wearing a cleanroom suit and under it a surgical clothing provided by the hospital. Prior entering the operating room each sampling device was purified with A12t 80% ethanol mixture. Also the overall shape of the operating room and its ventilation were inspected.

Multiple samples were taken in each operating room. The number of samples depended on the duration of the surgery. Only three samples were taken during short operations and they were all obtained from the critical protected zone which is situated around the operating table. During longer operations up to six samples per room were taken. Two of those were from the operating table, two from the instrument table (also protected zone) and two from the periphery area.

The air sampler was positioned on a table (h=0,7m) and a gelatin filter was attached to it. After that, the table was transferred to the desired location and the sampler was started. The air sampler suctioned indoor air for 10 minutes (50L/s, total of 500 liters) through the gelatin filter. During that time microbes stuck to the filter. When the sampling was finished the filter was removed from the sampler and put carefully to an agar plate. Once all the samples were taken the measurement was finished and the sampling person exited the room.

The objective was to place the sampler as close to the operating table as possible but due to patient safety the surgeon allowed the sampler to be placed approximately 1 – 1,5 meter from the surgical wound. The periphery area samples were taken from notably farther off the table where the air was considered to be as diluted as possible. However, the sampling locations varied considerably due to variation in operating room layout,

fittings and activities. Instrument table is considered to be protected zone in accordance with the draft standard.

After the sampling the filter filled agar plates were transferred to a laboratory where they were incubated in 35 °C for 48 hours. After that the cultured colonies were counted and analyzed. A closed reference plate was incubated along with the samples from each operating room. This was done to ensure that the samples were not contaminated during the process. Air sampler suctioned 500 liters of air during one sampling so the smallest observable microbe concentration was 2 CFU/m3. If the sample did not contain any cultured microbes, the concentration could only be deduced to be less than 2 CFU/m^3.

Results and Discussion

The study conducted measurements in a total of 32 operating rooms, 21 of which were laminar air flow systems and 11 dilution mixing systems. A total of 92 samples were taken from laminar operating rooms and 45 from dilution mixing rooms. These systems differ greatly from each other, but the draft standard imposes same operational CFU concentration demands for both systems. The results are displayed anonymously as the information regarding individual hospitals is confidential.

The operating rooms that were measured differed from each other also in other ways: age, size and supply air flow varied plenty. However, the air change rate of all the operating rooms exceeded the value of 17. The supply air flows and air change rates are shown in the Figure 1 below.

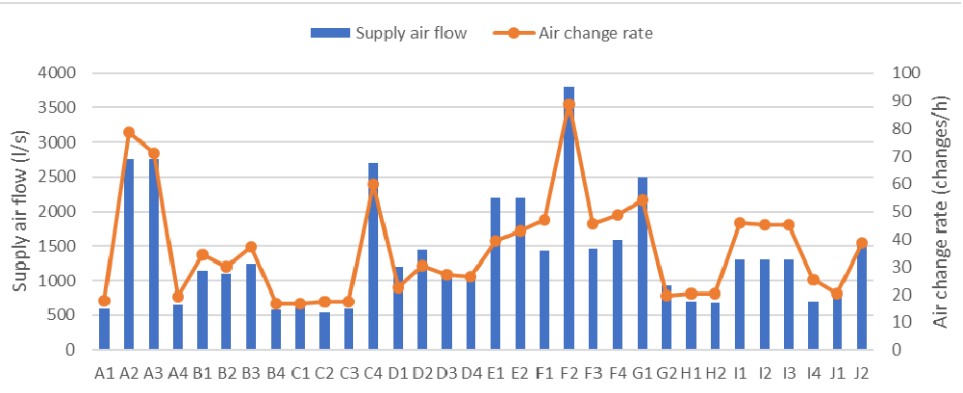

Figure 1. Supply air flows and air change rate of the operating rooms

Operating room has to maintain a positive air pressure compared to its surroundings in order to ensure that the leak air moves away from the room and not vice versa. A suggested positive pressure level is 10–15 Pa. This was achieved in only four operating rooms. These three rooms had tight doors which probably helped to reach this level of pressure differential. Most rooms had a clear 1¬–2 cm door gap which allowed the leak

air to flow through. However, the pressure differentials were positive with the exception of four rooms, two of which was slightly negative pressure and the other two in balance with the surrounding space. The pressure differentials compared to surroundings are presented in Figure 2 with a recommended pressure differential level for operating rooms (10 Pa).

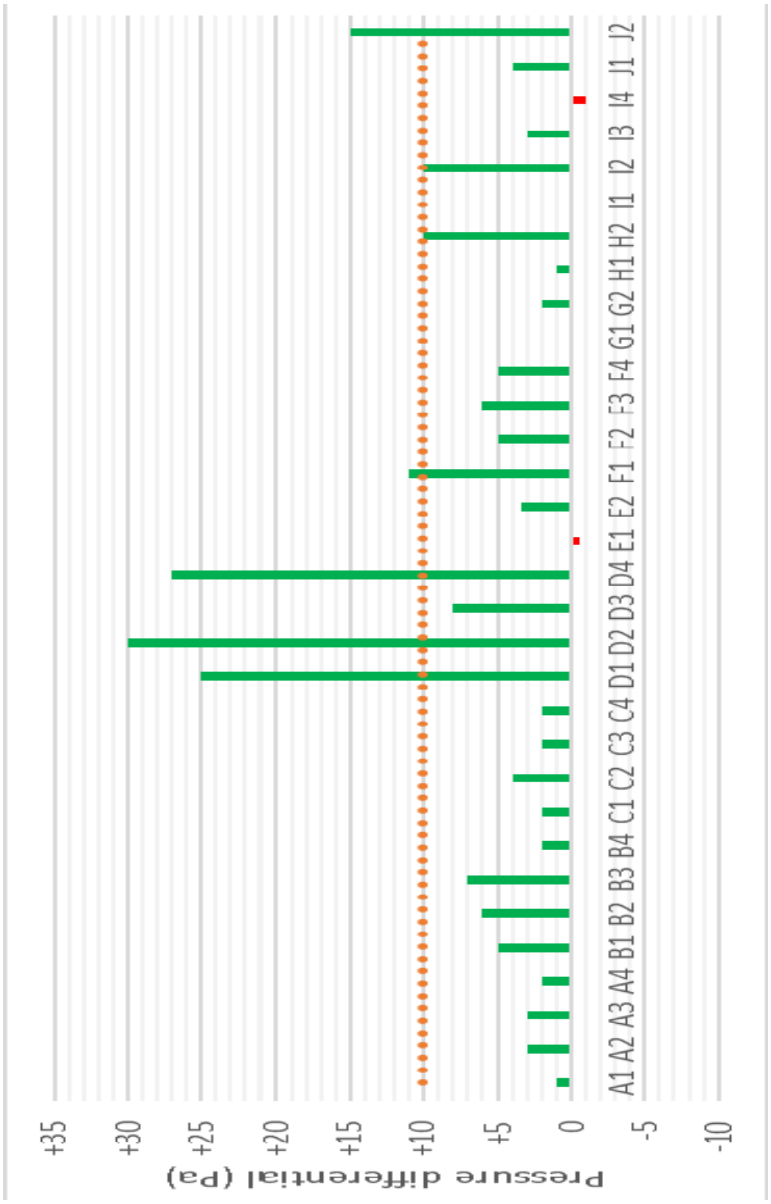

Figure 2. Operating room pressure differentials compared to surrounding area

Air change rate explains how many times indoor air changes during an hour. Thus it is a good indication of the level of ventilation. The higher the air change rate, the greater the amount of air in the room processed through the ventilation system. (Seppänen 2008) It could therefore be assumed that the operating rooms with large air change rate would have a lower CFU content. The measurements showed the indicated assumption to be true, although a direct relationship does not seem to occur. It was also possible to reach very low microbe concentrations with lesser air change rate values.

Every operating room measured reached the Clean Air purity class with considerable margin, based on both average value and peak value. Only two of the rooms had clearly higher values and exceeded the limits of Ultra Clean Air purity class with both average and peak value. The averages of all the other operating rooms were below the limit, and only a few individual samples surpassed it. The mean values and the highest values of the measurement results are shown in Figure 3 together with the limit values of the draft standard. The highest individual sample included 38 CFU/m^3 while the other higher values were around 30 CFU/m^3. So, the Clean Air purity class CFU limit (100 CFU/m^3) seems to be very high compared to the measurements.

Conclusions

A total of 32 operating rooms in ten hospitals were measured for the study. Rooms with both dilution mixing and laminar air flow system were studied. The hospitals decided which operating rooms they wanted to be measured, and thus the rooms varied a lot (age, size, air flow etc.). A total of 137 air samples were taken, 3-6 from each operating room. Because of all this variation, operating rooms cannot be directly compared with each other. There are a great deal of variables and their influences to CFU concentration level cannot be directly explained. However, the overall level of microbe concentration in Finnish operating rooms can be estimated and the results can be compared with the draft standard purity class levels.

The results show that microbe concentration level in measured operating rooms is quite low compared to the draft standard purity class limits. Most of the rooms reached the Ultra Clean class while the Clean Air class limit seems to be very high as every room reached it with ease even with smaller supply air flows. This raises a question how low supply air flow could be when the CFU concentration approached the value of 100 CFU/m3. An operation room used for more simple measures has an air change rate of around 10. Would this be enough to reach Clean Air class if the staff used surgical clothing? Also the pressure level would have to be taken into consideration as the room should be positively pressured compared to surroundings.

All but two operating rooms reached the Ultra Clean class based on mean value. Seven rooms had a peak value of over 10 CFU/m3. In many of these cases the peak values were only anomalies as the other samples indicated very low concentration levels. If the results had indicated high CFU concentration levels, a thorough investigation on an operating room is required. In that case it is not enough to examine only the ventilation or

cleanliness. Additionally, staff behaviour and clothing have to be taken into account as those have a significant impact on the air purity level of an operating room. Generally, the air purity level of Finnish operating rooms is at a good level compared to the draft standard. The results suggest even that Clean Air limit seems to be unnecessary high. The whole topic requires a more specific further research related to microbe concentration, surgical clothing and more in-depth analysis of causal relationship. Additionally, it would be advisable to develop clear guidelines which would help to resolve what could be the cause for high microbe concentrations.

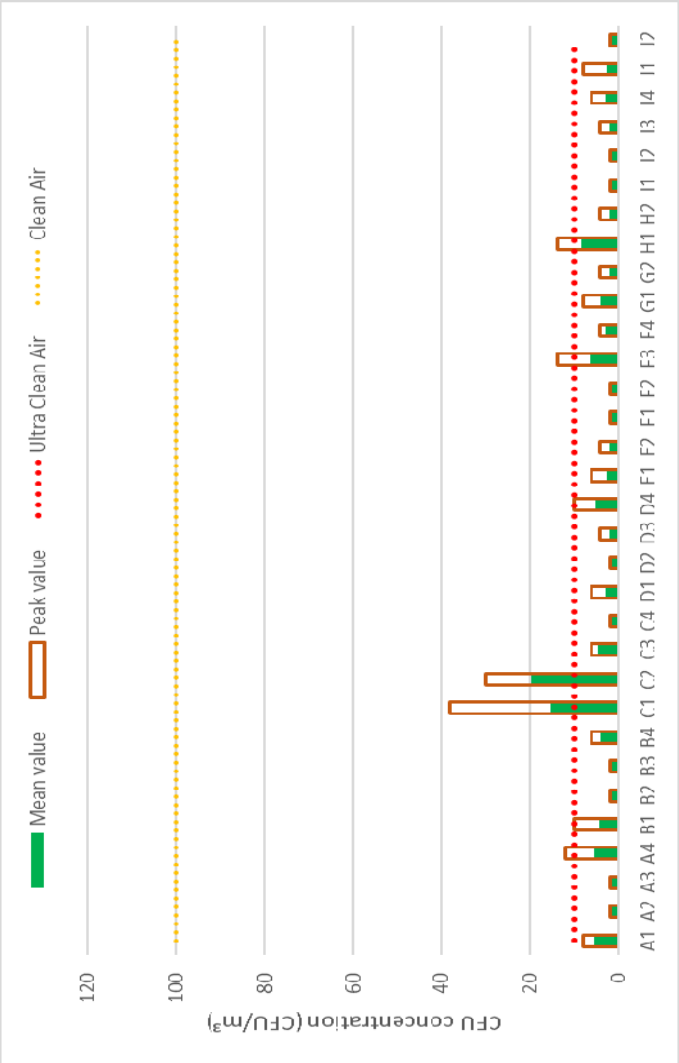

Figure 3. CFU concentrations of the operating rooms and CEN/TC156 WG 18 purity class limits

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Ensuring Operational Cleanness in Hybrid Operation Rooms with Modern Imaging Systems

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Introduction

Hybrid Operating Rooms (ORs) are ORs in which advanced imaging capability using devices such as C-Arms, CT (computed tomography) or MRI (Magnetic resonance imaging) combined with a fully functioning operating suite. The Hybrid OR configuration allows surgeons to combine a diagnostic procedure (by using real-time image guidance) with a therapeutic one, thus giving better surgical outcomes and at the same time being less traumatic for the patient. Such operation rooms are becoming common in modern hospitals. Compared to conventional operating rooms Hybrid Operating rooms are much more complex due to high degree of medical installations as well as complex and extensive operating lay-out. Our experience from multiple realized Hybrid OR installations is that they pose a specific design and operational challenges especially related to ventilation such as coordination of physical installation and maintainability, obstruction caused by medical installations, extensive heat loads and location of hygienically critical areas that should be tackled by interdisciplinary design approach between solution suppliers of medical ventilation and other disciplines. Hybrid operation rooms challenge especially old mantras in operating room ventilation.

Ventilation of Hybrid Operating Rooms

Traditionally a common air distribution principle for conventional ultra clean air operation rooms has been Unidirectional flow (UDF). This technology works as designed only when

there is no or very low disturbance of the air streamlines, which is not the case in most operations [1]. Moreover, the air cleanliness is only aimed in the area beneath the plenum when not affected by lighting or other devices disturbing the airflow. A two-sided problem, the challenge of fitting the laminar flow device into the physical installation and inability of vertical down-flow to reach critical operating areas obstructed by devices, has been shown to be present especially in hybrid operating rooms [2]. Furthermore, the operational instruments for intervention are often prepared during the operation further away from the operational area. Therefore, the area to be covered for air cleanliness can be much larger than just the area around operating table. Halton Vita OR Space 5 solution, a smart controlled-dilution flow provides the ultraclean conditions into the whole operating room. The solution has gone throughout verification by simulated and recently also in live operations for both conventional and hybrid operating rooms [3, 4] and is used in all 36 operating rooms in Nya Karolinska Hospital, Stockholm. This solution has also been applied to various Hybrid operating rooms with a success (Figure 1).

Figure 1 Hybrid Operating Room in Nya Karolinska Hospital, Stockhom, Sweden, equipped with Halton Vita OR Space 5 ventilation system

Case Study Ghent University Hospital

Ghent University hospital in Belgium had a need to build a new hybrid cardiac catheterization lab for transcatheter aortic valve implantation (TAVI) operations [5]. Such operation is an alternative for open surgical aortic valve replacement in selected patients with high operative risk. For this reason, an Ultra Clean hygienic level was set as criteria for the operating room environment. Additionally, hospital wanted to ensure excellent working environment for the operational staff (protection from radiation, thermal comfort, acoustic comfort with low noise level). In a hybrid cardiac catheterization lab, a complete C-arm is attached to the ceiling together with multiple other ceiling mounts whereas the operational instruments for intervention are prepared further away from the operational area (Figure 2). Therefore, the area to be covered for air cleanliness is much larger than just the area around operating table. Additional challenges to ventilation design in such environment are for example high, concentrated heat loads and location of the operating personnel around the critical areas of sterile instruments.

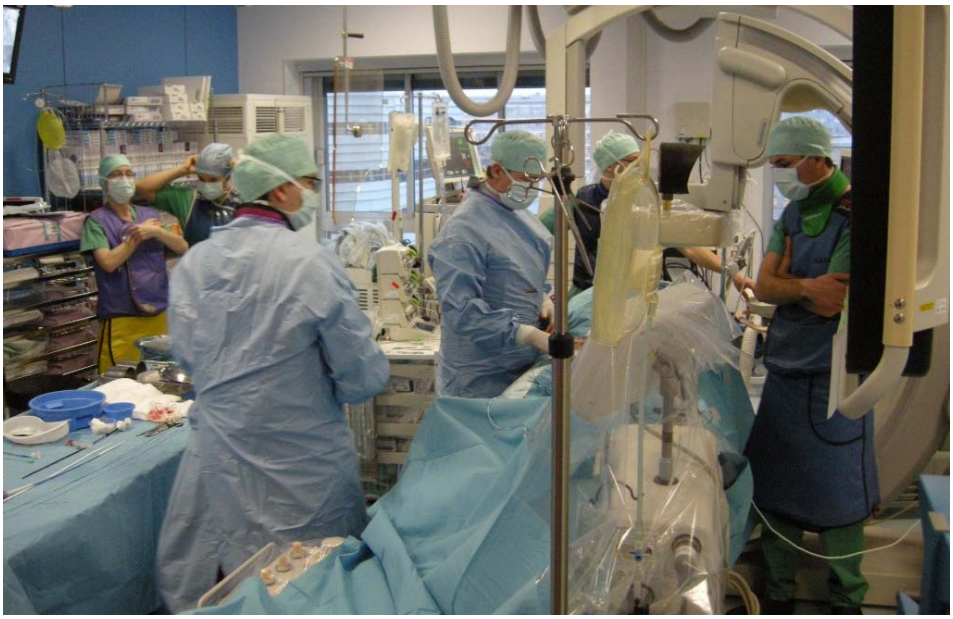

Figure 2 Hybrid cardiac catheterization lab at Ghent University Hospital, Belgium

During design it was necessary to verify that both hygienic and other customer requirements were met with the ventilation solution to be selected. To ensure this computational fluid dynamics (CFD) simulation was used to study alternative solutions. The CFD models used by Halton have been verified within our physical operating room laboratory to ensure reliability of such simulations. Alternative ventilation solutions, Zonal Protection with

Low-turbulent (LTF) downflow units, Controlled-Dilution (Halton Vita OR Space 5), and traditional mixing were studied. Among the alternatives only the Halton Vita OR Space 5 could satisfy customer's hygienic and environmental comfort design targets (Figure 3). Whereas for example LTF was not able to provide hygienic conditions to instrument tables, also the collision with C-Arm was causing high risk of discomfort within operating area. Additional challenge for using LTF was found, when physical layout was analysed; it would have been impossible to fit the LTF unit in place with the medical installation.

