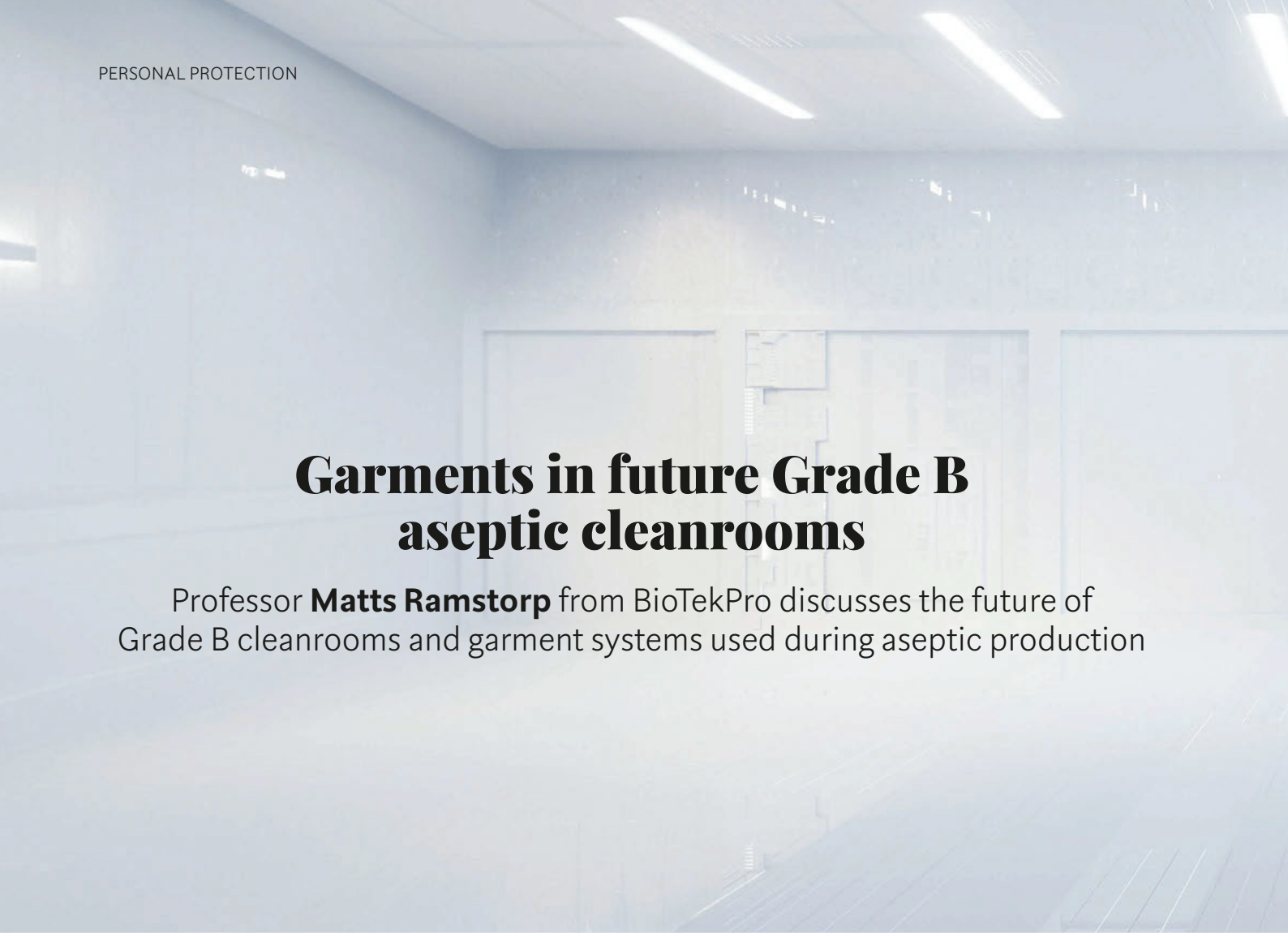


Garments in future Grade B aseptic cleanrooms

Professor **Matts Ramstorp** from BioTekPro discusses the future of Grade B cleanrooms and garment systems used during aseptic production

Working with aseptic procedures is the most challenging activity within the pharmaceutical industry and in pharmaceutical compounding units today. Aseptic production is, furthermore, the production principle that puts the end-user, the patient, at the highest risk, due to the lack of terminal sterilisation after filling and sealing the product in its vial.

This article discusses the future of Grade B cleanrooms and garment systems used during aseptic production.

Annex 1 recognises that traditional aseptic production is a high-risk operation by stating that barrier technology should be considered to increase the protection of the product. However, not all aseptic production can be performed using barrier technology, and, furthermore, the use of RABS, Restricted Access Barrier System, still requires the use of Grade B cleanrooms as background to the aseptic core.

Personnel in cleanrooms

During the introduction of cleanrooms in the air and space industry it was quite early discovered that operators are one of the largest sources of contaminants in the form of particles. This was due to the process of human skin renewal that generates and disperses an enormous number of particles, including microorganisms. This is the reason why humans are considered not only the greatest source of contaminants but also the source of the most critical contaminants, especially when working with biocontamination control.

The problem with operators in cleanrooms were partly solved by gowning the personnel in specially designed cleanroom garments to act as a barrier or a filter to minimise the possibility for skin particles, including microorganisms, from operators to be suspended into, and thus contaminating, the surrounding air of a cleanroom.

