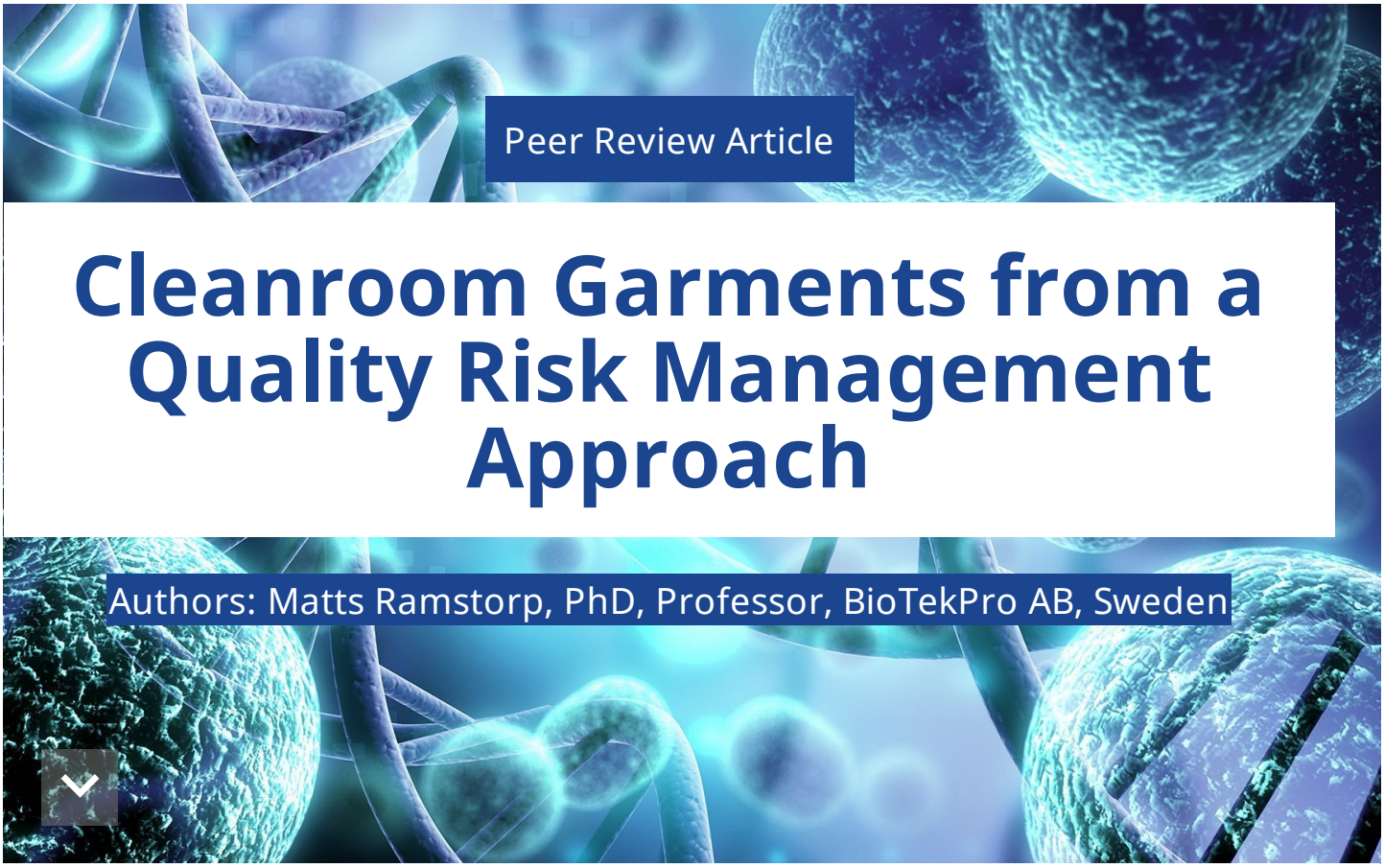

Peer Review Article

Cleanroom Garments from a Quality Risk Management Approach

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Introduction

Since the start of cleanroom technology, garment selection has been known to have a major impact on the cleanliness of cleanrooms. In general, the 'cleaner' the cleanroom – the more covered the cleanroom personnel must be; with garments acting like filters. Even though garments have been recognized as important tools in cleanroom technology, during the past 20 years, little effort has been put into the development and use of more modern and robust garments. The same applies to the different test methods that are available to control the integrity of cleanroom garments. In fact, nothing much has happened in these areas.