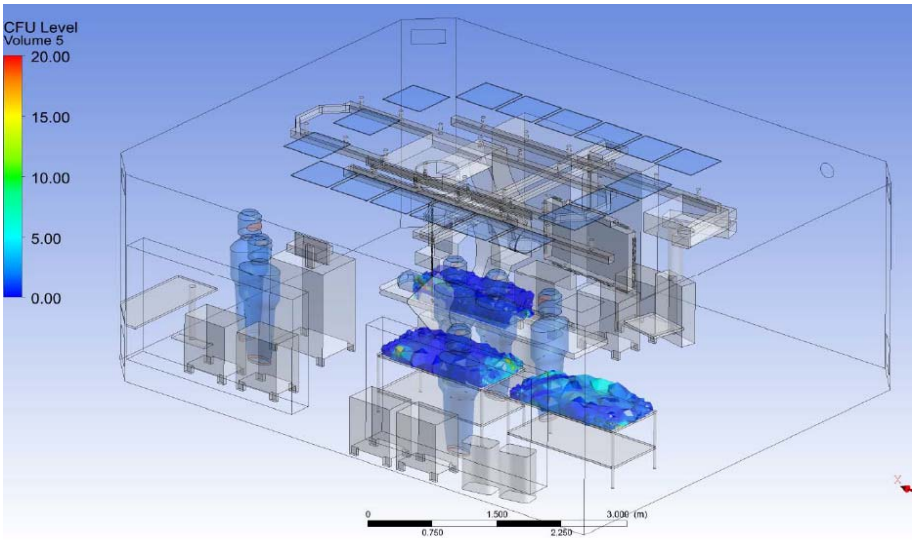

Figure 3. Simulated microbial cleanness (< 5 CFU/m3) on the critical areas of a hybrid cardiac catheterization lab in operation with a Controlled Dilution ventilation (Halton Vita OR Space 5)

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A Comparison between Measured Values of Airborne Viable Particles and Theoretical Calculated Values with the Dilution Principle in Operating Rooms Equipped with Low Velocities Unidirectional Airflow Systems

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Abstract

Many of the recently installed unidirectional air flow systems for operating rooms have low velocities (≤ 0.3m/s). Measurements of airborne aerobic colony-forming units were performed in such operating rooms during on-going surgery. Results show that, during on-going surgery, calculations with the dilution principle is valid in the surgical zone.

Keywords: Ultraclean operating rooms, unidirectional air flow (UDF), dilution principle, microbiological air cleanliness, colony-forming unit (CFU).

Introduction

Operating rooms for patients undergoing surgery susceptible to infections often have unidirectional air 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 and below 0.3 m/s. Measurements of airborne viable particles (aerobic CFUs) were performed during on-going surgery in operating rooms with UDF ceilings at three different hospitals in Sweden

(Gandra et al 2017). Data from these measurements for three different types of UDF units will be discussed in the following. The measured mean value concentrations of bacteria-carrying particles (aerobic CFUs) in the operating rooms with UDF units are compared to theoretical calculated values with the aid of the dilution principle, i.e., total mixing air movements. Airborne viable particles were collected using a filter sampler (Sartorius MD8®) and to a slit-to-agar sampler (Klotz FH6®). The sampling volume per sampling period for the two instruments was 1m3. Both samplers were operating according to the manufacturers' instructions. These two microbiological test methods are described as accepted methods for active sampling of air in SIS-TS39:2015 (2015). For a more thorough description, see Gandra et al (2017).

Operating Rooms with UDF

As mentioned earlier, three types of UDF supply air systems, all with high efficiency particulate air (HEPA)-filtered air, were studied and will here be called Case 1, Case 2, and Case 3. Data from the three cases are shown in Table 1.

Table 1. Data from three types of UDF ceilings (Case1, Case 2, and Case 3).

	Air flow UDF (m^3/s)	Additional air flow (m^3/s)	Total air flow[1] (m^3/s)	UDF velocity Mean value (m/s)	Air filter
Case 1	2.54	-	2.54	0.25	H14
Case 2	3.6	0.7	4.3	0.3	H14
Case 3	2.75	-	2.75	0.27	H14

[1] Additional air is supply air outside the UDF ceiling.

Source Strength

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

$$q_s = \frac{c \cdot Q}{n} \qquad (1)$$

Where q_s = Source strength, total particulates (number/s), bacteria-carrying particles (CFU/s)

c = Concentration; total particulates ($number/m^3$) bacteria-carrying particles (CFU/m^3)

Q = Total air flow (m^3/s)

n = Number of persons present (number)

The source strength is described as the number of total or viable airborne particulates per second emitted from one person. Data are given as mean values based on several persons dressed in specific clothing systems. The source strength, which is in this paper limited to the mean value of the number of aerobic CFU per second from one person is a valuable tool in describing the protective efficacy of clothing systems against bacteria-carrying particles. Ljungqvist et al (2004, 2014)

Clothing Systems

The same type of surgical clothing systems was used during the measurements of on-going surgery for the three cases. The clothing systems consisting of 50% cotton and 50% polyester were described by Erichsen Andersson (2013). The total number of air samples during surgery was 91. With the presented data from Erichsen Andersson (2013), calculation of source strength can be performed with the aid of Equation (1). Such calculations show that the mean value becomes 1.85 CFU/s and the 95 % confidence interval (t-distribution) for lower and upper level are estimated to be 1.5 CFU/s and 2.2 CFU/s, respectively. These values should be compared to the value of 2.0 CFU/s estimated by Nordenadler (2010).

Results

Comparison between theoretical calculated and measured CFU-values

When the air movements are total mixing, the dilution principle is valid. The theoretical mean value concentration of bacteria-carrying particles can be calculated if the total air volume flow is determined and the number of people in the operating room and their source strength is known. In this case, the CFU concentration (c) becomes:

$$c = \frac{n \cdot q_s}{Q} \qquad (2)$$

In Table 2 the mean value of number of people present, their source strength and the total air volume flow during on-going surgery are given. With these values the CFU mean value concentrations are calculated for the three cases. In Table 2 also the measured mean value, CFU concentrations are given.

Table 2. Comparison between theoretical calculated and measured CFU mean value concentrations. UDF ceilings, called Case 1, Case 2, and Case 3.

Case No	Number of people present (mean value)	Source strength (CFU/s)	Total air volume flow (m^3/s)	Concentration (CFU/m^3) Mean value	
				Theoretical* Equation (2)	Measured
Case 1	5	1.85	2.54	3.6	1-3**
Case 2	6.5	1.85	4.3	2.8	2
Case 3	5.6	1.85	2.75	3.8	2.9

* Concentration values are given with one decimal

** The value 3 CFU/m^3 was measured when the probe pointed slightly upwards.

The results from the three cases show that all mean value concentrations are less than 10 CFU/m^3 and that measured mean value concentrations of aerobic CFUs during on-going surgery in operating rooms equipped with UDF supply air systems (UDF ceilings) are little less, but in the same range as the mean value concentration calculated with the expression of the dilution principle (Equation (2)). When the air velocity of the UDF is low (≤ 0.3 m/s), this might depend on the fact that the air flow pattern above the operating table is affected by the presence of obstacles, such as operating lamps and monitors, and movements of the staff and their convection flows. This results in a disordered air flow pattern partly resembling that of mixing air. Figure 1 shows an operating room with UDF ceiling and equipment.

Figure 1. Operating room with UDF ceiling and installed equipment.

Activity Level

In Case 3 measurements of airborne viable particles were performed during on-going surgery at 11operations in five identical operating rooms with exactly the same type of UDF ceiling. The grand mean value of measured concentrations and the grand mean value of number of people present during the 11 operations are described by Gandra et al (2017) and given in Table 2. During the 11 operations there were different levels of staff activities, here called low staff activity and high staff activity. Tables 3 and 4 show concentrations of aerobic CFUs and estimated source strength with the aid of Equation (1) during different operations at low staff activity (Table 3) and at high staff activity (Table 4). Low staff activity occurred during on-going surgery when the staff were standing almost still and high activity was during on-going orthopaedic surgery.

Table 3. Concentration of aerobic CFU and estimated source strength (Equation (1)) during operations with low staff activity during on-going surgery in operation rooms equipped with UDF ceiling with an air volume flow of 2.75 m^3/s.

Operation (number)	Concentration* mean value (CFU/m^3)	Number of people* present (number)	Source strength* (CFU/s) (Equation (1))
1	1.0	7.0	0.4
2	1.8	6.4	0.8
3	1.0	5.5	0.5
4	1.4	4.0	1.0
5	2.3	5.0	1.3
6	5.3	6.5	2.2
Mean value	2.1	5.7	1.0

* Values are given with one decimal

Table 4. Concentration of aerobic CFU and estimated source strength (Equation (1)) during operations with high staff activity during on-going surgery in operation rooms equipped with UDF ceiling with an air volume flow of 2.75 m^3/s.

Operation (number)	Concentration* mean value (CFU/m^3)	Number of people* present (number)	Source strength* (CFU/s) (Equation (1))
7	9.3	5.3	4.8
8	6.3	5.0	3.5
9	1.1	6.6	0.5
10	1.0	4.0	0.7
11	1.0	6.5	0.4
Mean value	3.7	5.5	2.0

* Values are given with one decimal.

Tables 3 and 4 indicate that the source strength mean value during surgical procedures during low staff activity is half the mean value obtained at high staff activity at orthopedic

surgery. The difference between low and high staff activity level is in agreement with data given by Ullmann et al (2017). The source strength mean values calculated for the same type of surgical clothing system with data from orthopedic procedures given by Erichsen Andersson (2013) and Nordenadler (2010) are in the same range as the source strength mean value given in Table 4 (high staff activity during orthopedic surgery).

Conclusions

As a first approximation, when calculating necessary air volume flows or predicting CFU concentrations in an operating room, one can assume that the dilution principle is valid in the operating room during on-going surgery. In such cases, beyond the total air volume flow, the number of people, their activity level during surgical procedures and the source strength of the selected clothing system should be taken into consideration. This is in agreement with results by Nordenadler (2010) and recommendations by SIS-TS 39:2015 (2015). To sum up, when the air volume flows are the same during on-gong surgery, there are little difference in measured CFU levels between the two room air distribution principles, UDF with low velocity and total mixing air flows (dilution principle). Other parameters, such as clothing system, number of people and their activity level, play a more important role than the room air distribution principle.

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Protective Efficacy of Surgical Clothing Systems without and with Textile Knee-length Boots and Airborne Microorganisms based on Results from Measurements in a Dispersal Chamber and during ongoing Orthopedic Surgery

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Abstract

The main source of airborne microorganisms in an operating room is the staff and the patient. To reduce airborne bacteria-carrying particles from the staff, it is of importance that the surgical team wears functional clothing systems. Here results are compared from measurement studies of the protective efficacy, i.e., the source strength, of a surgical clothing system without and with textile knee-length boots. The studies were performed in a dispersal chamber and during ongoing surgery. The results show that the use of knee-length boots or not, have considerable influence of the source strength, i.e., microbial air cleanliness in the operating room.

Keywords: Ultraclean operating rooms, surgical clothing systems, source strength, microbiological air cleanliness, colony-forming unit (CFU).

Introduction

The hospital environment is contaminated by microorganisms and some of them are antibiotic resistant. The number of airborne bacteria-carrying particles 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 infection, it is desirable to keep the bacteria-carrying particles at a low number in the operating room air, especially during orthopedic prosthetic surgery. The main source of microorganisms in an operating room is usually the personnel and the patient. The surgical staff wears clothing system suitable for ultraclean air environment. The purpose of this paper is to compare data of the protective efficacy, i.e., source strength, of a clothing system when people are using shoes without and with textile knee-length boots over the shoes, respectively. The source strength is here described as the mean value of the number of airborne bacteria-carrying particulates per second emitted from one person. Measurements have been performed in a dispersal chamber as well as during ongoing surgery and been described by Ullmann et al (2017).

Material and Methods

Apparatus

Airborne viable particles were collected using a slit-to-agar sampler, FH3®, and sieve sampler, MAS-100®. The sampling periods for the two instruments were 10 min. The sampling volume per period become for the FH3® sampler 0.5 m^3 and for the MAS-100® sampler 1m3. The two samplers in comparison to the other impaction samplers have been discussed by Ljungqvist and Reinmüller (1998, 2008) and Romano et al (2015). Both instruments have a d50-value (cut-off size) less than 2µm and were operated according to the manufacturers´ instruction. Thus, the results from the two samplers are comparable.

Microbial growth medium for all tests was standard medium Tryptic Soy Agar (TSA) in 90 mm Petri dishes. The TSA plates were 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 colony-forming units (CFU) were counted and recorded as aerobic CFU/m^3.

Dispersal chamber

Tests in the dispersal chamber have been carried out to evaluate two Olefin surgical clothing systems with textile hoods, one with shoes and the other system with textile knee-length boots over the shoes. Concentration of airborne bacteria-carrying particles as aerobic CFUs were measured in the exhaust air of the dispersal chamber, where the air is turbulently mixed, by using the FH3® slit sampler, see Ljungqvist and Reinmüller (2004, 2014) and Romano et al. (2016). The principal arrangement of the dispersal chamber is shown in Figure 1.

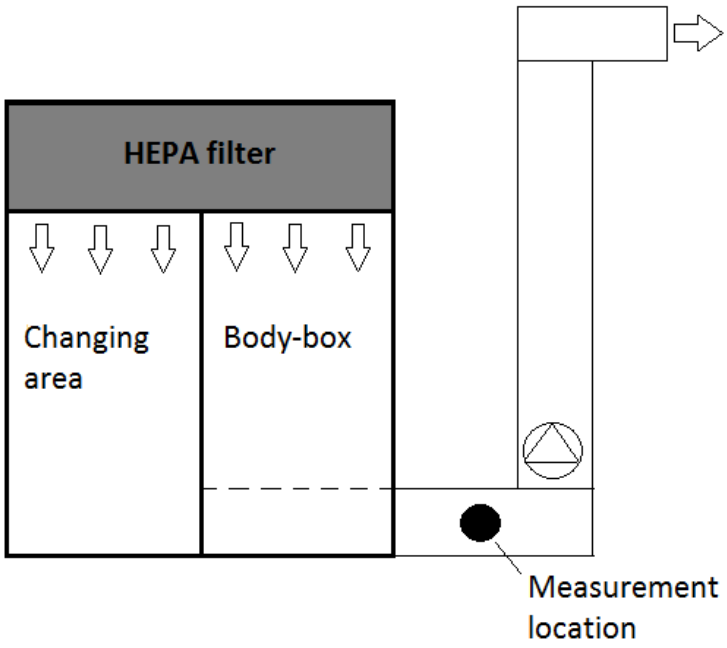

Figure 1. Principal arrangement of dispersal chamber (body-box).

During the measurements the male test subjects performed standardized cycles of movements that included arm movements, knee bends and walk in place at a set speed. These movements are, in principle, comparable with those described in IEST-RP-CC003.4 (2011). Prior to each cycle of movement, the test subject stood still to avoid the influence of particle generation from the previous test cycle. The evaluated clothing systems each had five test subjects performing the standardized cycles of movements four times, see Ljungqvist and Reinmüller (2004, 2014). The activity level in the dispersal chamber is considerable higher than that of orthopaedic surgery.

Operating rooms

The measurements were performed in operating rooms at a hospital in the Stockholm area. The tests were performed during ongoing orthopaedic surgery in operating rooms, where the air movements could be characterized as mixing air, i.e., the dilution principle is applicable. The supply air was HEPA-filtered with air volume flows of about 0.7 m^3/s, which give about 20 air changes per hour. The surgical clothing systems used during the surgical procedures were the same clothing systems used during the dispersal chamber tests.

The measurements were performed either with FH3®slitsampler or with the MAS-100® sieve sampler. The probes of the two air samplers were placed just beside the operating table with a distance of approximately 0.8 - 1.2 m to the wound site at two al-

ternative locations depending on the position of the surgical team. The sampling probe was positioned just above the operating table 1.2 m above the floor. Figure 2 shows the principle arrangements of the location of the sampling probe.

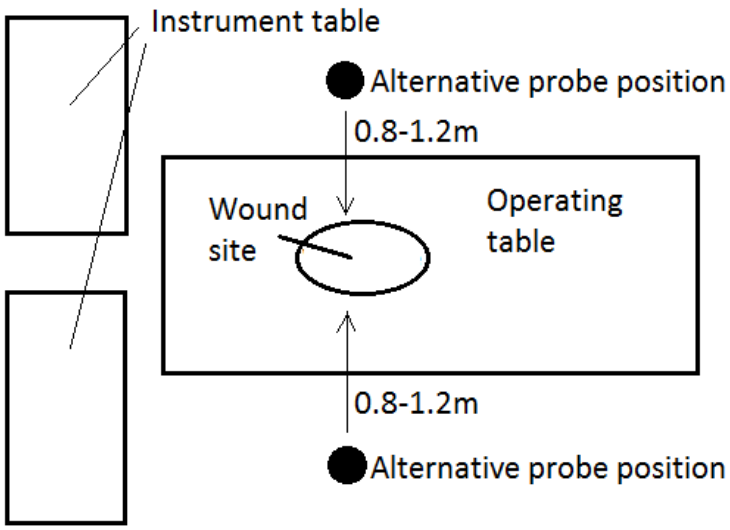

Figure 2. Principal arrangement of the alternative placement of the sampling probes beside the operating table.

Clothing Systems

The surgical clothing systems used were two systems made of synthetic fibre olefin. During surgical procedures the surgeon and the surgical nurse wore an additional disposable sterile coat over the surgical clothing system. The fabric olefin is consisting of 98% olefin and 2% carbon fiber, not antimicrobial treated. The blouse with cuffs at arms and neck, and trousers with cuffs at the wrists, were laundered ca 20 times. The weight is 125gram per square meter. Textile hoods with cuffs at the face and buttons below the chin were laundered ca 20 times, sterile disposable face-masks, and disinfected gloves were worn. None of the tested components were sterilized. The difference between the two Olefin clothing systems is the footwear. One clothing system had clean socks of cotton and disinfected plastic shoes while the other system had textile knee-length boots over the shoes. The textile knee-length boots with zip at the back of the leg were laundered approximate 10 times. Figure 3 shows the surgical team dressed in the Olefin surgical clothing system with knee-length boots.

Figure 3. The surgical team dressed in the Olefin surgical clothing system with hood and knee-length boots.

Source Strength

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

$$Qs = c\,Q/n \qquad (1)$$

where qs = Source strength; total particulates: number/s, bacteria-carrying particles (CFU/s
c= Concentration; total particulates: number/m^3; bacteria-carrying particles (CFU/m^3
Q =Total air flow (m^3/s)
N = Number of persons present, (number)

In the dispersal chamber there is only one person during the tests, why n=1 in Equation (1). The source strength is described as the number of total or viable airborne particulates per second emitted from one person. Data are given as mean values based on several persons dressed in specific clothing systems. The source strength, which is in this paper limited to the mean value of the number of aerobic CFUs per second from one person, is a valuable tool in describing the protective efficacy of clothing systems against bacteria-carrying particles (Ljungqvist and Reinmüller, 2004).

Results

Dispersal chamber

Source strength mean values of aerobic CFU from dispersal chamber tests with five test subjects are shown in Table 1,where the values are given when the test subjects were dressed in the Olefin clothing systems with textile hood, without and with textile knee-length boots.The air volume flow in the body-box part of the dispersal chamber was 0.23 m^3/s during all tests.Table 1 shows that the reduction of the number of aerobic CFUs with boots compared to without boots is about 57%.

Table1 Source strength mean values of aerobic CFU from dispersal chamber tests with five test subjects dressed in Olefin clothing systems with textile hood. Additionally, were worn open plastic shoes (sandals) without and with textile knee-length boots.

Test subject	Source strength mean values (CFU/s)*	
	Without boots	With boots
1	1.4	1.2
2	0.7	0.2
3	3.1	0.8
4	2.4	0.6
5	3.8	2.3
Grand mean value	2.3	1.0
Min – max	0.7 – 3.8	0.2 – 2.3

* Numbers are given with one decimal. Source strength values are calculated from data given by Ljungqvist and Reinmüller (2016).

Ongoing surgery

Table 2 shows concentrations of aerobic CFU and estimated source strengths during ongoing orthopaedic surgery in an operating room with dilution mixing air and an air flow of 0.7 m^3/s. The surgical team (5-6 persons) were dressed in Olefin clothing systems with textile hood, without and with textile knee-length boots. Measurements were performed during three operations and the sampling time of airborne CFUs was 10 min/sample. **Table 2** shows that the reduction of the number of aerobic CFUs with boots compared to without boots is about 67%.

Table 2. Concentration of aerobic CFUs and estimated source strength during ongoing orthopedic surgery in an operating room with dilution mixing air and an airflow of 0.7 m^3/s. The surgical team was dressed in Olefin clothing system with textile hood and private shoes without and with textile knee-length boots. Measurements were performed during three operations and the sampling time of airborne CFUs was 10 min/sample.

Air sample No	Without boots			With boots		
	No of persons (No)	Concentration (CFU/m^3)	Source strength* (CFU/s)	No of persons (No)	Concentration (CFU/m^3)	Source strength* (CFU/s)
1	6	4	0.5	5	<2	<0.3
2	6	10	1.2	5	<2	<0.3
3	6	10	1.2	5	2	0.3
4	6	14	1.6	5	6	0.8
5	5	12	1.7	-	-	-
Mean value	5.8	10	1.2	5	<3	0.4

* Source strength values are given with one decimal.

Conclusions

Even if the number of measurements during ongoing surgery is limited, the results indicate that the reduction during ongoing surgery (67%) is in the same range as in the dispersal chamber tests (57%).

Reinmüller (2001) describes tests in an aseptic filling room for pharmaceutical production, where the operators were dressed in cleanroom coveralls with hoods. The effect of knee-length boots compared to normal cleanroom shoes was evaluated. When knee-length boots were used a reduction of airborne particles and aerobic CFUs of approximative 90% was achieved. The high reduction with cleanroom clothing system might depend on the cleanroom operator being better covered than a person with surgical clothing, who has partly uncovered arms.

It should be noted that it is possible to achieve concentration values less than 10 CFU/m^3 during ongoing orthopaedic surgery in operating rooms with air flows of 0.7 m^3/s (around 20 air changes per hour) when proper surgical clothing systems and additional components are used.

A dispersal chamber test can be a valuable tool in the development of new clothing systems and the estimation of the protective efficacy. In summary, in operating rooms for surgery susceptible to infections, the selection of clothing systems for the operating room personal should no longer only be considered in terms of comfort but also in terms of patient safety.

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FOOD & BIOTECH SESSION

Good Manufacturing Practice (GMP) in the Food Industry – Requirements in Manufacturing Unit Design

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Abstract

Good Manufacturing Practice or GMP is a term that is recognized worldwide for the control and management of manufacturing, as well as the quality control of foods, pharmaceutical products, medical devices, and even packaging and food contact materials. EU GMP guidelines include EudraLex VOL 4 Good Manufacturing Practice (GMP) and for food manufacturing the code of practice and hygiene published originally by Codex Alimentarius. With the above-mentioned guidelines and related legislation, as well as with the support of manufacturers' hazard analyses and risk assessments, the minimum requirements are set which manufacturers must meet to safeguard the health of consumers and produce good quality food. So, what is the challenge? The GMP guidelines are not prescriptive instructions on how to manufacture products. They are a series of general principles that must be observed during manufacturing. When a company sets up its quality program and manufacturing process, it can fulfil GMP requirements in various ways. It is the company's responsibility to determine the most effective and efficient procedures, facilities, materials, equipment and controls.

Introduction

Key GMP include adequate and suitable utilities and services (such as water, steam, air, compressed air), the cleanability of the building and equipment, a suitable process flow with process design that minimises the potential for cross-contamination, effective pest

control, as well as proactive maintenance and personnel hygiene. The fundamental principle of good manufacturing practice is to ensure that foodstuff contamination is minimised and products are consistently produced, traceable and controlled according to the quality and safety standards appropriate for their intended use.

However, GMP guidelines provide only minimal guidance. Even when complemented with EU and national regulations, the guidelines and available product safety standards are not prescriptive instructions on how to manufacture products, nor do they provide guidelines for a single perfect plant design solution. The GMP requirements for food are deliberately general to allow individual variations by manufacturers to implement the requirements in a manner that best suits their needs. When a company sets up its quality program and manufacturing process, there are many ways to fulfil GMP requirements. The manufacturer (project customer) and the food safety authorities set the requirements for food establishments. These requirements are the starting points for plant design. Thereafter, it is a joint effort to determine the most effective, efficient and suitable procedures, facilities, materials, equipment and controls in advance and to ensure that safety objectives are consistently met.

Definitions and Regulations

Good Manufacturing Practice, commonly abbreviated to GMP, or prerequisite programme (PRP) are terms, which are recognized worldwide for the control and management of hygiene manufacturing, as well as the quality control of foods, pharmaceutical products, medical devices, and even packaging and food contact materials.

Codex defines GMP as: A combination of manufacturing, testing and quality control procedures aimed at ensuring that products are consistently manufactured to their designated specifications and safe for human consumption and use.

According to the regulations illustrated in Figure 1, every food manufacturing business has to establish and implement a food safety management system (FSMS in Figure 2) appropriate for the products being manufactured, supported by the GMP principles. Based on hazard and risk analysis, all reasonable precautions should be taken and the FSMS should be fully and effectively implemented and maintained. A process for control measure validation and FSMS and QMS verification and improvement supports the dynamic functioning of the system during any change in production, equipment or the product itself. It is vital that the FSMS and associated GMPs (prerequisite programmes) are continuously appropriate for the products and processes involved and the inherent level of food safety risk. In order to achieve GMP objectives, it is necessary to have the following in place:

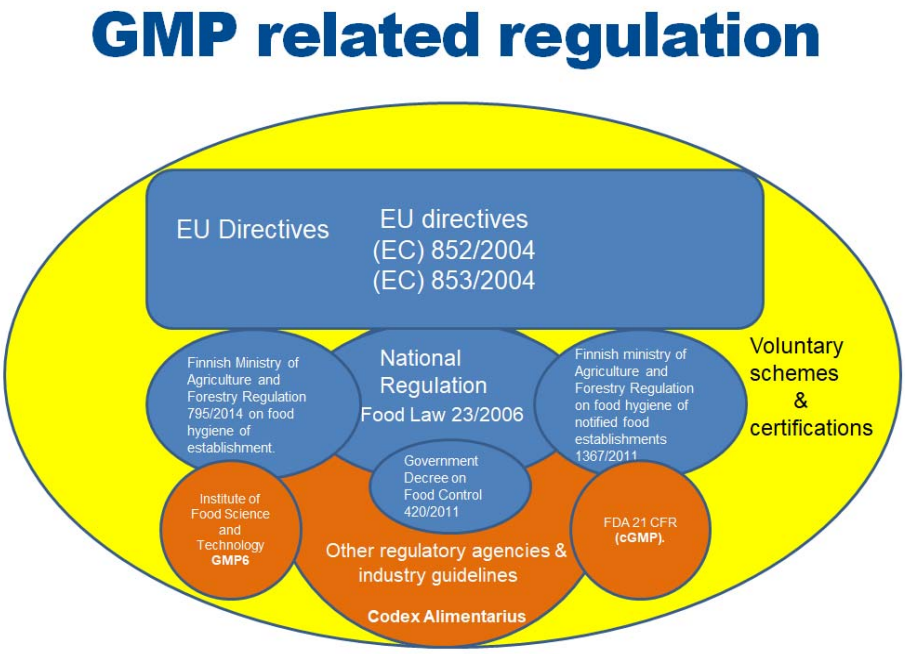
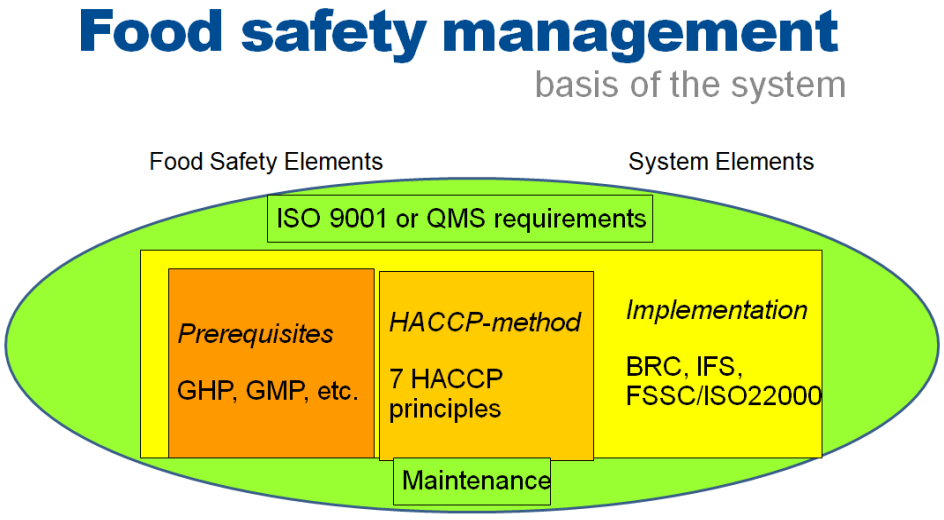


Figure 1. Many countries have created their own GMP guidelines for food and pharmaceutical manufacturers that correspond with their legislation.



Basis of the system is generally an ISO 9001 QMS with integrated aspects of food safety and prerequisite programmes originated from hazard analysis and critical control points (HACCP).

Figure 2. An illustration of a food safety system based on the HACCP plan with prerequisite programmes

1. Quality Assurance – to comply with the product specification: that is, to design and plan relevant raw material and packaging specifications, ingredient formulation, labelling, processing methods and conditions, processing equipment and processing environment, intermediate specifications, specifications for management and control procedures, distribution system and cycle, appropriate storage and handling with relevant instructions and documentation.
2. Effective Manufacturing Operations: that is, to validate and manage operational practices and personnel qualifications to ensure that the process meets its specific design parameters and that the resultant products consistently comply with product specifications.
3. Quality control: that is, to have an effective monitoring system in place with appropriate corrective action procedures supported by systematic verification procedures (covering e.g., management review) of the overall quality plan and compliance throughout the product´s shelf life.

Scope and Available Guidelines

For food manufacturing and food handling establishments, the original and most widely known guideline is **the General Principles of Food Hygiene (a set of GHPs that form the foundation of GMPs)** published by the Codex Alimentarius Commission, a body that was established in the 1960s by the FAO and WHO. Codex codes and principles define general practices for production, processing, manufacturing, transport and storage, but also practices for individual foods or food groups that are considered essential to ensure the safety and suitability of food for consumption.

In the UK, the Institute of Food Science and Technology has published a guide to the responsible management of GMPs – the current issue is the 6th edition (GMP6).

In the United States, GMPs are enforced by the U.S. Food and Drug Administration (FDA), under the title 21 CFR (cGMP). The FDA regulations use the phrase "current good manufacturing practices" (CGMP) to describe these guidelines, applicable e.g., in food, drugs, medical device manufacturing and even in cosmetics.

In summary, many countries have legislated that food manufacturers are required to follow GMP procedures and have created their own GMP guidelines that correspond with their legislation. Regulatory agencies (including the FDA in the U.S. and regulatory agencies in many European nations) are authorised to conduct GMP inspections.

In addition, voluntarily ISO management systems audits other product safety certifications/schemes can be certified by accredited certification bodies. Some of these schemes (e.g., BRC Food & IoP, IFS Food, FSSC 22000) are recogniszed by the The Global Food Safety Initiative (GFSI) international trade association The Global Food Safety Initiative (GFSI). In line with the main sub- parts of Codex, GMP6 and cGMP, below presented the GMP sub- parts according to FSSC 22000 and its technical specification ISO /TS 22002-1 are presented in Table 1.

Table 1. Scope of prerequisite programmes according to ISO 22002-1:2009 (a technical GMP part of FSSC 22000 system):

1-3 Scope, normative references, terms	11 Cleaning and sanitizing
4 Construction and layout of buildings	12 Pest control
5 Layout of premises and workspaces	13 Personnel hygiene and employee facilities
6 Utilities – air, water, energy	14 Rework
7 Waste disposal	15 Product recall procedures
8 Equipment suitability, cleaning and maintenance	16 Warehousing
9 Management of purchased materials	17 Product information and consumer awareness
10 Measures for prevention of cross-contamination	18 Food defence, biovigilance, and bioterrorism

What are the Challenges in Hygienic Design?

Firstly, **uniform conformance** with product specification is difficult with food and drink products. The main raw materials for food and drink manufacture are derived from nature and are subject to natural variation in primary production. Wide variations may occur, for example, among cultivars due to regions and seasonal and weather-related cultivation differences. Therefore, the food and drink manufacturer has to make a reasonably uniform product from variable raw materials, a combination of raw material selection, pretreatments, formulation adjustments and processing variations.

Secondly, the GMP guidelines, even when complemented with EU and national regulations on structural and functional requirements, traceability, temperature and personnel requirements, are not **prescriptive instructions** on how to manufacture products, nor do they suggest a single perfect solution for the hygienic design of a facility and process. There is, for example, not only one preferred flooring material or drainage system, or one proper manufacturing zoning and segregation solution. GMPs are merely a series of general principles that must be observed during manufacturing or taken into consideration during design and construction. Concisely, when a company sets up its facilities, a quality program and a manufacturing process, it can fulfil GMP requirements in various ways.

Thus, there are several feasible solutions for hygienic design of a food factory. The requirements for food, are deliberately general to allow individual variations by manufacturers to implement the requirements in a manner that best suits their needs. It is the company's responsibility to determine the most effective and efficient procedures, facilities, materials, equipment and controls. It all comes down to the products manufactured and the food manufacturer´s preliminary hazard analysis and finally, to the estimated CAPEX and OPEX **costs and available financing**.

Investment Planning Starts with Pre-engineering Studies

The manufacturer is responsible for employing appropriate and technically-competent personnel to specify the product formulation, factory processes and procedures, and to design suitable facilities to support safe production of food products. **By planning** these aspects **ahead** with appropriate validation and verification activities, as required by GMP guidelines, the manufacturer has exercised adequate precautions and diligence necessary to **comply with the law.**

For engineering and consulting companies, CAPEX- investment planning starts with a feasibility study in cooperation with the manufacturer in the so-called pre-engineering phase. Although investment costs will materialise during implementation, the costs will be mostly determined by the decisions and choices made during this pre-phase (Figure 3). The output from pre-engineering will, to a great extent, also determine how straightforward the implementation is and what the execution time of the project is.

In addition to the impact on future turnover and efficiency, the chosen process and plant concept have an impact on product safety and product quality. Therefore, a crucial part of pre-engineering is cooperation with the manufacturer in **setting user requirements** on effective and hygienic manufacturing operations, based on preliminary risks identified for the targeted products and their end users. As an output of the pre-engineering phase, this means specifying the following in the form of a study:

- Adequate design of premises and suitable manufacturing and storage spaces
- Suitable process flow with process design to streamline the process and minimise the potential for cross-contamination
- Choosing correct and easily maintained main equipment
- Appropriate storage and transport facilities
- Adequate and suitable utilities and services

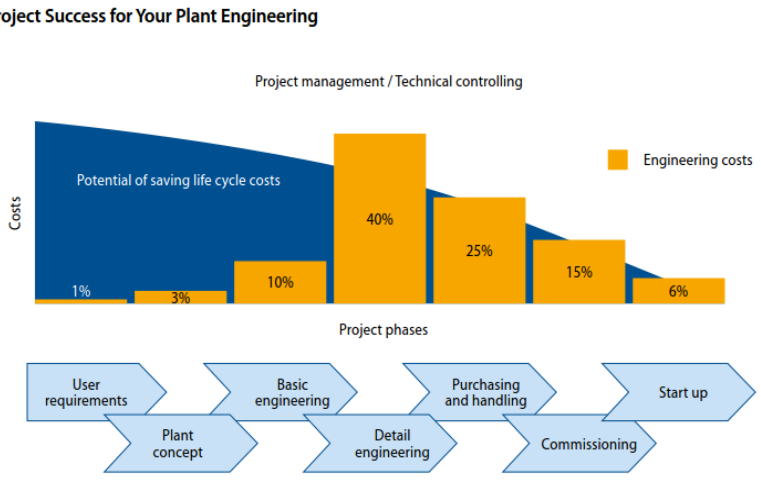


Figure 3. The success of an investment project is supported by EPCM services (engineering, procurement and contruction management) and step-by-step project management.

During the design phases, the targeted production and distribution capabilities are translated into specific design parameters that result, after appropriate validation and verification activities, in the intended product quality and production amounts. **The most crucial design guideline is to ensure that contamination is minimised in every decision made.** The manufacturer (project customer) and the food safety authorities set the requirements for food establishments. These requirements are the starting point for plant design. The most common investment types are greenfield and revamp projects, but also production efficiency related improvement projects are done frequently. Product and consumer safety requirements need to be built into plans while simultaneously considering the quality, hygiene, cost and schedule. It is the designer´s duty to find a balance between these requirements. Nowadays, HSE requirements and environmental impacts are also taken into consideration in food manufacturing unit design.

For manufacturing unit investments, at least the following documents are prepared

- Conceptual capacity study of production
- Preliminary manufacturing space requirement and layout with hygienic zoning
- Prliminary material and personnel flows
- A site plan with building layout and locations for production, service, storage areas and surrounding areas and main air intake/outlet locations etc.
- Investment cost estimate (target around ± 25-40 % depending on the complexity of the process) based on main equipment selection
- Preliminary project scheduling.

Reviews and acceptance of the concept design, purchasing specifications and estimated investment costs against set requirements from the manufacturer (customer) and authorities are vital parts of securing the success of the investment project. Before making any further decisions to proceed the manufacturer should, at the latest in this investment phase, already contact the food safety authorities and inform them of the investment plans. This obligation stems from the Finnish Food Act (23/2006), according to which a food establishment must notify the relevant supervisory authority prior to commencement of operations or a substantial change of activity. Food establishments of animal origin products must be approved by the authorities. Thus, a documented food establishment concept and other design documents from the pre-engineering study and a hazard analysis are prerequisites for a proper application.

During the next phases (basic and detail design) and construction, designers ensure that both the equipment and new manufacturing unit (or expansion of it) are further designed, fabricated and finally constructed and installed according to sound hygienic design parameters. This entails cooperation between all design disciplines (process, building, EIA, HVAC, steel structures and plant), equipment and system suppliers and the food manufacturer. In terms of output documentation, more detailed decisions need to be made by the project team related to all areas of the factory:

- Buildings and their surroundings
- Construction of specific elements of the building
- Factory and industrial services
- Equipment, layout and installation
- Cleanability of the building and equipment
- Ease of maintenance.

The accuracy level of documents depends on the specified guidelines and regulations of the product category, as well as the chosen contractors and their capabilities.

Figure 4. As EPCM service providers, designers can be involved in every project phase on behalf of the customer.

Suppliers should be selected based on their ability to supply products or services that meet the defined requirements (Figure 4). Only approved suppliers with hygienic application references should be used, if possible. In addition, the control of incoming products and services is a key prerequisite within a GMP system.

During the construction and installation phase, the designer can act as the site supervisor that coordinates material and equipment deliveries to the site, performs delivery inspections, and supervises installations. In this supervision work, HSE and GMP coordination plays a major role in **ensuring safety during construction and that contamination is again minimised on site**. Finally, a commissioning plan is generated that also includes validation and inspection steps to secure that the manufacturing lines and supporting systems are approved for full-scale production. This usually includes production test runs with microbiological sampling and shelf-life testing.