This article covers cleanroom garments, garment materials as well as the different test methods available to study safety aspects, filtration efficiency, and life cycle, in relation to Quality Risk Management - QRM.

The purpose of this article is to summarize the subject of cleanroom garments related to historical and present safety demands, as well as to future QRM demands. My intention is that the article will serve as a basis of discussions in order to highlight the importance of garment selection, and lead to a more scientifically based understanding and use of cleanroom garments in the future.

“The primary barrier between the personnel and the cleanroom”

“Cleanroom clothing and gloves are the primary barriers keeping contaminants, generated by personnel, from being emitted into the cleanroom and deposited on products”. This was stated by Mr Alvin Lieberman in the introduction of a book he wrote in 1992 (1).

It has long been established that people are the biggest source of contaminants (2), and furthermore, in most cases the source of the most critical contaminants when working in cleanrooms. There are many ways to deal with this situation. Examples include minimizing the number of personnel in the cleanroom, training the personnel to behave in ways to minimize the generation of contaminants during work and dressing the personnel in clean garments that more or less acts as a barrier or a filter between the personnel, the surrounding environment and (or) the product handled.

Thus, cleanroom garments play an extremely important role when creating and maintaining a desired level of cleanliness, in order to protect the final products, and most importantly, when producing medicinal products, in keeping the patient safe.

Demands on cleanroom garments

When cleanrooms were introduced in the air and space industry during the 1950s and 1960s, it was recognized that contaminants, i.e. particles from various sources, had a major impact on the materials and equipment handled. It was discovered early on that the personnel were the major source of contaminants comprising of particles, such as skin flakes, microorganisms, hair, saliva, textile fibres from private clothing as well as clothing worn during work. NASA, for example, generated numerous studies on personnel, resulting, among other things, in the extensively recognized results shown in Table 1 (3).

Kind of movement	Number of particles per minute (≥ 0.3 µm)
Sitting or standing (no movement)	100 000
Sitting slightly moving head, arms and hands	500 000
Sitting slightly moving body and foot	1 000 000
Standing up from sitting position	2 500 000
Walking about 1 meter per second	5 000 000
Walking about 1.5 meter per second	7 500 000
Walking quickly	10 000 000
Climbing stairs	10 000 000
Gymnastic exercise	15 000 000 – 30 000 000

Table 1. Results presented by NASA showing the number of particles generated by persons performing different activities, measured as the number of particles with a size greater to and equal to 0.3 µm

Cleanroom garments are used in order to minimize the risk that particles, including microorganisms, from operators, will negatively impact the cleanroom environment and ultimately, the products handled.

Cleanroom garment fabrics

Cleanroom garments are, from a general point of view, produced from two different types of fabrics:

· Woven textile fabrics

· Non-woven fabrics

Woven textile cleanroom garments are intended for repeated use, need to be washed, and in some cases, such as aseptic production, sterilized prior to use. Non-woven garments, on the other hand, are generally intended for single-use, and will only be subjected to washing and sterilization once, since these garments are discarded after use. In this article, textile cleanroom garments will be referred to as re-useable garments, and non-woven cleanroom garments as single-use garments.

Cleanroom garment attributes

Cleanroom garments should perform four major and important functions:

· Act as a barrier or a filter

· Be sufficiently clean

· Retain their integrity over their entire lifecycle

· Supply operator comfort

"Sufficiently clean" means that garments should be cleaned in such a way to not compromise the cleanliness of the cleanroom. Furthermore, they should be manufactured of a material that will not, by itself, be a contamination hazard. In other words, the garment should not generate particles by itself.

Cleanroom garments should retain their integrity throughout the entire lifecycle, since damaged garments can result in garment material being released. Additionally, a damaged garment will have less possibility to act as a barrier and will represent a risk of contamination of the environment.

In some cases, there is also a need to protect the operators from dangerous compounds during cleanroom work. However, cleanroom garments used for protection of operators are not covered in this context.

The balance between comfort and filtration efficiency

Many parameters are presented in commercial brochures when outlining what type of cleanroom garment to use. Some of these parameters are difficult to understand from an end-user point of view. The most difficult parameter is comfort. Comfort is a subjective characteristic, which contradicts the most important parameter in a cleanroom garment: the capability of the garment to act as a barrier or a filter.

Parameters such as air permeability, equivalent pore size diameter, water vapour transmission, weight per unit surface area, and tear strength, impact both filtration efficiency and comfort. When discussing the balance between filtration efficiency and comfort, re-useable cleanroom garments can only be compared with other re-useable garments, and, single-use cleanroom garments can only be compared with other single-use garments. In each of these fabric categories; the better the filtration efficiency, the more uncomfortable the garment is to the user. Conversely, the better the comfort for the user, the worse the filtration efficiency.

Many of these parameters are hard to translate when stating demands for cleanroom garments. On the other hand, comfort is more easily acknowledged, especially through operator verbal complaints.

Patient safety versus comfort of the personnel

Is it possible to balance these two aspects? In some cases, I get the impression that comfort for the operators is more of a focus area than filtration efficiency, and ultimately patient safety.

One of the largest and state-of-the-art hospitals in Sweden has 35 newly built operating theatres with ventilation based on mixed or turbulent airflow. Despite this, the general cleanliness demand of the room air has been stated as < 5 CFU per cubic meter. This air cleanliness cannot be obtained by this ventilation principle alone, demanding the personnel to wear a specially designed and less porous surgical work suit in order to minimize the CFUś generated.

The specialized surgical garment was purchased and used by the personnel, but the garments turned out to be too impenetrable. In other words, the barrier function was good enough for the desired cleanliness, but not for the comfort of the personnel. The personnel were unable to wear the new garments due to comfort and related skin problems, and thus continued to use the traditional older-style garments. Thus, the cleanliness demands in the operating theatre could not be obtained, and as a result, the hospital was forced to decrease their cleanliness demands.

In the above case, operator comfort had a higher priority as compared to patient safety. This shows the complex challenge between comfort for the personnel versus patient safety.

Cleanroom garments in GMP operations

Different cleanroom cleanliness grades or classifications will require different types of garments to be worn by personnel. In lower classification cleanrooms, personnel often dress in less-covering garments and, to some extent, in garments made from, for example, textile material that does not fully comply with the attributes stated above. In the European GMP – Good Manufacturing Practice, four different cleanroom cleanliness levels or grades are defined: Grade A, Grade B, Grade C and Grade D, respectively. Grade A is the cleanest and grade D the least clean (4). Each grade has a different coverage requirement.

When working in a Grade D cleanroom, it is quite normal that the personnel wear trousers and a coat. Moreover, personnel also use designated shoes or shoe covers and cover hair with a bouffant. The material used for garments in Grade D is not specified in the present Annex 1 of Volume 4, which in practice means that blended textile materials, i.e. mixtures of cotton and polyester, are used.

According to Annex 1, when working in the cleanest cleanroom, Grade B, the following is specified: “The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.” In practice, this means that no natural fibre-based materials are to be used. In other words, Grade B cleanroom garments are mostly made of 100 % polyester or similar material.

Grade B cleanrooms are used together with Grade A clean zones when performing aseptic filling or aseptic handling. This is the most critical operation within the pharmaceutical industry, and it is also the operation that puts the end-user, the patient, at highest risk, since there is no terminal sterilization of the product in its sealed container after filling.

Quality Risk Management

QRM – Quality Risk Management – is not new. It has been around for a long period of time and is also mentioned in the present Annex 1, in Volume 4 of the Eudralex (4). However, the draft Annex 1 (2017) (5) states in its first and

introductory part: “This Annex provides general guidance that should be used for all sterile medicinal products and sterile active substances, via adaption, using the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and pyrogen contamination associated with microbes is prevented in the final product”.
Although much “detailed” guidance is presented in the draft Annex 1 regarding cleanroom garments, in practice, both the handling and the use of these important cleanroom tools always must be subjected to QRM.