How Do Designers Turn General GMP Principles to Design Parameters?

To ensure that

- the equipment and factory can be effectively operated,
- does not contain hazards, does not rapidly deteriorate and
- can be appropriately cleaned and disinfected,

designers and those responsible for construction of food factories rely on their experience of industry best practises and applied technology in previous food industry revamp projects. Furthermore, designers follow the applicable EHEDG guidelines in addition to local legislation and national building standards.

EHEDG (The European Hygienic Engineering and Design Group) has developed and published a variety of **practical guidance documents on adequate hygienic design** in different areas of food production equipment and machinery, as well as on the construction materials and food manufacturing infrastructure in general. Currently, EHEDG also participates in the GFSI Working Group on the topic of “Hygienic Design of Food Facilities and Equipment” for GFSI recognition and acceptance.

The EHEDG organisation has identified five key areas of hygienic design in line with Codex GHP/GMP principles – hygienic building design, utilities, equipment and process design, cleaning and sanitation and personnel hygiene. In order to assist the implementation of these key areas, supporting hygiene engineering guidelines exist. The guidelines include, for example, cleaning validation, hygienic design of belt conveyors, construction materials for equipment in contact with food, hygienic welding of stainless steel tubing, air handling, water treatment and its storage and distribution, food-grade lubricants, hygienic design of pumps, homogenisers and dampening devices, and valves for food processing. Altogether, 47 guidelines currently exist.

Some examples of design parameters provided by the EHEDG guidelines that support pre-engineering and the basic and detail design phases are provided in the following paragraphs. During the pre-engineering phase, the focus is on premises, equipment and facilities that need to be located, designed and constructed to ensure that contamination is minimised; design and layout that allow appropriate maintenance, cleaning and disinfections and minimise airborne contamination.

Examples of EHEDG-design parameters in pre-engineering - Layout & segregation:

- Building design provides internal separation with walls between departments in which edible (e.g. food and food ingredients) and non-edible materials (e.g. boiler rooms, workshops, and machinery rooms) are handled. In addition, air, waste and drainage flow effectively out of higher hygiene zones into lower hygiene zones.
- Cross-contamination is reduced by segregation that takes into account the flow of the product, the nature of materials, equipment, personnel, waste, airflow, air quality and utility provisions and lastly, the isolation of microbiology laboratories, particularly those handling pathogens.

- A minimum clearance under the equipment is specified dependent on equipment widths: E.g., for equipment approximately one meter wide, there should be a minimum clearance of 30cm. For equipment access, a minimum clearance of 90 cm from walls and between equipment of 120-150cm is suggested.
- Waste routing – waste should be moved out of high hygiene areas via openings in the segregated barrier. Waste storage should be in a separate room or in an external area that is constructed with impervious materials and suitably sloped and drained.

The fundamental issue to remember, is that the degree of hygienic design applied and appropriate hygienic zoning (basic, medium and high hygiene areas) will depend on:

- the product range (perishable foodstuffs, low moisture foods, frozen and chilled ready-to-eat foods etc.),
- the degree of microbiological decontamination undertaken (processing),
- the likelihood of spoilage and pathogenic microorganism growth or survival in the product and
- the risk of cross-contamination from the external environment.

Thus, the hazard analysis and decisions require a multidisciplinary approach and cooperation between the manufacturer´s specialists and engineering specialists in every investment phase, covering procurement steps and finally the supervision of construction and commissioning. During later design phases, all areas of the factory and manufacturing process are further planned and dimensioned with descriptions, procurement specifications, plant models and drawings to support the construction and installation phase.

Examples of EHEDG –design parameters in basic and detailed design phases − Factory services, utilities and materials:

- Steam should be generated from potable water and should be adequate to meet operational requirements and should have traps to ensure adequate condensate removal and the elimination of foreign materials.
- Conditioned air should have a relative humidity below 55 % to restrict the growth of microorganisms, in particular moulds.
- Air control facilities including temperature, humidity and filtration, appropriate to both the operations within the processing area and to the external environment.
- Air flow from higher to lower hygienic zone and from lower to higher dust load areas.
- Sufficient air changes per hour in medium hygiene processing areas (typically between 5-25 changes per hour, filters EU-class M5 to F7) and high hygiene areas (>10 changes per hour, filters F7 or greater).
- Compressed air, CO2, nitrogen and oxygen shall be filtered through a micron filter (to remove particles of 5 microns or greater) located close to the point of use and should have non-return valves to preclude the entry of food.

- Process and transport air should be drawn from the atmosphere outside the process plant building through an inlet at least 3 meters above ground level. Any air intake should be sited as far as possible (min 10m) from any outlet air streams or other exhaust ducts, wet scrubbers etc.
- EHEDG Guidance document no. 32 deals with materials of construction for equipment in contact with food. Stainless steel, hot dipped galvanised steel, aluminium, fiberglass, polyvinyl chloride and nylon are examples of food grade materials.
- Wall exteriors should not have horizontal surfaces (gradients >/= 45°). External walls are commonly constructed out of concrete, brickwork, steel plating or sandwich panels. Internal walls of reinforced concrete in production areas should always have a finishing consisting of mould-resistant coating approved for food use. Plastic panels made of uPVC and glass fibre reinforced polyester or epoxy resin, stainless steel panels for high wet use targets, are available.
- Floors may have to meet requirements for chemical resistance – against acids (spirit vinegar or mineral acids etc.), alkalis, oils, fats, cleaning products (solvents such as alcohol or even peppermint oil) and disinfectants (sodium hypochlorite, per acetic acid, hydrogen peroxide etc.) – for abrasion, resistance, temperature and thermal shocks. All joints are weak points in a floor and should be positioned away from areas of regular discharge of liquid.

Summary

The prevention of contamination of food products is the fundamental reason why hygienic design principles are applied. Poor GMP-level indicators include e.g., inadequate drainage leading to ponding of water on the floor, surface defects, equipment with dead pockets with product residues, signs of corrosion, traces of lubricants or detergents in products, untight doors and transport docks, open windows, and pipework with visible dirt accumulation. In addition, indicators such as seasonal variations in hygienic conditions in production resulting, at worst, in quality complaints and high operating costs related to maintenance and cleaning, can result from poor GMP practises.

Hygienic food processing equipment and manufacturing units should be easy to maintain to ensure they perform as expected to prevent food safety and quality issues. Furthermore, it must be possible to monitor and control all the functions that are critical for food safety. The engineering design process is a series of steps that engineers use in creating functional products, processes and even manufacturing units based on user requirements. Sometimes, the hygienic design requirements are in conflict with functionality and costs. An acceptable compromise, preferably pre-planned already in the pre-engineering phase, must **never put food safety at risk**. Other than securing safety, the targeted benefits of the pre-engineering phase are also the potential of increasing the life expectancy of equipment, reducing maintenance measures, enhancing sustainability and lowering operating costs.

It is the responsibility of designers and each manufacturer to establish a GMP framework and requirements for each product type or family that will result in quality products that are safe, from raw material handling though production and warehousing all the way to distribution. It is a complex task balancing costs, safety regulations and user requirements. However, with step-by-step project management, EHEDG hygienic engineering guidelines, equipment suppliers and contractors that are familiar and experienced in GMP and with appropriate validation and verification activities, our **joint preventative and predesigned efforts** will secure food products that meet the quality and hygiene system requirements and attract consumers now and in the future.

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Contamination New ISO16890 for Air Filters – Focus on Clean Air in Food & Biotech Processing

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Abstract

After a long process over several years all involved countries in the world have finally come to a common decision. The future global test standard for air filters is called ISO16890 and it will replace the existing standards, EN779:2012 (Europe) and ASHRAE 52.2 (USA, Asia and Middle East). EN779:2012 will be deleted in the end of August 2018 and until then, both standards are valid. ISO16890 has a completely new way of classifying air filter products. All manufacturers must make new tests and adapt all their products accordingly. With the new ISO16890 standard we can get a relation between the outdoor air particles and the effect of the inlet air in regards of filter efficiency. The old (but still existing) EN779:2012 is based on filtration efficiency focused only 0.4 µm particle size, but new ISO16890 gives more intuitive filtration performance related to particulate matters PM10, PM2.5 and PM1. Clean air is one important ingredient - the “invisible raw material” – in sensitive Food, Beverage, Biotech and BioPharma manufacturing processes. Hygienic aspects and standards must be considered at the production stages, which will maintain and possibly also improve the product safety.

Contamination Control in the Food Industry

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Abstract

Over the years a distinct distance can be observed between the worlds of cleanroom-oriented contamination control and the food processing industry. Current developments in detection techniques as well as increasing understanding of contamination mechanisms open the pathways to more adequate control. Furthermore, hygienic design has been developing to avoid open process steps, reduce accumulation and to improve cleanability. As a case a typical integrated hygienic spray drying factory, designed and build according hygienic and contamination control standards such as EHEDG DOC 47 and ISO14644-4, producing ingredients for baby food, is illustrated.

Keywords: Food, Hygiene, Contamination Control, Zoning, High hygiene

Introduction

Cleanroom facilities for the micro-electronics, the pharma-biotech, the medical devices and healthcare do differ significantly from high care / high risk food processing facilities. Still food processing is an interesting area for professionals with a contamination background and vice versa. In a world full of classifications and requirements (ISO-14644-1, EU-GMP, FDA, e.g.) the lack of distinct cleanliness requirements in for the food is noticeable. This is obvious for there are many different types and formats of food products. As hygiene in food processing includes contamination control, the vast variety in substances, processes and the huge volumes make the food processing world take a different ap-

proach. The main elements of difference will be addressed, the challenges discussed and based on a specific case the results illustrated.

Contamination Control in the Food?

Within the approach of the ISO TC209 on the ISO 14644 and ISO 14698 cleanroom standards a ‘cleanroom’ has to have a classification by particle concentration in air as per ISO 14644-1. One might suppose that any room, not having such a classification, will not be of interest considering contamination control. Typical for food production plants this is not the case. Basic guidance on this is given in the Codex Alimentarius. This Codex standards are based on sound science provided by independent international risk assessment bodies or ad-hoc consultations organized by FAO and WHO. The code of practice “General Principles of Food Hygiene, CAC/RCP 1-1969 (2003) addresses contamination. It contains the following definitions:

- *“Contaminant - any biological or chemical agent, foreign matter, or other substances not intentionally added to food which may compromise food safety or suitability.”*
- *“Contamination - the introduction or occurrence of a contaminant in food or food environment.”*
- In section IV on Establishment: Design and facilities the Objectives are given:
- *“Depending on the nature of the operations, and the risks associated with them, premises, equipment and facilities should be located, designed and constructed to ensure that:*
  - contamination is minimized;
  - design and layout permit appropriate maintenance, cleaning and disinfections and minimize air-borne contamination;
  - surfaces and materials, in particular those in contact with food, are non-toxic in intended use and, where necessary, suitably durable, and easy to maintain and clean;
  - where appropriate, suitable facilities are available for temperature, humidity and other controls; and
  - there is effective protection against pest access and harbourage.

RATIONALE: Attention to good hygienic design and construction, appropriate location, and the provision of adequate facilities, is necessary to enable hazards to be effectively controlled.”

TYPICALS

Product specific requirements

The essential aim of the Codex Alimentarius is the requirement to secure the product safety to the customer. This is comparable to the pharma industry to the extent that the production has to be controlled, as well as the traceability from raw materials all the way

to finished products. Where for pharmaceutical products (especially the aseptic ones) rather clear levels of cleanliness of are established, for food products only limited levels for certain pathogenic species are given. This is very much in line with current thinking in CEN TC243 WG13 on bio contamination, where a difference is made between levels of specific harmful microbiology and the overall nonspecific non-harmful general microbiology level. This might add to the improvement of control and monitoring. An increase in products shelf life and the reduction of preservatives are drivers for better production processes and environmental control when exposed. In recent years additional substances are identified as contaminants: allergens and in some cases endotoxins. This has already led to major changes in production facilities. Essential is the worldwide requirement to implement a quality management system that covers the essential quality and safety aspects. The approach used usually is Hazard Analysis and Critical Control Points (HACCP).

Hygiene and Cleaning and Zoning

Focusing on process steps where contamination can occur the (European Hygienic Engineering & Design Group EHEDG has defined principles for hygienic design. EHEDG Guideline 8 Hygienic design principles (draft) taking a look at process equipment and its surroundings. Furthermore, levels of hygiene are identified. There is not a very stringent definition of those levels, as they are determined by the HACCP analysis. It has been identified that the design of the surroundings where product matter is or can be exposed needs to allow for the way the cleaning will be accomplished. Three types of cleaning are identified: (a) Wet cleaning; such as high pressure, high temperature and/or high detergent water-based fluids, (b) Controlled wet cleaning; using wetted cloth or wipers and (c) Dry cleaning; using dry cloth or wipers. A combination of each hygiene level and each cleaning procedure can be used to identify zones in a facility. The typical zones are given in Table 1.

Table 1. hygiene zones and cleaning methods from EHEDG Guideline 26

Level of hygiene	Wet cleaning	Controlled wet cleaning	Dry cleaning
High	Hw	Hcw	Hd
Medium	Mw	Mcw	Md
Basic	Bw	Bcw	Bd

An important reason for this approach is the nutritious nature of all food products and the much larger quantities. Water and nutrition are the key factors to support live from molds, yeast, bacteria up till rodent. For that reason, contamination control in starts in the landscaping and fencing around a facility to avoid easy intrusion of animals and insects, all the way through gowning rooms, air locks, towards areas of food processing.

Reduction and (Re-)Contamination

To control microbial growth in raw material and product various reduction treatments are utilized, such as blanching, pasteurization, sterilization, additives, pH-changes. Apart from very specific cases such as parenteral food, all food products are not sterile. Sterility is not feasible because the taste and constitution of the product would be lost. As bio contamination continues to grow such reduction steps require stringent hygiene to avoid additional or recontamination. The effect is indicated in Figure 1.

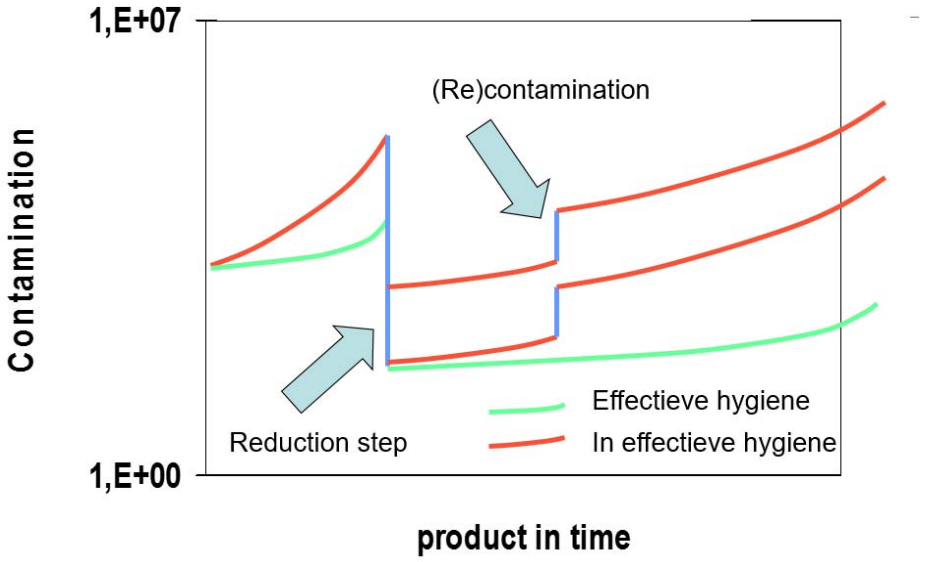

Figure 1: The effect of hygiene to control the level of biocontaminants

As control over the cleanliness of product when exposed to the environment is so important the best way is to reduce the area to be cleaned by minimizing the exposure of the product. Comparable to ISO 14644-4 Annex A Figure A1 indicating zoning and material and personal flows a food facility can be designed.

Product specific requirements

Product spilling can abundant and wet cleaning is quite frequent in food processing facilities. Paying much attention to cleanability, not only inside process equipment but outside as well has made EHEDG define various guidelines on the hygienic construction of equipment and facilities (Figure 2) this has much more focus than many pharma-biotech plant crowded with formulation vessels, bioreactors, downstream processing equipment (Figure 3).

The challenge then is to avoid any un cleanable areas and surfaces. Where pharmaceutical plants especially for sterile products put emphasis in concealing as much as possible inside walls and above spaces in technical voids to reduce exposed area that

needs to be and remain clean, a food production zone where some waste material is nearly unavoidable, needs to have no hidden areas were pest nor microbial control can be survive and grow. Therefore, in hygienic design piping, cabling, equipment are all at sufficient space to walls, ceilings etc. as to be able to clean them, or outside a critical hygiene zone at the other side of a boundary.

Figure 2: Cleanable arrangements of control cabinet and cabling

Figure 3: Un-cleanable bioreactor by congestion and poor design

The humidity challenges

Another important factor is the need to control the humidity and avoid condensation, as water is a very important factor to microbial growth. This implies that surfaces that are or can be cold below dew point need to be well insulated. At the same time the relative humidity needs to be below a certain level. Especially when high pressure high temperature water cleaning takes place this is a great concern. The impulse of the water will remove the soil but also adds vast amounts of live giving water. Whenever these types of cleaning are needed only very solid walls and ceilings can be recommended. Special care should be taken when recirculation is employed in the air handling and filters can become saturated. In such cases HEPA filters can be found showing fungi growing through.

Product specific requirements

A more effective way is to separate equipment in such a way that it can be outside a zone of high classification. This requires a close study of the logistics of a production process. The various zones are segregated by physical barriers in combination with a pressure-flow cascade. A schematic example is given in Figure 4.

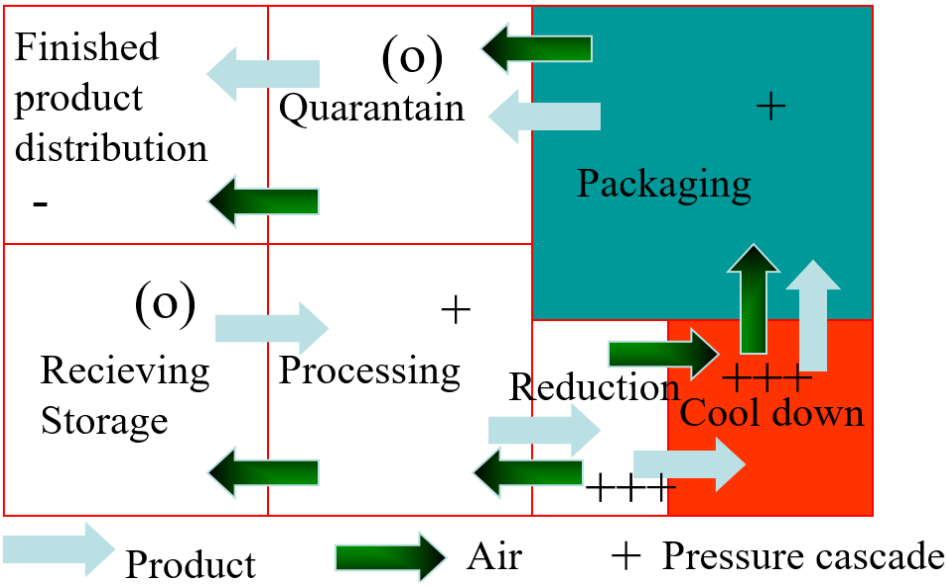

Figure 4: Schematic routing showing segregated zones and pressure flow cascade

Case Study

In designing the specific spray dry plant for small scale production (≤ 1 MT/yr) for VitaSquare Wolvega Netherlands many design considerations are implemented. First of all process steps are identified and assessed for: product susceptibility, the risk of spilling, the method to clean in place as well as the exterior, including the room. Logistics of materials, product, staff and waste are planned for.