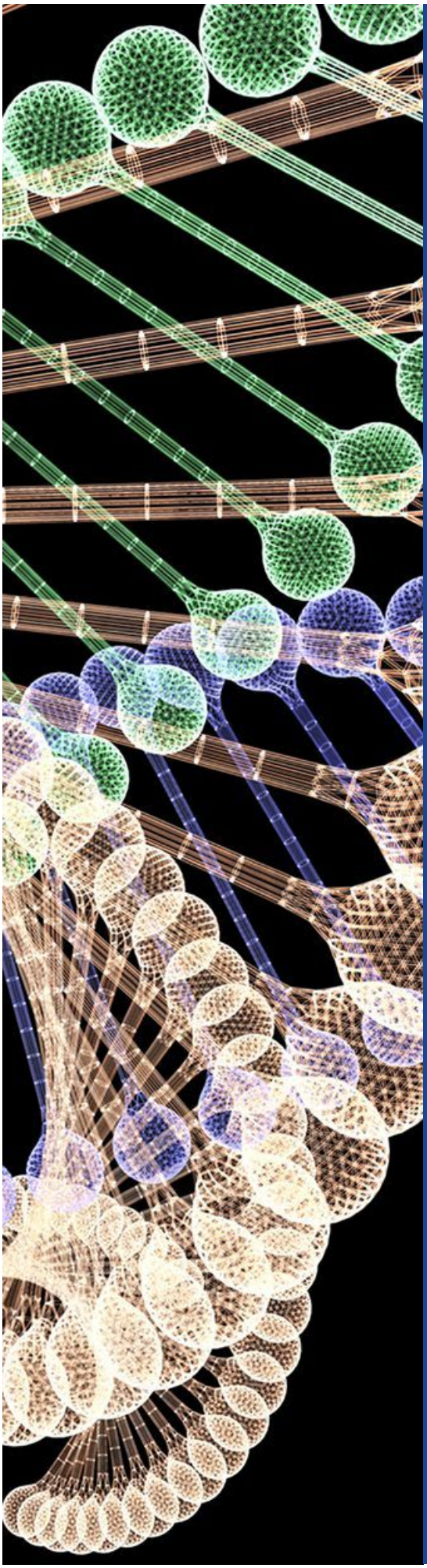
Quality Risk Management Cleanroom garments
Even though QRM has been generally described and used for quite a long period of time, cleanroom garments have not truly been subjected to risk management principles in detail. Furthermore, the development of fabrics, cleanroom garments and all the parts of a garment system, has not been emphasized. The bottom line: Not much has happened during the last 20 years, when it comes to re-usable textile cleanroom garments.

Cleanroom use and cleanroom garments in the future
The new demands stated in the draft Annex 1, indicate the need to look more thoroughly at all aspects on cleanroom garments. Longstanding and well-known test methods must be scientifically judged, to determine if, and in what respect, they can be used in the context of QRM, and (or) if new test methods or totally new approaches must be developed and adopted for cleanroom garments.

The part covering Aseptic Preparation (5), section 8.9 states: “Where possible, the use of equipment such as RABS, isolators or closed systems, should be considered in order to reduce the need for interventions into the grade A environment and minimize the risk of contamination”. The intent of this guidance is to minimize the potential risk of contamination from operators during interventions.

Isolators as well as closed systems, for aseptic production, can be placed in a surrounding cleanroom with lower cleanliness, whereas RABS (Restricted Access Barrier Systems) must be used in Grade B cleanrooms, the same cleanliness level needed when using open clean zones, UDF- and (or) microbial safety cabinets class II.

When working in lower classification cleanrooms, (Grade C or Grade D), and using isolators and closed process systems, a lower degree of body coverage could be considered. However, Grade B garments will still be used to a very large extent, since all processes cannot be performed in isolators or closed systems, and RABS will still demand a Grade B background. In sum, the demand of the Grade B cleanroom garment system will remain strong, even in the future.



Testing cleanroom garments

Since cleanroom garments are of fundamental importance for the outcome of the manufacturing process, the quality of the final products, and hence patient safety, different test methods have been developed. The overall purpose of these test methods can be divided into two parts:

· To obtain information of the performance of the garment
· To give the end-user guidance on which garments to chose

The Institute of Environmental Sciences and Technologies (IEST) has published several Recommended Practices that are to be used as practical tools when getting cleanrooms working to desired specifications. In the Recommended Practice covering cleanroom garments, (IEST-RP-CC 003.4) (6) different test methods are specified, focusing on the garment material, the fabric, and on ready-made garments, respectively. The different tests described in this document, shown in respect to their purpose, are:

Cleanliness of fabric and (or) garment:

· Releasable large particles test
· The Helmke drum test

Filtration efficiency

· The particle penetration test
· The microbial penetration test
· The body box test

Test for equivalent pore size diameter

· The bubble point method

Filtration efficiency testing

The three tests normally used to study the filtration efficiency of cleanroom fabrics are:

· The particle penetration test
· The microbial penetration test
· The body box test

The two penetration tests above are not subjected to undesired variations, such as using different test persons, differences in movement pattern of the test persons, etc. This might be a problem when performing the body box test. The body box test is performed on persons dressed in different cleanroom garments, and performing different movements in a test chamber, in which the particles generated during test are measured.

The particle and microbial penetration test give an idea of the quality of the fabric, whereas the body test is a tool to compare the different garments and (or) garment systems in an environment that comes closer to real use. For comparison purposes body box testing should, however, be done with the same operator and under exactly the same test conditions. The body box test gives an idea on how the garment is performing as a whole.

Equivalent pore size diameter

The bubble point test is used to determine the equivalent pore size diameter of a fabric. This term is normally used to describe the filtration efficiency of the fabric. This is not fully accepted, since the filtration efficiency is not based on "pore size" only, but also on the thickness of the fabric. When performing the bubble point test on a single as compared to a double layer of fabric, the same equivalent pore size diameter will be obtained, even though double layers of fabric will enhance the filtration efficiency enormously.

Use the correct cleanroom garment parameters

All the different tests have one thing in common: they serve as means to describe different aspects of the garment material, the fabric and (or) the cleanroom garment. However, the problem remains that these results are not easily understood by the end-user. This is troublesome, since many of these parameters are not discussed with end-users, making it extremely hard to understand the properties of cleanroom garments, and ultimately to produce a User Requirement Specification (URS).

Cleanroom garment end-users normally reference the recommendations stated in the Recommended Practice from IEST when choosing the correct garment system, which outlines the recommended choice of different apparel. By combining this information with, for example, the Annex 1 of Volume 4 in the EudraLex, the end-user can be confident that they have chosen a cleanroom garment system that is in "compliance" with the stated demands.

The life cycle of cleanroom garments - Practical approach today

At present textile cleanroom garments are used to a major extent. The use of textile garments demands that these are repeatedly used which means that these garments must be washed, or washed and subsequently sterilized, when used in Grade B cleanrooms for aseptic production. The process of washing and even more sterilization will have a negative impact on the function of the garments and must be considered when discussing the life cycle of the garment.

Re-usable cleanroom garments are washed and, if to be used in Grade B/A applications, also sterilized. From a general point of view, the "cleanroom" laundry companies around the world have full control of their washing process, and in most cases the washing processes and the sterilization processes are validated. In some parts of the world, cleanroom garments are washed in "in house" laundries or "industrial" laundries, where chemicals, temperatures as well as air cleanliness used for washing and drying also have an impact om the life span of the garments, and not always considered in quality performance of laundries. Many of the "cleanroom" laundry suppliers also have historical knowledge of the impact of these processes regarding the impact on the garments handled, but normally the actual

garments used by the end-users, have not been subjected to a full validation.

Contamination Control Strategy – CCS

In the draft to Annex 1 (2017) a new term is introduced – Contamination Control Strategy – CCS, which is explained in the following way:

"Quality Assurance is particularly important, and manufacture of sterile products must strictly follow carefully established and validated methods of manufacture and control. A contamination control strategy should be implemented across the facility in order to assess the effectiveness of all the control and monitoring measures employed. This assessment should lead to corrective and preventative actions being taken as necessary.

The strategy should consider all aspects of contamination control and its life cycle with ongoing and periodic review and update of the strategy as appropriate.

Contamination control and steps taken to minimise the risk of contamination from microbial and particulate sources are a series of successively linked events or measures. These are typically assessed, controlled and monitored individually but these many sources should be considered holistically."