Dosing and fine ingredients mixing

Logistics are set up to handle most raw material in bulk containers, positioned outside the process rooms, are hooked up to the process lines. (Figure 5) This all is done in a non-classified but controlled area of basic hygiene level. Spilling is not expected as all raw materials here are in containers or per piping such as feed water. Also, the CIP and waste flows are run as fixed piping.

Figure 5: Process vessels and stacked raw material containers at 1st floor level in not classified basic hygiene zone as back side of Figure 5.

Specific additives are added in the processing room via a tank lid (Figure 5). The tank itself is at the other side of the wall, with all its pumps, valves, sensors, actuators, wiring and supports. This leaves the processing room quite easy to clean. The various connections for the process and transfer steps can be made by transfer panels. The fine ingredients come to this processing room by an elevator from the ground floor. The elevator acts as an airlock as it is interlocked and flushed by overflow air maintaining the pressure flow cascade.

As shown in Figures 5 and 6 the logistics are well separated as well as the majority of the process equipment located in a non-classified hygienic zone. The area of exposure is very limited and in a controlled; ISO 9, ≥0,5 µm, operational environment. Where the product is transported and processed further in closed equipment basic hygiene is maintained although not particularly necessary unless a breakdown or maintenance situation would occur. All fluid piping is designed and equipped to be clean in place (CIP) treated. A specific part of the facility is designed around the spray dry tower and equipment. Unique design features are:

- Clean corridor concept in combination with a pressure flow cascade design. This implies the corridors surrounding the process equipment areas to be cleaner and better controlled than the process area. The benefit of this is twofold: a) any product residues spreading out of the equipment is prevented to spread around and b) only clean supply ducting outside the process perimeter is needed (Figures 6-7).
- Box in Box design. The influence of any pressure/flow dynamic from wind attack is taken away by a surrounding extra envelope. This also allows visitors to gain visual access to the plant without gowning up and entering (Figure 8).
- Gravity settling of product spill. The extract air is returned via a wide shaft with a very low air velocity upwards to the air handling system. This will allow any relative large spillage particles to settle at the bottom. Only airborne particles will be carried upwards and away. For areas that require wet cleaning a specific exhaust is opened when cleaning and drying to avoid undesirable damp air recirculating.

Figure 6: Connecting, dosing fine ingredients area

Figure 7: The clean corridor as a distribution duct towards process rooms

Figure 8: The box in box design with the production zone at the left

Specific data of the system (shown in Figures 9- 13):

- Supply air filtering: F7, F9 (EN779) and final filtering E11 (EN1822)
- Classification by particles in air in operation ISO 8 at 0,5 ≥µm
- Process air E12 (EN 1822) to the spray dryer at ISO 7 at 0,5≥µm
- Passive overflow cascade design with nominal highest pressure of 40 Pa.
- Twice or trice reused all overflow air in clean corridor concept reducing the required total air volume by factor 2.5.

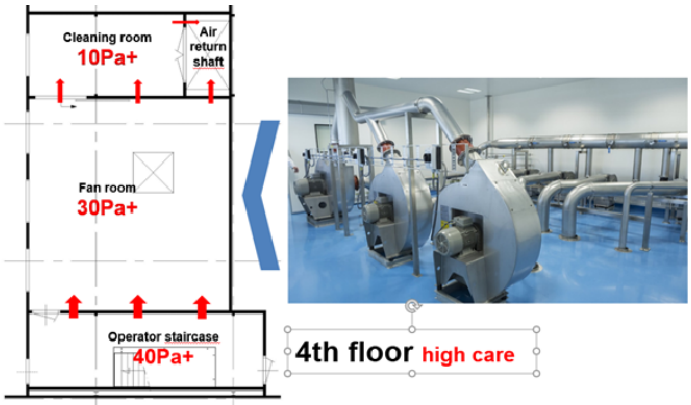

Figure 9: The fan area for the spray dryer inlet on the 4th floor

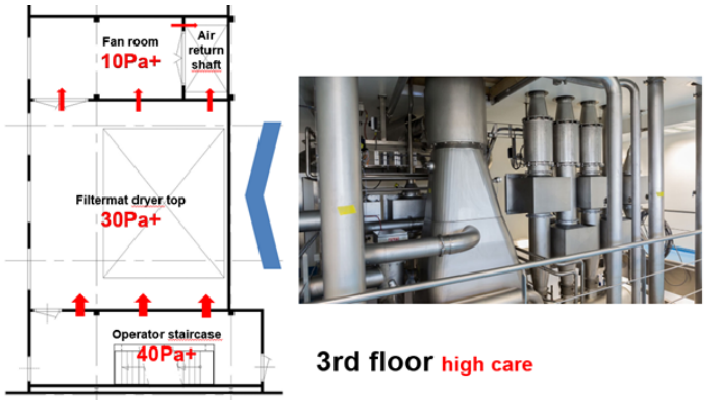

Figure 10: The fan area for the spray dryer inlet on the 3rd floor

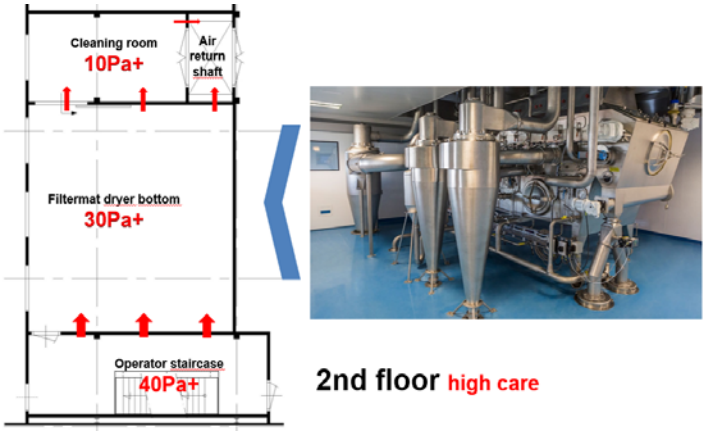

Figure 11: The spry dryer filtermat bottom at the 2nd floor

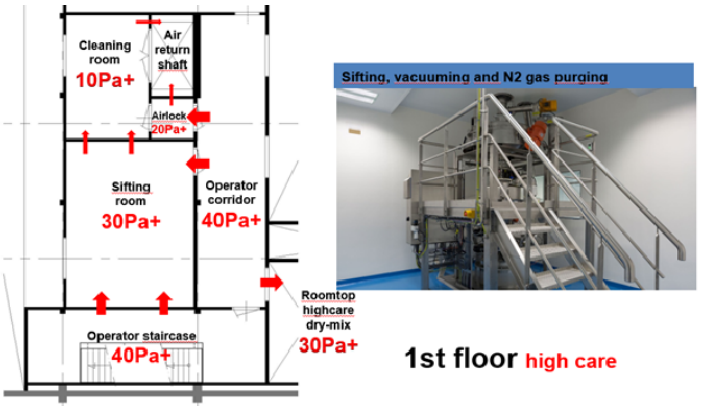

Figure 12: The sieve for the spray-dryed product on the 1st floor

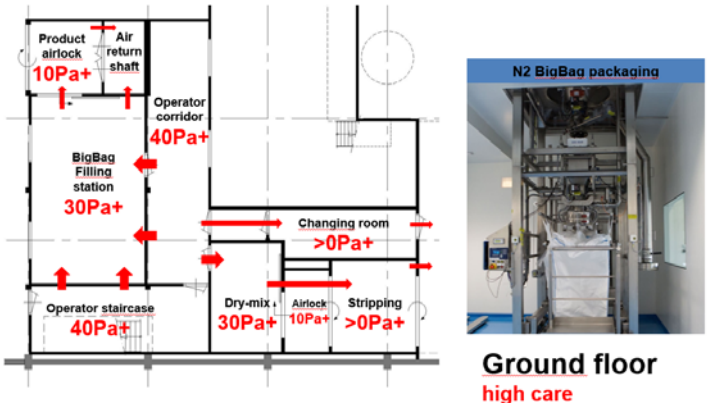

Figure 13: Big bag filling, dry mixing, gowning and airlocks on the ground floor

Differences in Approach

The hygienic design aspects of food processing plants are not specified in required cleanliness levels as for example is the case for sterile pharmaceutical products. In the EHEDG DOC 47 (sept 2016): 'Guidelines on air handling systems in the food industry', information is given on how an air handling system should be designed and constructed. For those areas of High hygiene, no direct criteria for levels of contaminants are given. For the design only, the essentials to be considered and the recommended filtration steps are given as shown in Figure 14.

Table 1: Overview of system recommendations for air handling

	Zone B	Zone M	Zone H
Filtration of environmental air (First, second or third filter stage) See also Section 5.8.7	Minimum one filter stage: 1. Stage M5-F7	Minimum two filter stages: 1. Stage F7 (+ GF if required) 2. Stage F9	Minimum three filter stages: 1. Stage F7 (+ GF if required) 2. Stage F9 3. Stage E10-H13 (depending on risk)
Positive air movement from higher to lower zone (Controlled overpressure)	--	optional	✓ essential[1]
Temperature control	optional	✓ essential	✓ essential
Humidity control	--	Optional depending on risk evaluation	Optional depending on risk evaluation
Minimum air changes per hour to maintain air quality[2]		5	10

GF = Gas phase or molecular filters (e.g. activated carbon filters) to filter gaseous contaminants

Figure 14: Recommendations from EHEDG DOC 47 'Guidelines on air handling systems in the food industry', including zone H (High hygiene)

In the section on Air Quality monitoring (section 7.5) the recommendation is given: “Air quality monitoring in a food manufacturing environment should be implemented to control dust and microbiological contamination risks caused by people, the processes and the environment…”. ….”Air quality monitoring may include:…….Airborne particle concentration monitoring….Microbiological monitoring based on zoning hazard analysis, optional for zone B, recommended for zone M and essential for zone H”. Comparing the above to the EU-GMP Annex 1 on Sterile manufacture of medicinal products, it is clear the food industry has a challenge in establishing and demonstrating control on the safety of their products.

Conclusion

Contamination control is essential in high hygiene production zones, but no specific classes or levels of contaminants are given. Microbial (re-)contamination is the most important concern, where specific pathogenic contaminants are of special focus. The HACCP approach is essential to establish and demonstrate control. EHEDG guidelines contribute to the design for processes and their surroundings. Integrated design is mandatory and has the most optimized outcome with respect to investment, operation, and cleanability.

Genomics in Assessing Microbial Contamination Risks

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Extended Abstract

Humans serve as a walking culture medium for heavy loads of microbes1. Microbes live in and on the human body, and all of our exposed body sites such as mouth and rest of the gastrointestinal tract, urogenital, nasal and respiratory tract and skin [2]. These dense and extensively diverse microbial communities all together constitute **microbiota** [2]. Traditionally, these microbes have been analyzed by culture, which needs the ability to grow viable bacteria in vitro, i.e., outside their natural habitat [1]. Culturing the entire microbial ecosystems is demanding, and for example require specific, complex culture media and specific equipment1. Thus, still to date it is commonly estimated that as much as 80 % of the bacterial species found by molecular tools in the human microbiota are either uncultured or even impossible to culture1. However, estimations vary a lot depending on the source or reference [2].

Recently, various molecular techniques targeting the bacterial 16S rRNA gene (i.e. universal key marker that is highly conserved among bacteria that measures the evolutionary proximity of organisms and enables taxonomical classification) or other genetic markers have remarkably advanced the study of entire, complex microbial communities [3]. Current analysis methods of choice are summarized in Figure 1. These molecular methodologies enable the analysis of both cultivated and non-cultivated members of microbiota, thus providing more comprehensive view of the microbial community structure than culturing [3]. The selection of molecular methods is relatively broad. During the last decade, mostly used DNA-based molecular analysis methods have included for example quantitative PCR, DGGE, fluorescent in situ hybridization and DNA microarrays [3].

In recent years, Next Generation Sequencing (NGS) has revolutionized the microbiota research [3]. NGS enables fast and high-throughput analyses, since the entire microbial ecosystems and not their single representatives are simultaneously analyzed. This is meaningful approach since in nature microbial metabolic processes always occur in communities [4]. Currently, the number of available NGS methods is extensive. The most employed analysis pipelines such as Illumina metagenomics approaches will be reviewed in this presentation. The possibility to analyze all the microbial DNA at the same time enables the build up of extensive gene catalogues from samples of interest [4]. However it is worth to recognize that NGS approaches produce an enormous amount of data, and it is quite a challenge to set up the bioinformatics pipelines and pick up correct data handling tools [3].

Traditionally, cleanrooms have been considered microbial-reduced or even -free environments that are utilized to protect human health and industrial product assembly [5]. However, analyses based on NGS methodologies have revealed that actually rather diverse microbial ecosystems i.e. “the collective microbiota” exists in cleanrooms [6]. Typically, the microbiota in cleanrooms derives from human skin or from the environment that are transferred to cleanroom via personnel, dust or material transfer. Thus, most common microbes in cleanrooms that have been detected from cleanroom are usually gram positive bacteria. However the recognition and more accurate knowledge of the pattern and composition of this microbial collective is important both for the contamination control and deeper understanding the cleanroom environment. Thus, modern analysis methodology repertoire will increase our knowledge of the strict controlled built environments.

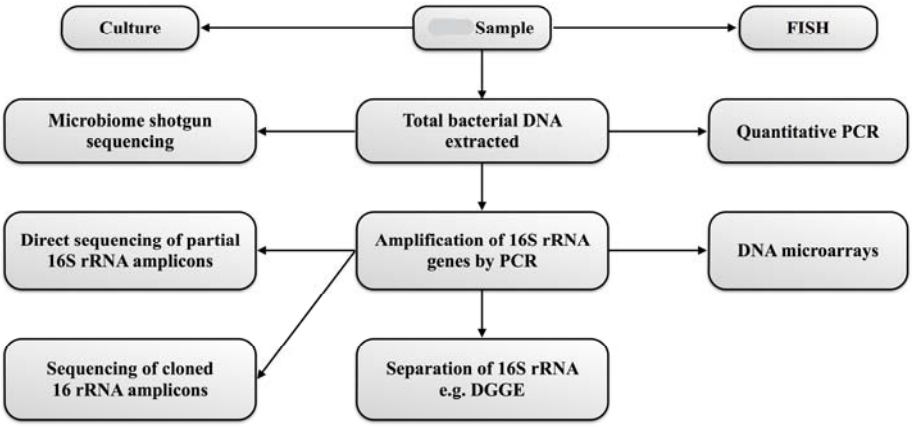

Figure 1. A summary of molecular microbiology methodologies currently utilized in gut microbiota research[5]. DGGE **=** denaturing gradient gel electrophoresis, FISH = fluorescense *in situ* hybridization, PCR = polymerase chain reaction

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High Quality Ph. Eur. Water by Membrane Technology - The Design and Main Principles of Producing High Quality Water According to Modern Requirements (Ph. Eur.) by using Membrane Technology

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Extended Abstract

The European Pharmacopoeia is responsible for compulsory quality standards throughout the pharmaceutical industry in Europe. It is used for controlling the legal and scientific quality of medicines, and the ingredients used to develop, manufacture and market them.

European Pharmacopeia Monograph Water for Injections (0169) was taken under revision to re-determine the specifications of production. Since April 2017 European Pharmacopeia allows generation of WFI by non-distillation methods such as double-pass reverse osmosis (RO) coupled with other suitable techniques. The decision was based on survey, expert workshops and multidisciplinary forum involving various stakeholders. The new monograph states that correct operation monitoring and maintenance of system are essential to ensure the appropriate quality of water. Any system for Water for Injection, regardless of technology must be designed by experienced company in accordance with regulations. Installation and validation are followed by careful monitoring and maintenance to a high standard.

System design begins with gathering all essential information; feed water quality, treated water specifications, hourly flow rate, total daily volume and nature of any peaks in water demand. The plant must be large enough to replenish storage tanks between

demand peaks, especially if they occur frequently. A simplified system design consists of pre-treatment, main treatment, storage and distribution (with recirculation).

Pre-treatment includes filtration, softening and absorption processes. Chemical dosing is possible yet not preferred in pharmaceutical environment. At this stage the focus is on control of microbiological growth but it cannot be totally eliminated. In main treatment the philosophy is to “over-purify” the water to avoid further treatment in the distribution system. The temperature has to be controlled because higher temperature than 20°C will increase the risk of microbial contamination. The temperature control can be done with start/stop operations, heat exchanger, plant room cooling and reduction of effluent volume from recirculation. In ambient distribution the water temperature is ideally below 15 °C (acceptable below 20°C) and for hot distribution it should be ideally greater than 80°C but acceptable if greater than 65 °C).

Storing the water is the weakest link in the system and it should not allow degradation of water quality. The tanks should be closed with proper vents and the head space should be effectively wetted (i.e. spray ball). The tanks should also be equipped with sanitary pressure-relief valves and bursting discs to avoid over/under pressurization. All storage tanks should be ensured with adequate turnover; no less than 1-5 times per hour.

The definition of “Product” (water) is accurate once the determined quality requirements are met. In order to achieve the requirements, the system design must consider different aspects in lay-out, materials and other critical elements. Firstly, a continuous turbulent flow of water has to be ensured (> 2100 Re). This means that the water has to move at the velocity of ~ 1,0 m/s. In order to remove biofilm, a velocity of 1,5 m/s with antimicrobial agent has to be reached. The distribution system should however be sized based on the peak demand flowrate +25-50 % return flow. Recirculation of water is necessary to minimize microbial re-growth, with minimum velocity of 1,0 m/s. Design on recirculation must consider the product utilization in both maximum demand and zero demand.

In order to prevent microbiological contamination, dead-legs should be avoided. Dead-leg is any area in system, in which water might stand still or is not exchangeable during rinsing. FDA has set a rule that “Pipelines for the transmission of purified water for manufacturing or final rinse should not have an unused portion greater in length than 6 diameters (the 6D rule) of the unused portion of pipe measured from the axis of the pipe in use”. However, industrial experts are designing systems with dead-legs limited to 3D.

The system must be equipped with necessary instrumentation which is identified as critical or non-critical. A critical instrument is needed for direct process control and measuring, affecting final water quality. These critical instruments need to be commissioned and certified as well as included in periodic calibration procedure. A non-critical instrument is not used for process control and they only need to be commissioned, not certified. Most common critical instruments used in WFI RO system are conductivity meters, TOC meters, flow meters, temperature sensors, pressure sensors and ozone monitors.

Distribution and storage systems should be designed to allow thermal sanitization as a routine to eliminate all bacteria and endotoxins which will be abolished in high tempera-

tures. In distillation the distribution loop if often operated at a continuously high water temperature which prevents any endotoxins or microbial growth. RO system loops run at ambient temperature which requires regular facilitation of sanitation. Sanitation can be done with hot water or ozonation coupled with UV. The lower operation temperature of an RO system is safer for its user compared to continuously high temperatures of a distiller. If the system is steam sterilized, it should be sloped and fully drainable to assure complete condensate removal. Internal surface finish of stainless steel fabricated items should be 0.4 – 1.0 microns Ra.