One way to explain the purpose of a Contamination Control Strategy is to detect and fill gaps that are identified when assessing the system and controlling and monitoring individual events from a holistical point of view.
A Contamination Control Strategy must, therefore, incorporate cleanroom garments, the production of the garment, and all the different treatments that the garment is subjected to, such as washing and sterilization, packaging, transportation, use, … etc. In other words, suppliers' recommendations on garment life, in respect to repeated washing and sterilization is not good enough. A proper validation based on scientific evidence is the only way to ensure patient safety.

Cleanroom garment supplier's recommendation

> In the Nordic countries there is a widespread understanding that traditional cleanroom garments made from 100 % polyester can withstand 150 washing cycles, or 50 washing cycles followed by sterilization in an autoclave. This has been known for over 25 years. However, to my knowledge, the end-users or wearers of cleanroom garments do not perform their own tests to validate whether or not this is true. Instead, they rely on the supplier of laundered and in some cases sterilized garments for this validation.
> In a warning letter (FDA) from 2016 (7) the following was stated:
> "In response to this letter, provide an action plan that describes how your firm will do the following.
> - Select appropriate gown suppliers. Include the role of the quality unit in making supplier selection and ongoing qualification decisions.
> - Reduce your maximum number of gown sterilizations to ensure that gowns are discarded before they show signs of breakdown. Provide the maximum number of re-sterilizations you will allow and describe how you will document and validate this procedure.
> - Correct your visual inspection procedures for sterile garments to improve detection and rejection of defective garments.
> - Ensure that the quality unit makes final decisions relating to release of raw materials and supplies (e.g.,garments) you use in production.
> - Conduct a risk assessment of the effects of damaged garments on your drugs. "
>
> In two Inspection Reports from FDA from 2017 (8) the following is stated:

"… the QA department has not validated the number of cleaning and sterilization cycles through which the garments and goggles can be processed without compromising the integrity of the sterile equipment".
"However, you have not validated the number of cleaning and sterilization cycles through which the garments can be processed and are relying on the supplier's recommendation of cycles."
These report findings, together with the wording found in the draft Annex 1 (2017) of the Eudralex, Volume 4, stating "After washing and before sterilization, garments should be checked for integrity" confirm that the integrity of cleanroom garments over time, is quite significant!
The key points are: How is a cleanroom garment to be integrity tested? Is it even possible to integrity test cleanroom garments?

Single-use or re-usable cleanroom garments?

From a quality risk management perspective, the use of re-usable cleanroom garments, that have been used in operation and washed and sterilized up to 50 times, is a big challenge. The impact of multiple use in operation, repeated laundering and repeated sterilization will negatively influence the filtering and barrier performance of re-usable garments. Furthermore, it is impossible to integrity-test cleanroom garments individually, in order to confirm the protective ability of the garment, due to lack of practically approved technologies, as well as time constraints.

Single-use garments do not suffer from these drawbacks, since these are only washed and sterilized once, and discarded after use. From a historical point of view, when facing the option of selecting single-use versus re-usable garments, re-usable garments where often the simpler choice, due to lack of good enough alternatives. However, from a quality risk management perspective, together with the wording stated in draft Annex 1 (2017), from a patient risk perspective, single-use garments might be a better and much safer option in Grade B/A in the future.

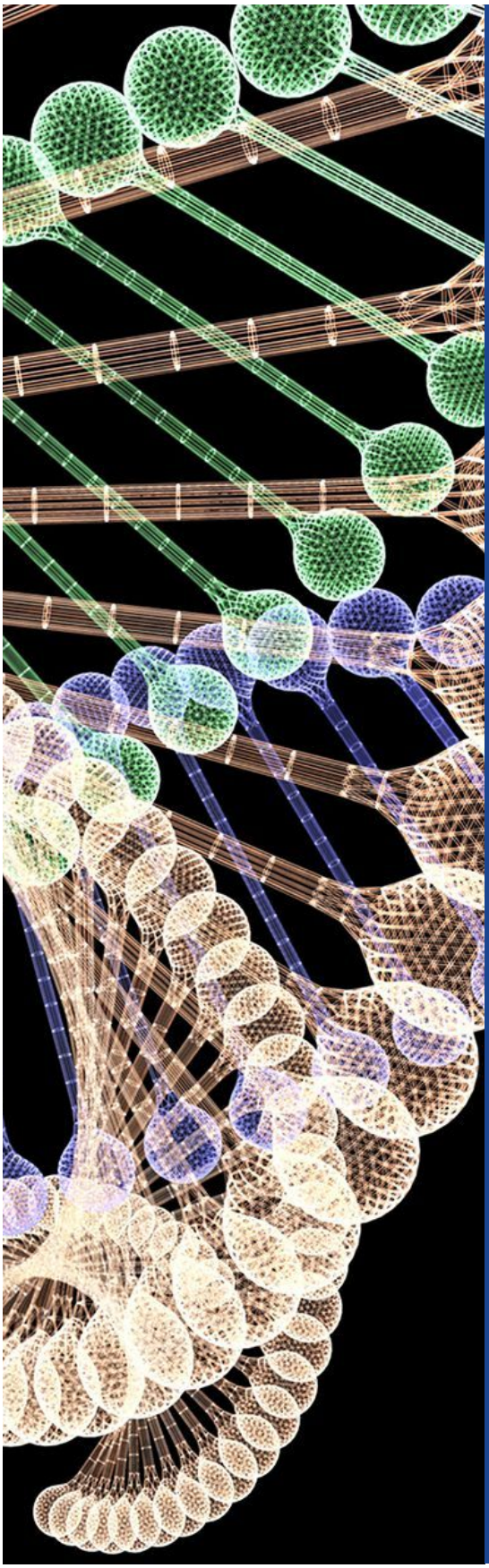
The raw material used in single-use cleanroom garments as well as the preparation of the garment, should be produced under controlled conditions, and the garment must offer consistent properties.

What differentiates single-use from re-usable cleanroom garments is that these garments are only used once, and subjected to washing and subsequent sterilization only one time. Therefore, when using single-use garments, the impact of repeated use, repeated washing as well as repeated sterilization are not issues.

End-user responsibility for the future

Until now, many end-users have been relying on the recommendations of their supplier regarding the use of re-usable cleanroom garments. When working with aseptic production in Grade B cleanrooms and Grade A clean zones, this will be a challenge for the future. Contamination Control Strategy – CCS, which is the holistical evidence, including the scientifically based validations obtained through QRM, shows that the operation is in total control. In this context, suppliers' recommendations will not be good enough.

The end-user must therefore put much stronger demands on their supplier for validation data, and not only rely on their recommendations. The challenge for re-useable cleanroom garments is to give proof of the performance during its full life cycle. Today the life cycle of re-usable garments is much too long.



Summary and thought

Cleanroom garments have been used for many years, without much adaption to general developments in the industry. Patient safety is the main objective when producing medicinal products and medical devices, and this emphasizes the need to keep operators as far away from the product and the process as possible. As suggested in draft Annex 1, the patient safety objective is obtained by increasing use of isolators, closed process systems and RABS (Restricted Access Barrier Systems).

In some cases, this development will result in use of cleanrooms with lower cleanliness grades; but in many cases, Grade A and Grade B will still be used with operators present. Cleanroom garments will be needed in the future to a high extent. The performance demands on cleanroom garments will increase, in order to provide the ultimate and necessary patient safety. Re-usable cleanroom garments pose a major risks to patient safety, since the repeated use, wash and sterilization of textile garments is not fully validated throughout the entire value-chain and lifecycle. Suppliers recommendations, without validation, is not enough.

Operator comfort will be of great importance even in the future. Therefore, end-users must, not only specify garment performance from a barrier point of view, but also include operator comfort in their User Requirement Specification – URS.

Conclusion

As stated in the introduction, the purpose of this article to serve as a basis of discussion. Moreover, this article is intended to be a "wake-up call", especially for businesses working with aseptic production, since there is no terminal sterilization of the product before patient use. Cleanroom garments play a critical role in this context.

From a QRM – Quality Risk Management and a CCS - Contamination Control Strategy point of view, end-users must demand scientifically based validation and testing data from their suppliers of re-usable cleanroom garments or consider using single-use cleanroom garments as the alternative to ensure the safety of the patient.

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