Validation protocol is always carried out in implementation of WFI system. It establishes documented evidence that assures a specific procedure to continuously produce a product (water) which meets the predetermined specifications, quality characteristics and user specific requirements (USR). There are many guidelines for general process of validation; provided by organizations such as FDA (the Food and Drug Administration) and MHRA (Medical and Healthcare Regulatory Agency). The procedure often consists of design qualification (DQ), installation qualification (IQ), commissioning, operational qualification (OQ), and performance qualification (PQ). In addition to European Pharmacopoeia, there are further regulations (European cGMP) and guidelines (ISO9001) which specify how to manufacture water.

Distillation techniques have traditionally been considered less risky than reverse osmosis based systems due to biofilm formation. Hot water sanitization (HWS) membrane systems can control the biofilm formation and tied with adequate control system offers low risk solution. Real-time microbial control such as TOC monitor (Total Organic Carbon) allows detecting any development of microbial contamination in the water system. In order to assure the quality of produced water, technologies such as ultrafiltration, electrodeionization and UV-treatment should be considered during the design phase to utilize downstream of the RO. This will ensure the removal of any remaining microorganisms. When choosing a WFI production method, both costs and risks ought to be considered. RO based system offers OPEX savings and lower water footprint which makes it highly attractive nowadays.

GENERAL SESSION

Safety Ventilation in Ultra Clean Air Operating Rooms – A Review

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Extended Abstract

Mechanical ventilation was rarely used in hospitals until the 1940s and where mechanical ventilation was used, it was more for comfort than contamination control, i.e., to reduce bacteria-carrying particles. Studies in hygiene were performed during the 1940s with newly invented samplers for airborne bacteria, see e.g., Bourdillon et al (1948), and it was after the end of the second world war that mechanical ventilation in hospitals was installed, for the purpose of contamination control. By the early 1960s air distribution systems providing turbulent mixing air were well known. This principle is based on the concept of mixing incoming air relatively quickly with air present in the room, whereby complete mixing is achieved.

Blowers and Crew (1960) investigated a series of different air distribution systems and one of the observations was, when the air was turbulent mixing, the results improved proportionately to the amount of air supplied, until this reached a level of about 20-25 air changes per hour. Beyond this there was little further improvement, unless an air distribution system creating downward air movements was used. When two people were walking in the room the downward air movements were disrupted and became more or less turbulent mixing. Furthermore, the authors suggest that to prevent ingress of contaminated air from other parts of the hospital an operating room should be pressurized by the flow of filtrated air, where the filters should have an efficiency of 99.9 per cent for 5 μ-particles.

The book Hospital Infection by Williams et al (1960) shows that in the early 1960s that operating rooms with turbulent mixing air were well established. Airflows of at least 15 air changes per hour were suggested. The second edition (Williams et al (1966)) mentions

that tests with parallel air movements have been performed. The authors express that there is not yet (1966) enough evidence to discuss the usefulness of this method.

To achieve increased cleanliness during ongoing operations Charnley (1964) developed an operating enclosure, known as a “greenhouse”, which consisted of a room within the operating room. The enclosure had a filtered supply air with downward air movements. According to Charnley, the speed of the downward airflow must be fast enough to counteract rising currents of air caused by movements of the surgeons’ arms, by heat from the operating lamp and the surgeons’ bodies and air movements caused by nurses walking in the room. The downward air velocity should be at least 0.3 m/s to neutralize the upward air movements and the air flow rate should be at least 100 air changes per hour. In later studies Charnley and Eftekhar (1969) showed that further improvements were achieved if the supply air was filtered and the air change rate was increased to 300 changes / hour.

Charnley (1972) summarized results from 5 800 total hip replacements between 1960 and the end of 1970. The infection rate fell from 7-9 per cent to less than 1 per cent purely as a result of measures taken to prevent exogenous infection in the operating room. Prophylactic antibiotics were purposely avoided in this study. It was believed that of all precautions taken against infection in the operating room, the most important was clean air, but this measure alone did not reduce the infection rate below about 1.5 per cent. The further reduction from 1.5 per cent to 0.5 per cent level was believed to be due to measures taken to avoid penetration of bacteria through the textile of the surgeon’s operating gown by using body-exhaust suits, and due also to improved methods of wound closure. Lidwell at al. (1982) reported a multicenter study in which 19 hospitals took part and over 8 000 operations for the replacement of the hip or knee joint had been recorded. Each surgeon was allocated at random between conventional and ultraclean air operating rooms.

The results showed that ultraclean air in operating rooms reduced the incidence of deep sepsis after total joint replacement operations and that this reduction was enhanced when the operating team wore special suits, i.e., whole body-exhaust suites. Table 1 gives the median values of airborne bacteria-carrying particles per m^3 in relation to ventilation system and clothing. The values in Table 1 show that downflow systems perform better than horizontal systems. This might be explained by the fact that in horizontal air flows the accumulation of contaminants can occur in wake regions of people. Downflow systems with walls perform better than those without. Wearing body-exhaust suits clearly enhanced the reduction in the concentration of airborne bacteria-carrying particles, especially in ultraclean systems.

Data discussed in a paper by Lidwell (1983) lead to the conclusion that infection in the joint after an operation for total joint replacement is most likely to be derived from the airborne flora unless this is reduced to very low levels by an ultraclean air system. Lidwell stated that the sepsis rate without prophylactic antibiotics is proportional to the square root of the concentration of bacteria-carrying particles (CFU/m^3 with aerobic cultivation).

Table 1. The concentration of airborne bacteria-carrying particles per m3 in relation to ventilation system and clothing, (Lidwell et al (1982)).

Ventilation system	**Median No of bacteria-carrying particles/m^3**	
	Conventional clothing	**Body-exhaust suit**
Conventional (turbulent mixing)	164	51
Allander	49	14
Horizontal flow	22	1
Downflow without walls	10	-
Downflow with walls	2	0.4

Whyte et al (1983) suggested that the air in the wound area should, on average contain not more than 10 CFU per m3. It could be noted that during ongoing operation the recommendations in Sweden are less than 10 CFU per m3 for surgery susceptible to infections and less than 100 CFU per m3 for other surgery not infection-prone. (Spri (1989), SFVH (2003) and Socialstyrelsen (2006)). Furthermore, a technical specification published by the Swedish Standard Institute, SIS (2015) (SIS-TS 39:2015), suggests half as large CFU-values as above. It should be noted that since the 1990s most ventilation systems with unidirectional air flow are installed without sidewalls or with partial walls.

Chow and Yang (2005) described a numerical study of an ultraclean system with unidirectional air flow. Air velocity at the supply diffuser was identified as one of the most important factors in governing the dispersion of contaminants. Higher velocities reduce the contamination risks. The position of the operating lamps was also found to be critical. Omission of partial walls may increase the contamination risks due to entrainment of room air from the outer zone to the inner zone of the operating room.

The influence of person's movements on contaminant transport during an orthopedic surgical operation in a unidirectional air flow system with a velocity of 0.32m/s was examined by Brohus et al (2006) by using computational fluid dynamics (CFD) and smoke visualization. It was found that the influence of persons' movements might cause a local but serious risk of transport of contaminants (bacteria) from the non-clean outer zone to the inner clean zone.

Measurements in operating rooms with air supply systems providing unidirectional air flow have been performed by Nordenadler (2010). When the air velocity is below 0.3 m/s the air flow pattern above the operating table occurs in a disordered manner, which resembles that of total mixing air movements. However, when the air velocity exceeds 0.4 m/s, the air flow pattern more closely resembles unidirectional air flow, and the sweeping action above the operating table seems to be significantly improved. Most air supply systems providing unidirectional air flow, such as those which have been installed in Sweden and in many other countries in Europe in the past 20 years, have air velocities

below 0.3m/s. This indicates that the air movements above the operating table become turbulent mixing and entrainment of air from the outer zone to the inner zone can occur.

Conclusions

This literature survey shows that the concentration of airborne bacteria-carrying particles (CFU/m^3) in operating rooms depends on the air flows, air movements and enclosures. Most of the recently installed unidirectional air flow systems in Europe are without or with partial sidewalls and have air velocities below 0.3 m/s. This results in a disordered airflow pattern above the operating table resembling that of total mixing air, and also shows that entrainment of air from the outer zone to the inner zone can occur. This shows that the dilution principle starts to become valid.

Furthermore, the chosen clothing systems play a determining role and that it is possible to classify the clothing systems by the definition of their source strength of bacteria-carrying particles, which is described as the mean value of the number of viable particles per second from one person. This shows that the number of people present in the operating room has an impact on the concentration of airborne bacteria-carrying particles, see Ljungqvist and Reinmüller (2013). As a first approximation, when calculating the necessary air volume flow in operating rooms, one can assume that the dilution principle is valid in the sterile zone during ongoing operations. In such cases the number of people in the operating rooms and chosen clothing systems should be taken into consideration.

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From Individual Thermal Sensation to Smart Control of Heating and Cooling

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Extended Abstract

Thermal satisfaction is one of occupants' basic needs. There is strong scientific evidence that either too cool or too warm thermal environments have negative impacts on both personnel's working productivity and patients' recovery process. Traditionally, thermal environment has been controlled utilising more or less fixed temperature set-point values. Such methodology is based on manual adjustment or pre-defined scheduling of set-point temperature values.

According to the latest scientific results, obtained from both sophisticated calculations and field test questionnaires, there are significant differences in thermal expectations between individuals. These variations are related to individual body composition and especially to individual fat-free mass. Since optimal operative temperature can vary even 6ºC (with identical activity and clothing insulation levels), more attention ought to be payed to improve thermal satisfaction of occupants.

In an on-going HumanTool project, a new control concept ($HTM_{control}$) has been developed and field tested in order to improve thermal satisfaction of individuals (Figure 1). In the first step of this concept, an on-line monitoring system of thermal environment has been implemented in an office building and two hospitals. In the second step, based on the data obtained from this monitoring system and individual body composition measurements, individual thermal sensation index values has been estimated by Human Thermal Model (HTM). In the third step, in case individual thermal sensation index values deviate from thermal neutrality, new optimal temperature set-point values are defined and written automatically to individual spaces via building automation systems.

According to the preliminary results obtained from the field tests, this new generation control concept is able to adjust thermal environment for individuals. However, more testing during different seasons and climatic conditions as well as in different building types (in terms of building service systems, thermal mass and insulation levels, and building automation systems) need to be performed prior to wider utilization of this new control concept.

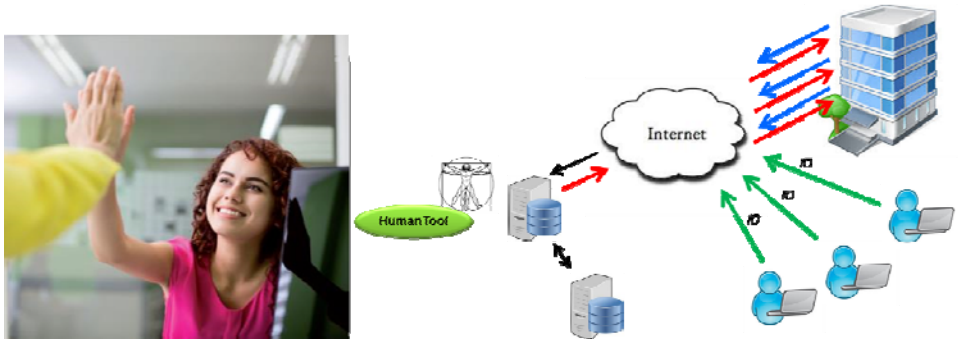

Figure 1. Improving thermal satisfaction by demand-based control of thermal environment.

Lean to Enhance Cleanroom Efficiency

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Background

The design, building and especially upkeep of cleanrooms is costly. Cleanrooms are approximately 30-50 times more energy intensive than average commercial buildings [1]. Furthermore, hospital cleanrooms, operating rooms (OR) are among the costliest and most resource-intense units in the entire building. Thus, cleanroom efficiency should be held at a high level in order to maintain an adequate level of productivity and cost-efficiency. The notion applies regardless of the industry sector.

However, too often this notion fails to materialize: In today's hospital OR usage rate as well as management of personnel's work tasks have often been perceived as inadequate. For example, staff and room scheduling may not be optimized and thus lead to poor utilization of the costly cleanrooms. Moreover, inefficient work processes compound the issue. As waste and productivity impact profitability, their management is crucial, especially in cleanrooms. Thus, it is of utmost importance to utilize a methodology that effectively helps eliminate waste and increase cleanroom productivity.

For several decades, Lean approach has proven useful in increasing work process efficiency by streamlining work processes and eliminating non-value-added steps, also known as waste. Lean has gained ground among several branches of industry and its popularity has significantly increased in service industries in the past few decades. Especially the success of Lean in the field of healthcare has been widely acknowledged. As could be expected, resource-intense cleanrooms have also awakened the interest of cleanroom personnel and management as well as other stakeholders seeking to benefit from Lean methodology.

Keywords: Lean thinking, healthcare, pharmacology, biomedicine, work processes, cleanrooms

Material and Methods

In this study, several research studies assessing use of Lean in cleanrooms (healthcare, pharmacology and biomedicine) have been reviewed. The used Lean tools and methodologies included e.g. A3 problem solving tool, value stream maps, Kaizen Events/Rapid Improvement Workshops, Kanban, Lean Six Sigma, and 5S. This study analyzes and illustrates research results of several Lean improvement initiatives carried out in cleanrooms thus far and presents a few development needs for future Lean cleanroom initiatives.

Results

Lean has become a prominent framework for improving healthcare, pharmacology and biomedicine processes and facility design. Although Lean methodologies are currently utilized in cleanrooms, they could be more prominently utilized to increase cleanroom efficiency by e.g. streamlining work processes and eliminating non-value-added steps.

According to the study results, Lean initiatives had improved several key areas regarding cleanroom work processes. The use of Lean had led to several positive outcomes, including decreased variation among patient volumes and improved workflow in the preoperative processes, improved scheduling, and an improved usage rate of healthcare facilities, e.g. surgery wards [2,3]. Staff communication, information flow and teamwork had also become more transparent and efficient in healthcare settings due to Lean [3]. Similar results have been achieved in pharmacology and biomedicine.

Lean and Lean Six Sigma – a synergized managerial concept of Lean and Six Sigma; an approach very similar to Lean – have also improved cleanroom work flow, cost-efficiency and work process efficiency and safety in cleanrooms. For instance, in a study by Olson et al. use of Lean had led to increased productivity and decreased R&D (research and development) costs, while increasing technology capacity and reducing cycle and queue times in a multi-technology R&D cleanroom facility [5]. In another study conducted by Lamm et al. use of Lean principles had improved workflow and efficiency at an adult infusion clinic and reduced chemotherapy turnaround times from 60 to 26 minutes [6]. A study by Popielarski et al. points to use of Lean in efficiently streamlining cleanroom work flow and minimizing cross-contamination risks [7].

Despite several Lean improvement initiatives, a significant portion of employees' work time is still oftentimes spent on wasteful activities, such as unnecessary traveling in the work environment, doctors spending time preparing the patient, repetitive phone conversations, filling redundant paper-based forms, fixing mistakes caused by human errors, etc. Many of these wasteful activities can be eliminated by applying Lean principles and

methods into cleanroom work process management. The Lean “tool-box” includes several methods/tools to improve cleanroom work processes:

- Kaizen Events have been utilized for staff training and change management purposes.
- 5S is a tool designed to eliminate waste in a work environment and it has proven beneficial in optimizing cleanroom efficiency. The 5S tool has resulted in cost reduction by improving human errors and minimizing time spent in looking for tools and supplies. It has also improved productivity by improving the employees’ work flow.
- Kanban signs and value stream maps have been beneficially utilized for cleanroom workflow management
- A3 tool has been proven beneficial in healthcare environments for continuous improvement and problem-solving initiatives.

Conclusions

Lean initiatives have shown remarkable capability to enhance hospital cleanroom work process efficiency. Several positive research results have highlighted the importance of Lean in improving cleanroom work processes and work environments. Yet, the initiatives and projects carried out thus far have merely scratched the surface of the deep potential Lean has to offer. Creativity is needed in order to innovate new Lean methods to facilitate cleanroom work process design. Moreover, new solutions and approaches are needed on how to utilize Lean in cleanroom work environment design process. All in all, a need exists for far more thorough, systematic implementation of Lean among cleanroom work process and environment design.

Based on the study results, future development needs for a successful Lean cleanroom implementation project include comprehensive personnel training, utilization of dynamic development teams and use of value stream mapping for work processes. Moreover, Lean implementation projects require top management support, commitment, engagement and transparent communication between the participating stakeholders. Lastly, success in Lean cleanroom projects predicates Lean facilitation by experts, a wide-ranging system approach as well as successful change management and resource management.

The collected results apply to cleanrooms, especially in the field of healthcare. However, the results can also be applied to other specialties. Furthermore, Lean could be applied to OR facility design as well to other healthcare services.

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The Antimicrobial and Air-purifying Effect of Blue Light

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Introduction

The antimicrobial effect of blue light has recently attracted a lot of attention, even more since the increased antibiotic and biocide resistance among microbes has been recognized as a global threat. The situation calls for urgent action as it is now evident that antibiotic resistance is life-threatening in the same sense as cancer, both in numbers of cases and likely outcome. Although the mechanisms of action are not fully understood, there are known endogenous photosensitizers within microbial cells that absorbs blue light effectively. This will subsequently result in production of cytotoxic reactive oxidative species (ROS). Studies have shown different wavelengths of blue light to be effective in inactivating a wide range of microbes; Gram-positive and Gram-negative bacteria, moulds and yeast, both in planktonic and biofilm forms. In addition, there are several ways to enhance the effect of blue light.

Blue light

Antimicrobial blue light is emerging as a potential technology for disinfection in hospitals, food industry, any cleanroom or industrial settings that require a high level of contamination control. Visible blue light is defined as 400-780 nm by the Radiation and Nuclear Safety Authority in Finland, although some authorities will categorize 380-780 nm as blue light.

New possibilities to study the biological effect of specific wavelengths has emerged due to the development of the LED light technology. LEDs offers certain advantages over

lasers and are more versatile. Studies have established that both laser and LED light sources exert similar antimicrobial effects and biological responses. The more crucial factors, from a biological point of view, are wavelengths and doses of illumination used.

Antimicrobial properties of blue light

Blue light is known to inhibit and destroy microbes due to naturally occurring endogenous porphyrins and flavins that effectively absorb blue light. This will subsequently lead to the production of various reactive oxygens species (ROS) that exhibit cytotoxic effects (Figure 1). These photosensitive compounds are exclusively produced in microbial cells (not mammalian cells). Studies have shown that blue light can effectively eliminate a wide range of pathogenic microbes, regardless of their antibiotic or biocide resistance profile.

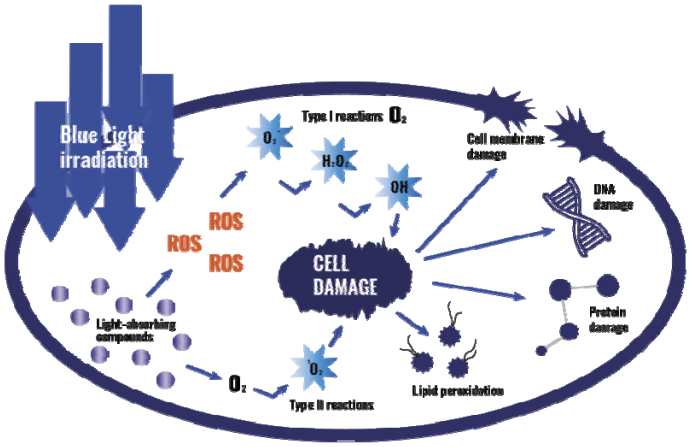

Figure 1. Antimicrobial properties of blue light.

Healthcare-associated infections (HAIs) and in acute care hospitals.

European Centre for Disease Prevention and Control (ECDC) completed a survey in European hospitals 2011-2012, 29 EU/EEA Member States and Croatia participated. It was established that 6% (country range 2.3%–10.8%) of all patients are infected with at least one HAI (Health-care associated infection) during their hospital stay. Based on these results, it was estimated that 81 089 (95%CI 64 624–105 895) patients with an HAI is found on any given day in European acute care hospitals. The total annual number of patients with an HAI in European acute care hospitals in 2011–2012 was estimated at 3.2 million.

The 11 microorganisms most frequently isolated from HAIs in the survey was; *Escherichia coli* (15.9%), *Staphylococcus aureus* (12.3%), *Enterococcus spp*. (9.6%), *Pseudo-*

monas aeruginosa (8.9%) *Klebsiella spp.* (8.7%), *Coagulase-negative staphylococci* (7.5%), *Candida spp.* (6.1%), *Clostridium difficile* (5.4%), *Enterobacter spp.* (4.2%), *Proteus spp.* (3.8%), *Acinetobacter spp.* (3.6%). Many of the isolated organisms had reported selective antibiotic susceptibility (antibiotic resistance). There are extensive studies showing that these microorganisms can be inactivated by blue light, some examples are shown in Table 1.

Table 1: Examples of microbes successfully inactivated by blue light. Although varying results of the antimicrobial blue light efficacy can be observed in different studies, all microbes seem to respond fatally to blue light. The observed differences in efficacy can partly be explained by varying experimental conditions.

Microbe	Wavelength	Dose	Inactivation	Referenses
Clostridium difficile	405 nm	48 J/cm2	4 $\log_{10}$	(MacLean *et al.*, 2013)
Escherichia Coli	405 nm	133 J/cm2	6,3 $\log_{10}$	(De Lucca *et al.*, 2012)
MRSA	450 nm	28 J/cm2	81%	(Makdoumi, Goodrich and B€ Ackman, 2017)
MRSA (inside biofilm)	460 nm	360 J/cm2	> 80 %	(Yang *et al.*, 2017)
Pseudomonas aeruginosa	470 nm	8 J/cm2	96 %	(De Lucca *et al.*, 2012)
Salmonella enterica	470 nm	110 J/cm2 165 J/cm2	84-93 % 100%	(Bumah, Masson-Meyers and Enwemeka, 2015)

Photocatalysts and photosensitizers –
enhancing the antimicrobial effect of blue light

Blue light is not as effective as UV light in inactivating microbes, but the effect can be enhanced for a more rapid inactivation in situations that are time-sensitive. There are many known agents that show synergistic effects with blue light; antibiotics, disinfectants and various nanoparticles. In addition, metal oxide nanostructures with known photocatalytic properties activated by UV-light (sunlight) has been used in building materials, coatings and paints for decades. $Ti0_2$ (titanium dioxide) is widely used and is known for its ability to oxidize air pollutants and inactivate microorganisms.

In recent years, modified versions of $Ti0_2$-coatings have been developed, to give them properties that respond to visible blue light. These visible light responsive $Ti0_2$ photocatalysts provide a promising way to enhance the antimicrobial effect of blue light. Furthermore, blue light-activated $Ti0_2$ can be utilized for photocatalytic degradation of indoor air pollutants such as organic pollutants and volatile organic compounds (VOCs).

Conclusions

Blue light is proven to be antimicrobial, and the effect can be further enhanced with photosensitizers and photocatalysts. The observed synergetic effects with other known anti-

microbial agents provides an interesting addition that should be explored and investigated further. Antimicrobial blue light is an innovative approach that is worth paying attention to in the battle the increasing microbial resistance problems.

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Introduction to Cleanroom Technology

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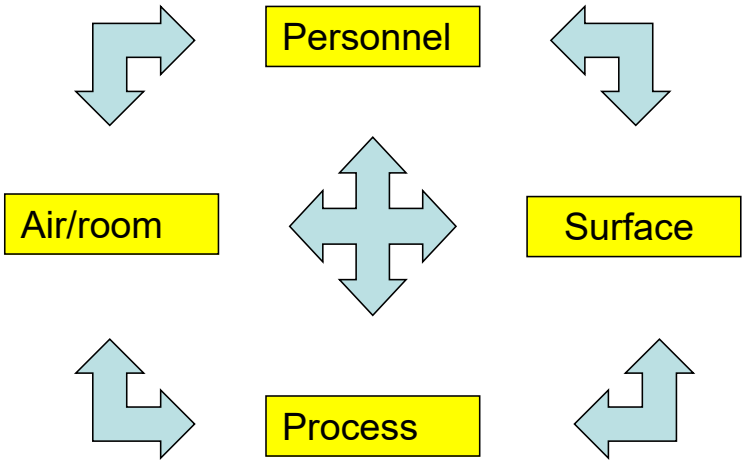
What is cleanroom technology?

This can be described as one or several technologies used to create cleanliness for a process / product. The next question then pops up quickly. What is clean? Here you probably get as many answers as people ask. The answer you get is subjective, we have all the different levels / requirements for what we think is clean. We usually relate purely with visually clean or the degree of how dirty things may be, that is acceptable to me e.g. the room, the dishes and clothes. The degree of cleanliness is also dependent on what requirements I have for my process. What contaminants (pollution) am I worried about? What gives me a level that is not acceptable to my process / product?

Cleanliness can be divided into visually clean, chemically clean, microbiologically clean, but also particulate clean (particles not visible to the naked eye). A basic rule regarding sampling and cleanliness is: If it´s not visually clean, you can ignore it being chemical, microbiological or particulate clean. Then you do not need to take any tests to understand the result.

In all clean spaces there are more or less contaminants (such as dirt, contaminants that you do not wish in this local / process). The biggest challenge is that these contaminants do not occur near by the most critical area of the process. A process can be, for example surgery, manufacturing of pharmaceuticals or medical devices, microelectronics, optics or food products. In different processes, the requirements differ in cleanliness. Certain processes are sensitive to living contaminants, but small particles are no problem. Other processes do not care for living organisms on the particle, but it is the particle as such that creates problems. In other words, different processes have different challenges to handle.



What is required to succeed with its "cleanliness" in a process?

To succeed, a holistic approach is required. We can create the best conditions technically, but unless the staff follows set rules (attitudes) or do not have the right education / skills for a task, the result will not be satisfactory. However, poorer technical conditions can nevertheless provide a good result if you have the "right staff". The old cliché "Nothing is stronger than its weakest chain" fits very well here.

Design of High Containment Research Facilities

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Abstract

The design of modern and functional high containment facilities should attract top researchers and allow long-term stable operations. Today, high containment facilities are often experienced as unpleasant spaces with elevated operational costs and uncertain funding. In this presentation, practical approaches to the design phase will be discussed. For example, how are the room tightness requirements defined, and what are the consequences? Why does the design team require information about flow of personnel, materials and waste? Which primary and secondary containment issues are important to resolve? How should the technical areas be placed in order to serve the containment area? Future visions on how surrounding areas may add value to the containment area will be discussed.

The Principle of Containment Design

Containment facilities are in use within hospitals and clinical treatment, diagnostics, production, research and teaching. The aim is to create a safe environment where research on microbial agents, and/or treatments, can be performed in a safe manner for the personnel, patients, products and environment.

As defined by the World Health Organization, microorganisms are divided into four risk groups (RGs), RG-1 to RG-41. RG-4 presents the microorganisms with the highest risk based on their pathogenicity, environmental and economic treat. RG-1 presents the microorganisms with the lowest risk.

The principle of containment design is based on the need to create an appropriate containment of the microbial agents in use in the facility. Corresponding to the four RGs,

there are four containment levels CL-1 to CL-4 2-5. Each containment level is defined by a set of requirements that must be met in order to create a safe workspace.

The presentation will focus on high containment design, i.e. CL-3, CL-3Ag and CL-4. In CL-3 and CL-4 laboratories, the aerosols are contained in biological safety cabinets, isolators, transfer containers or other containment devices, and the room envelope is the secondary containment barrier. However, CL-3Ag is a designation for large animal containment spaces where the room envelope is the primary containment barrier. CL-3Ag facilities have high biosafety and biosecurity standards, at a similar level as CL-4 laboratories.

In high containment design, there are several interdisciplinary aspects between the engineers and the architects that are important to solve. The design reflects the fact that the purpose of the building is to work as a machinery 24/7, in order to process and prevent the escape of unwanted microbial agents to the environment, and to protect the users and maintenance staff.

Practical Approaches to the Design Phase

Despite the fact that several design processes have tight delivery deadlines, it has to be a process of

- involving the researchers, the maintenance staff and the biosafety officers together with the architect and the engineers
- further developing the conceptual project plan into a functional design
- finalizing the programming
- economic analyses
- risk assessments
- shared knowledge

An iterative design process, where the design team consults with stakeholders in subsequent zoom in/zoom out perspectives, could refine and optimize the facility design and decrease time and costs in latter stages.

A main event in the design process that enables functional design of the facility is to determine the flow of personnel, equipment, materials, samples and waste. The creation of flow diagrams with quantities, volumes and weights are must-haves for several interdisciplinary aspects and dimensioning, including the dimensioning of the air locks for personnel, air locks and pass boxes for materials, as well as the air- and waste handling systems. In addition, these diagrams are tools to verify routes for transportation of large equipment in/out of the facility, the layout of the technical areas that serve the containment area and access controls.

Room surfaces and inventory must be designed to be easy cleanable and resistant to the detergents and fumigation medias that are planned to be used in the laboratory. During my work on high containment design, there is one issue that is frequently discussed, and that is the definition of realistic air tightness for the high containment facility (Figure 1). A negative pressure hierarchy in the containment area permits a dynamic contain-

ment. To achieve a stable pressure hierarchy, it is necessary to construct a defined and controllable airtight structure. This includes the interdisciplinary details on how piping, ducts and electrical supply is a part of the airtight construction. Validation methods for room tightness applied in Norwegian projects are smoke test or determination of building air leakage at 50 Pa in accordance with NS138297. In addition, some facilities, adapt the pressure decay test 4,5, in order to test the room envelope, i.e. a test of the static containment in case of loss of negative pressure or over pressurization. Examples will be given in the presentation.

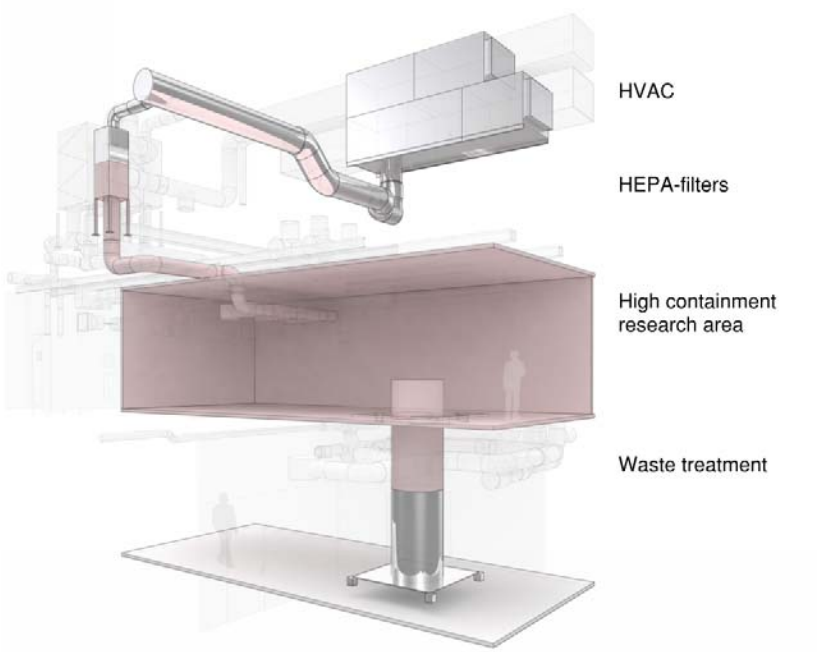

Figure 1. High containment facility geometry. The principle of the containment barrier, as illustrated by M. Jepsen, Henning Larsen Architects[6].

Future Visions for High Containment Facilities

High containment facilities are referred to as exhausting spaces to work in. This is for instance due to the amount of operational procedures and the impression of the surroundings. The design process could explore potential layout and flow synergies between the high containment area and its connecting area. There might be several interesting perspectives and synergies, as inspiring surroundings, synergies between research groups, in addition to low construction-, operational- and maintenance costs in the connecting area. Examples will be given in the presentation.

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Cleanroom Disinfection - An Important Part in Contamination Control and GMP

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Abstract

Detailed cleaning and disinfection routines should be followed when working with manufacturing of medicinal products and several factors can affect what type of cleaning and disinfectant we should choose to use in our most critical areas. How efficient a disinfectant is and other critical factors should be considered when determining a cleaning and disinfection policy.

The suitability of a particular disinfectant will vary and will be dependent on its spectrum of activity (the range of different types of microorganisms that the disinfectant is active against) as well as other factors (e.g. health and safety considerations, compability with surfaces being disinfected, compability with detegents etc.).

Chemical Groups of Disinfectants

- Alcohols
- Aldehydes
- Amphoteric compounds
- Biguanides
- Halogens
- Peroxygen compounds
- Phenolics
- Quaternary ammonium compounds

Alcohols - Several alcohols possess antimicrobial properties. Ethanol and isopropanol are the most widely used disinfectants. Generally, alcohols have rapid bactericidal activity against vegetative bacteria, but are not sporicidal. They evaporate at room temperature and leave no visible residues. But because of their volatility they creates a risk of overexposure by inhalation and are therefore suitable for small scale use, rather than use on large surfaces such as walls and floors.

Aldehydes - Aldehydes are very effective disinfectants but due to their carcinogenicity, aldehydes are today regarded as unsuitable as disinfectant.

Amphoteric Compounds - Amphoteric compounds are effective against most vegetative bacteria. Their spectrum of activity and mode of action is similar to the quaternary ammonium compounds (QACs), but they are compatible with a wider range of detergents. Amphoteric compounds also tend to have a higher tolerance to organic matter than QACs have, stable in both the concentrated and in the diluted form and are freely soluble in water.

Biguanides - Biguanides have a wide spectrum of activity against vegetative bacteria but can be less active against Gram-negative bacteria. They are stable in both the concentrated and diluted form. In water they are freely soluble. Biguanides can be affected by the presence of soaps and anionic surfactants.

Halogens - The most important halogens for use as antiseptics and disinfectants are iodine and chlorine compounds respectively. Iodine is commonly used for surgical skin disinfection. Chlorine compounds are effective disinfectants with sporicidal activity and are commonly used for hard surface disinfection. Hypochlorites have a wide antibacterial spectrum and are among the most potent sporicidal agents.

All chlorine releasing agents are to some degree: corrosive, susceptible to inactivation by organic matter, and will leave visible surface residues and therefore it is important to

Peroxygen Compounds - Hydrogen peroxide and peracetic acid are the two main examples of peroxygen compounds. These can be used as surface disinfectants or by fogging or gassing. Both have a pungent odour and may require PPE to be worn. Peracetic acid is a very potent disinfectant. Its vapour is an irritant and its solution, also an irritant, is corrosive to some metals. Additives and pH modification can reduce the corrosive properties.

Hydrogen peroxide is bactericidal, fungicidal and to some extent sporicidal. The decomposition products, oxygen and water, are innocuous and therefore Hydrogen peroxide is considered more environmentally friendly. The main challenges of using 3-6% hydrogen peroxide are that it takes a longer time to achieve a reduction in microbial activity.

Phenolics - Phenolics are bactericidal but have limited fungicidal efficacy and are non-sporicidal. Preparation of phenolic disinfectants from concentrates requires careful measuring, due to their relatively high concentration exponent values.

Quaternary Ammonium Compounds - Quaternary Ammonium Compounds are cationic surface-active agents, which possess bactericidal activity and weak surfactant properties. They are primarily active against Gram-positive bacteria but can be lethal to Gram-negative bacteria at higher concentrations (Pseudonomas aeruginosa is often insusceptible). The quarternary ammonium compounds are incompatible with a wide range of chemical substances. Quaternary Ammonium Compounds tend to be free from odour and colour, are stable, show low toxicity and are non-corrosive in dilute form.

Formulated Compounds - Formulated materials could result in increased activity e.g.:

- Broadening the spectrum of activity
- Effective against organisms theoretically more resistant
- Reducing the concentration through combining the action of two substances

Intactivation of Chemical Disinfectant Groups

All chemical disinfectants are to some extent inactivated by certain materials:

- Soaps and detergents: Where there is any doubt about the risk of inactivation should the advice of the disinfectant supplier be sought.
- Disinfectants: One disinfectant may inactivate another. Therefore, when rotating from one to another an intermediate rinse with water or alcohol may be needed (alcohol leaves no visible surface residues after use and therefore inactivation of other disinfectant groups is not a problem).
- Organic and soiling matter: To ensure maximum efficacy the disinfectant should be applied to a visibly clean surface. An effective regime should include periodic cleaning in conjunction with disinfection.
- Hard water: Salts in hard water inactivate many disinfectants.
- Other natural materials: Other natural materials can lead to a variable degree of inactivation.

Modes of Action

Disinfectants often have mutiple target sites. The mode of action is usually dependent on disinfectant concentration, the state of the organism as well as other factors.

Critical Lethal Parameters of Antimicrobial Action

The efficacy of disinfectants will depend on the chemical substance itself, but also on a number of factors such as concentration, pH, and the temperature at which it is used.

Concentration

Careful and accurate measurement of the disinfectant and diluent is important. There is an exponential relationship between concentration and potency, which have resulted in the use of the term concentration exponent. Increases in concentration can result in a marked increase in disinfectant activity. But over concentration can lead to less available water which can mean the disinfectant is not taken in by the microorganism. Overly concentrated disinfectants can also lead to residue formation.

Acidity (pH)

The pH of a disinfectant needs to be controlled. The activity of disinfectants can be affected by pH due to the chemical effect on the disinfectant solution itself or to the effect it can have on the microbial cell surface.

Temperature

An increase in temperature can increase disinfectant activity. When using disinfectants in cold rooms, a longer contact time may be requiered to achieve the same level of efficacy as at room temperature.

Conclusion

The choice of disinfectant always involves an element of compromise, balancing the needs of efficacy against the area of application and consideration of the potential harmful effects.

Microbial Surface Hygiene

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Introduction

Pathogenic microbes have been reported to form biofilms on equipment surfaces and in pipelines. Outbreaks with pathogens have seriously damaged the consumers' trust in safe production. In European Union (EU) in 2014 there was a total of 5,251 food- and waterborne outbreaks reported. Most outbreaks were caused by viruses, followed by *Salmonella*, bacterial toxins and *Campylobacter* sp. In the EU there has been an increase in confirmed human cases of campylobacteriosis, mostly from broiler meat, since 2008. The number of human listeriosis cases has also increased, despite that *Listeria monocytogenes* in ready-to-eat foods seldom exceeded the safety limit (≤ 100 CFU/g) in EU. The number of verocytotoxigenic *Escherichia coli* infections in humans was at the same level as in 2013. These facts show that there is a need of development of optimal pathogen management strategies in the above-mentioned processes.

Therefore, it is important to prevent biofilm formation in processes through good design and manufacturing practices e.g. hygienic design, choice of surface materials, building of equipment and process lines, cleaning as well as disinfection procedures in processes. The maintenance of cold processing conditions is also important in reducing the microbial growth both on surfaces and in moist products. Furthermore, training is needed to keep process hygiene and product safety at a high level and diminish process based microbial deterioration of products. The accessibility, cleanability and drainability are important tools in combating biofilms in the food, pharma and biotech industry.

Biofilm formation on process surfaces

A biofilm consists of microbial cell clusters with internal channels or voids, which allows nutrients and oxygen to be transported from the liquid to the cells in the matrix of extracellular polymeric substance (EPS). The microbes tend to form protective EPS of polysaccharides and glycoproteins to be able to survive hostile environmental factors, e.g. heat and chemicals. The microcolony formation or microbial adhesion is the first stage in both reversible and irreversible biofilm formation. The reversible phase involves the association of cells close but not attached to surfaces. Cells associated within the EPS formation bind the cells irreversibly to the surface. When the biofilm build-up is described more thoroughly phases like transportation of cells to a wetted surface, absorption of the cells into a conditioning film, adhesion of microbial cells to the wetted surface, cell replication and detachment of biofilm from the surface are included. It is also important to remember that up to 96 % of a biofilm consists of water, which means that less than 5 % of the total biofilm volume is detectable on dry process surfaces. Contamination of persistent microbes means that microbes for long periods has caused contamination in the process. Once a biofilm is formed on either the contact or environmental surfaces, it can be a contamination source for products processed in the process line(s).

The microbes can form biofilms on any commonly used process surface material, where either moisture or water is available. Harmful microbes may enter the manufacturing process through/with e.g. raw materials, air in the manufacturing area, process waters, additives, equipment, and/or the factory personnel and reach the end-product. Microbes prefer attaching on solid surfaces rather than swimming in the liquid and therefore microbial process contamination is often related to biofilm formation. Several microbes e.g. *Pseudomonas* sp. produce sticky and/or slimy biofilm structures with microbial cells embedded on the surfaces. The attachment of microbes on both abiotic and biotic surfaces is also affected by presence of organic material e.g. organic residues as well as by temperature, acidity and cell-to-cell communication. Physical parameters e.g. fluid flow rate, surface hydrophobicity, roughness and charge as well as other material properties affect the attachment of cells to the surfaces.

General principles and requirements

Development of optimal biofilm management strategies in processes requires knowledge of contaminants and their routes and how various foods e.g. salads, deli meat or stews becomes a vehicle for disease transmission. General principles and requirements in the European law on food safety in the whole chain from farm to fork are specified in the EC Regulation No 178/2002. The European process hygiene criteria are given in the EC Regulations 852/2004, 853/2004, 854/2004, and the Machinery Directive 2006/42/EC. The hygiene rules in the EC regulations 852/2004 on the hygiene of foodstuffs, 853/2004 on specific hygiene rules for food of animal origin and 854/20014 on specific rules for the

organisation of official controls on products of animal origin intended for human consumption were all adopted in April 2004 and they became applicable from beginning of 2006. The food contact materials must be safe to use in food processing and should thus fulfil the EC Regulation No. 1935/2004.

More specific information can be found in the hygiene standard EN 1672-2+A1:2009 “Food processing machinery standard - Basic concepts - Part 2: Hygiene requirements” and the European Hygienic Equipment & Design Group (EHEDG) guidelines with both basic and specific design rules for process equipment, lines and facilities. The most fundamental EHEDG guidelines are: Document 8 ‘Hygienic equipment design criteria’, Document 10 ‘Hygienic design of closed equipment for the processing of liquid food’, Document 13 ‘Hygienic design of equipment for open processing’, Document 22 ‘General hygienic design criteria for the safe processing of dry particulate materials’, Document 26 ‘Hygienic engineering of plants for the processing of dry particulate materials’ and Document 44 ‘Hygienic Design Principles for Food Factories’. Best practices in civil engineering is the base for the Document No. 44. In the quality management standards, e.g. ISO 22000 and British Retail Consortium Standard there is information how to produce safe products. The hygiene rules, which evolve with time, state that the primary responsibility in food safety is by the business operator and that the food safety shall be implemented based on the Hazard Analysis and Critical Control Points (HACCP) principles.

Prevention of biofilm formation

The aim of microbial control in a process line is two-fold to reduce/limit the number of microbes in liquids and products and their activity as well as to prevent/control the biofilm formation on surfaces. In the food, pharma and biotech industry, equipment design plays an important role in combating biofilm formations. The adherence of microbes to both contact and non-contact surfaces can be due to the complexity of process equipment, in which residues are collected and which are hard to clean. In preventing biofilms on surfaces through hygienic design attention should be drawn to dead spaces, corners, crevices, cracks, fasteners, screw heads, threads, seals, gaskets, and valves. Other hygienic design features like weldings and joints should be designed to prevent the accumulation of soil and allow easy cleaning thus prevent biofilm build up. Surface materials and their roughness treatments e.g. grinding and polishing can take part in active rejection or passive removal of biofilms. If the design is not improved poor designs can lead to persistent organisms in the process equipment, lines or even premises through adaptation to disinfectants in improper structures i.e. in places where disinfectants in sub-lethal concentrations can be harboured subsequently affecting the microbes. Improper cleaning and disinfection procedures of contact surfaces contribute to formation of biofilms.

The key to effective cleaning in a food, pharma or biotech factory is that the personnel understands the nature and type of soil, e.g. fat, proteins, carbohydrates, sugar and salts, including microbes they must remove from the surfaces. An efficient cleaning procedure consists of a sequence of detergent and disinfectant applications at effective concentra-

tions and correct temperatures as well as water rinses. Prolonged exposure to cleaning chemicals of surfaces in the process equipment/lines improves the soil removal. The cleaned equipment and process lines should be left to dry in well ventilated areas, because microbes do not grow on dry, clean surfaces. Equipment that commonly causes problems in process hygiene are conveyors, plate heat exchangers, tanks with pipelines, slicing and cutting equipment, as well as filling and packing machines. These types of equipment can cause safety problems due to biofilms of spoilage microbes e.g. lactic acid bacteria and/or pathogens e.g. L. monocytogenes and B. cereus. More about biofilm control measures in the latter articles in this series.

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Cleaning Technology in Controlled Areas

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Introduction

Cleaning technology is based on knowledge in proper and high-quality cleaning. It should fulfill growing customers' demands. Cleanroom, controlled room, patient room, they have all different usage and even in cleanrooms all surfaces are contaminated with different kinds of dirt, dust, microorganisms and condensed matter. To keep clean is to reduce any pathway ultimately transporting mass into the surface layers. Only two methods have been introduced for removing dust and dirt: ventilation and cleaning. Clean ventilation systems prevent the dust and dirt from accumulating on the surfaces. The criteria that 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. In this paper, I describe the Finnish way of professional cleaning in controlled rooms and how the procedures can be done. To start, there are some standards and definitions to show the background. Cleaning as a part of contamination control explains some reasons why cleaning should be done properly. Different kind of dirt has been explained to ensure differences in choosing the right cleaning method. Some examples of good procedures are mentioned below.

Cleaning standards and determinations

In Finland, there have been standards to determine cleaning vocabulary since 1983 and for cleaning machines since 1989. In 2010 the Finnish Standards Association SFS published a new vocabulary of cleaning industry (SFS 5967)[1], which combines the old ones and has further determinations. In the standard, the cleanroom cleaning is determined as

a cleaning to be done in areas where the cleanliness and the area is defined by the standards, for example by the standard SFS-EN ISO 14644-1.

Cleaning can be determined as an assistance work for the main operations. Cleanroom cannot be clean without cleaning. Whyte (2003)2 gives in his book reasons, why a cleanroom must be cleaned. He wonders why so much money and effort is used to designing and construction, but only some thoughts are given to making and keeping the room clean. Cleanroom surfaces do get dirty and must be cleaned even if they seem to be clean and no visible dirt can be seen. Ramstorp (2000) explains that the purpose of cleaning cleanrooms and clean zones is to release, collect and remove all undesired contaminants from surfaces with the regard to cleanliness.[3]

In controlled areas, the latest standard to determine requirements for cleaning in the health care sector is DS 2451-10. The standard makes it possible to establish levels for the cleanliness considering the demands of hygiene in controlled rooms.[4]

Contaminants and dirt

The vocabulary of cleaning industry defines dirt as follows: “Dirt is uncleanness that reduces the value of the use of surfaces”1. Dirt can be divided into groups consisting of solid materials, chemicals and physical conditions. It is important to define what is to be considered as a contaminant and what is to be considered as a critical contaminant.[1, 5] Even in cleanrooms, some dust might be acceptable when it is high up and not reachable, but on process tables, the same dust can be dangerous.

If cleanroom entrance from outside is blocked, the main dirt comes with people or products. In many cases, the dirt in cleanroom might be particles and microbes attached to them, and the main force that holds particles on cleanroom surfaces is the London-Van der Waal’s force as an inter-molecular force. Electrostatic forces might occur, but it depends on the type of materials used. After wet cleaning and without proper drying, some biofilm can form on surfaces and there might be some residues of detergent on the surface. [2, 5]

Cleaning cycle

Cleaning or Zinner cycle5 consists of all those things that are needed in the cleaning process. They together create the entire process used to remove particles from surfaces. The components are chemicals, temperature, time and effect. The effect part can be divided into technique and scrubbing as Kääriäinen did in Finland.5 In cleanroom facilities, much energy cannot be used, so scrubbing as a mechanical work should be restricted. Chemistry cannot be replaced with using more time, work and temperature. All four components should be included in the cleaning process and the water used must be the same as in the process.

Instructions how to clean and work in cleanrooms

Dimensioning has played an extremely important role in the development of cleaning work in Finland. Dimensioning includes use of time and method standards as a development tool for cleaning work.6 Proper working instructions for cleanroom cleaning must be specified, all details should be mentioned. In the working plan, at least these things should be included: Time of cleaning, Work order, Materials used, Equipment and detergents used, Schedule of the work to be done, checking list, in the text specified method explanations and the name of that person who has made the instructions and the updating date.[2,3,7] Much more attention to the Critical control points should be paid and that might increase the costs. Existing control points vary in different kinds of cleanrooms, which means that every area needs to be calculated separately. When supplying cleaning equipment and agents, the mentioning of the word cleanroom might triple the price of the product. Some equipment from the field of food technology could be used instead of so called “cleanroom products”. Good equipment should be easy to sanitize and /or sterilize. The used amount of cleaning agent can nowadays be only 2 ml / 5 l water and there might be cleanrooms that do not need actual cleanroom agents at all if the wipes are made of good quality microfiber. More important, the same type of water should be used as in the process. Surfaces must be clean before they can be disinfected. The challenge of cleaning-controlled rooms includes contamination that cannot be seen, wearing garments, gloves, masks, and head coverings. There should be proper protocols established and proper cleaning tools as well as communication on the cleaning processes provided.[8]

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Legal Requirements in Building Process Equipment

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Abstract

In EU legislation constitutes the basic demands concerning hygienic design of food processing equipment. Since 1995 the Machinery Directive has been in place as the foundation document prescribing that equipment must be cleanable, materials smooth and free of imperfections and that it shall be possible to verify the hygiene status. Furthermore, a proper risk assessment must be conducted in order to address relevant risks towards the consumers. The Machinery Directive contains only general information thus it is supported by harmonized EU standards which deals with the specifics and are considered to demonstrate the current state technical state in the area covered by each standard. This will be covered in detail along with the EU legislation focusing on documentation and handling of food contact materials. The combined EU legislation in this field is a subject food producers and equipment manufactures alike must know about in order to fulfill legal demands and good stewardship in order to protect consumers against any hazard arising during production of food products.

Basic Criteria in Hygienic Design

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Extended Abstract

The general framework for food safety is given in the Regulations 178/2002 (about the general principles and requirements of the food law, the European Food Safety Authority and procedures in matters of food safety), 852/2004 (on the hygiene of foodstuffs), 853/2004 (specific hygiene rules on the hygiene of foodstuffs) and 854/2004 (specific rules for the organisation of official controls on products of animal origin intended for human consumption). The rules on both official controls performed to ensure verification of compliance with feed and food law and animal health and animal welfare rules are in force are given in the regulation 882/2004. In addition, rules on materials and articles intended to come into contact with food are given in the regulation 1935/2004 and on good manufacturing practice for materials and articles intended to come into contact with food in regulation 2023/2006. The European food legislation consists of both horizontal and vertical measures, and an example of a horizontal measure is the standard of hygiene in food processing machinery SFS-EN 1672-2 + A1:2009 (Food processing machinery - Basic concepts - Part 2: Hygiene requirements). Design requirements for food equipment are given in the Directive 2006/42. Furthermore, European Hygienic Engineering & Design Group (EHEDG) has published more than 40 Guidelines, which provides practical suggestions how food production facilities, process lines and equipment should be planned, so that they are hygienic.

Hygienic site design principles are dealing with defences against both external and internal factory hazards. Detailed information on these principles can be obtained from the EHEDG Guidelines No. 44 “Hygienic design principles for food factories” published in December 2014. At the building level there should be various barriers protecting the products produced from external, environmental and non-food manufacturing activities as

well as internal cleaning and maintenance activities. In hygienic factory design focus is also on the building materials for e.g. floors, walls, doors, windows, ceilings and roofs and on services e.g. electrical installations, lighting, heating, ventilation and air conditioning (HVAC) as well as production of steam and compressed air. The space for the various process lines should be reserved at the planning stage. The external and internal structures should protect the process against pests, vermin, microbes as well as foreign bodies and chemical pollution.

Common hygiene requirements for machinery used in preparing and processing food and feed must be met to maximise food safety. However, the equipment functionality and the hygienic design principles can sometimes be inconsistent. Generally, compromises can be found, in case no compromises are found the functionality must be sacrificed, because non-hygienic equipment cannot be cleaned in automatic cleaning procedures. In the horizontal standard EN 1672-2 + A1:2009 there are principles, which can be applied to other machineries and equipment used in food and feed processing. Furthermore, there you can also find examples of hygiene risks with acceptable solutions. Detailed information on hygienic design of both closed and open equipment can be found in several of the EHEDG Guidelines e.g. in No. 8 on “Hygienic equipment design criteria”, No. 10 on “Hygienic design of closed equipment for the processing of liquid food” and No. 13 on “Hygienic design of equipment for open processing”. The minimisation of safety related risks to personnel arising from the use of the equipment are covered by the CE-mark system. Food processing equipment which are problematic to clean are conveyors, plate heat exchangers, tanks with pipelines, slicing and cutting equipment, as well as filling and packing machines. They can cause problems due to biofilms of spoilage microbes e.g. lactic acid bacteria and/or pathogens e.g. Listeria monocytogenes and Bacillus cereus.

The choice of surface materials is of great importance in designing and building facilities, process lines and process equipment for food and feed production. The process lines and equipment are easy to clean, when the surfaces are smooth and in good condition i.e. without crevices, cracks, corners and dead ends. Joints, screws, bolts, nuts, threads and also gaskets are vulnerable spots for accumulation of biofilm. Nearly all commonly used materials in food processing can support biofilm formation. Most of the adherent bacterial cells have been found in the grain boundaries of stainless steel and thus the surface structure of stainless steel is very important in avoiding build-up of biofilms. Stainless steel is the most useful material in food processing equipment, because it can be treated using e.g. mechanical grinding, lapping, electrolytical polishing or mechanical polishing to improve the surface smoothness. Experiments carried out with pathogens and spoilage microbes on elastomers and rubbers, which are used e.g. in gaskets, have shown that the cleanability of surfaces is important. These rubber and elastomer surfaces are prone to microbial growth that some of the microbes even decomposed rubber as energy sources for growth. The smoother a surface is and the younger a biofilm is the easier it is to eliminate the microbial colonies from the process equipment and lines.

Hygienic and/or aseptic systems comprise individual components, machineries, measuring and management systems and automation in production of food and feed,

pharmaceuticals, cosmetics, home and water products. Systems and components are frequently put together in a way that creates places prone to build-up of microbial and allergenic hazards. Lack of information have often caused failures at different stages e.g. design, design-changes, fabrication, installation and commissioning and the failures are often caused even though there are specific design guidelines available, because these documents are not well understood. These sequencing and content errors can also result in major penalties due to delays and costs of components and construction. The horizontal guideline 34 is about the safe hygienic integration of food production and processing equipment in the process line. This document examines integration aspects affecting hygienic design, installation, operation, automation, cleaning and maintenance. System flow charts and case studies describing the integration processes and decision steps are used. It does not provide detailed guidance on specific manufacturing processes, products, buildings or equipment. In the guideline there are values for minimum clearance under and between equipment or from the wall for cleaning and maintenance purposes: 20 cm clearance for equipment under 90 cm, 30 cm clearance for equipment of 90 – 150 cm size, 45 cm clearance for equipment of 150 – 210 cm size and 60 cm clearance for equipment above 210 cm.

Improvements in hygienic design can be carried out using new materials and new techniques based e.g. on 3D printing. The 3D-printing can be used to an affordable price both in planning new, hygienic process solutions and also in making new copies of nozzles, which are hard to keep clean. In 3D-printing good quality materials must be used to achieve hygienic items. The biofilm growth on surface can also be reduced by using new nanomaterials in which e.g. silver or copper has been incorporated. The major issue with these materials is that they must be properly studied to show that they are safe to use in food processing. In improving the process hygiene ultrasonication can be used for cleaning difficult constructions in conveyor belts, dry-ice cleaning for heavily soiled surfaces and both ozone and UVC-irradiation treatments for air quality.

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Construction Materials in Food Equipment

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Abstract

Construction materials intend to come in contact with food products should be inert to foods produces. This to the extent that there is no migration from the material to the food product that make either a noticeable alteration of the food product or endanger human health. Different classes of construction materials will be covered with the main focus being on the most common stainless steels, plastics and rubber for gaskets. The materials of cause need to be durable and withstand the continuous contact with the foods produced and also the cleaning agents applied. Thus, different grades of stainless steel will be covered and related to their corrosion resistance, for the plastics focus will be on migration and migration testing and for the rubbers the matter is compatibility with food products and life time in real processes. All in all a comprehensive guide to food contact materials is presented.

r³nordic

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R³-Nordic, the Nordic Society of Cleanroom Technology, is a non-profit, independent association for the promotion of new technologies in cleanroom technology and contamination control in the Nordic countries. The aim of the annual R³Nordic Symposium is to provide knowledge within the pharmaceutical, food and biotech industries as well as hospitals and hospital pharmacies.

This year the sessions at the 49th R³Nordic Symposium are Pharma & Hospital Pharmacy (2 days), Hospital (1 day), Food & Biotech (1 day) and General (2 days) sessions. The presentations deal with construction and design, planning, auditing, contamination control, cleanroom technology and management, sterilization techniques, cleaning of clean rooms, protective clothing, monitoring techniques, rapid test methods and regulations in clean and controlled rooms. This publication contains the accepted full papers and extended abstracts that were presented at the symposium.

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