The cleanroom garment is an important barrier: Alvin Leiberman wrote in one of the first books on cleanroom technology that "The cleanroom garment and gloves is the primary barrier between the operator and the surrounding air of a cleanroom …". It must be noted that the garment is not only the primary barrier but also the only barrier.

Annex 1 and aseptic production

One of the most striking aspect of Annex 1 is

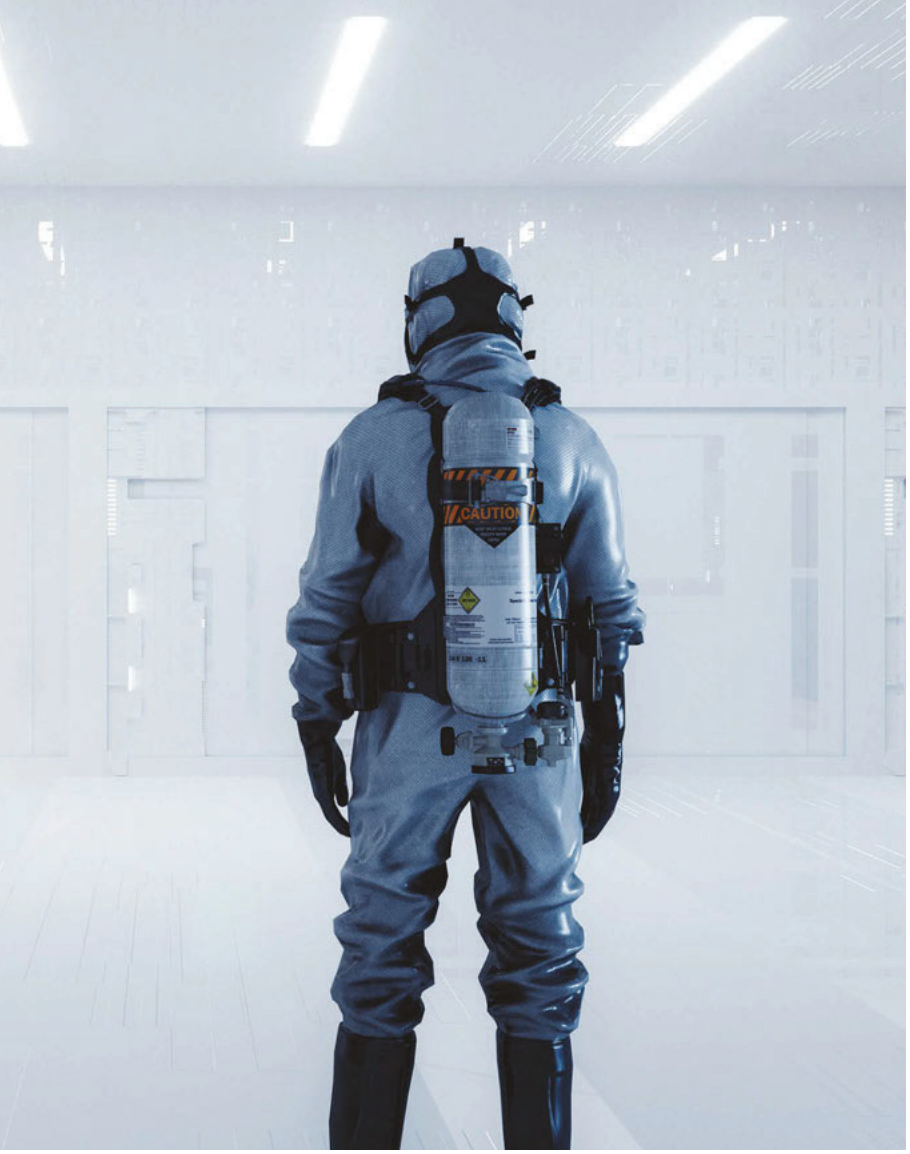
150

Number of times textile cleanroom garments can be washed

VS

Number of times textile cleanroom garments can be washed and sterilised

50



the requirement of using barrier technology. This means that, during critical handling and manufacturing of pharmaceutical products, the operators should be physically separated from the product handled using various barrier concepts. A barrier system can comprise of using isolators, closed process systems and (or) RABS - Restricted Access Barrier System.

Aseptic cleanrooms in the future

Traditionally, aseptic production has been performed in a Grade A clean zone placed in a Grade B cleanroom. The Grade B cleanroom acts as background to protect the desired cleanliness of the Grade A clean zone.

The main purpose using barrier technology is of course to minimise the risk of contaminating the product in the Grade A environment and consequently to increase patient safety. However, in some cases barrier technology will also have an influence on the background cleanroom cleanliness.

Closed process system and isolators can for example be placed in lower grade cleanrooms, i.e. Grade C or Grade D, based on type of barrier system and most importantly based on risk assessment.

A RABS is, from a technical perspective, a traditional vertical UDF cabinet supplied with a barrier, mostly in the form of a glass panel, equipped with glove ports, placed between the operator and the working chamber in which the product is to be handled.

> **Not all aseptic production can be performed using barrier technology**

The glass panel in a RABS is not hermetically sealed to the UDF cabinet, meaning that the product protective air flow inside the RABS will continue out into the cleanroom without restriction. To meet the requirements in Annex 1 a RABS therefore must be placed in a Grade B cleanroom, acting as a clean enough background for the aseptic procedure.

In practice this means that Grade B cleanroom will still be used to a high extent in the future, and consequently also the strictest garment system.

Cleanroom garments – A clean barrier concept

Cleanroom garments are to be viewed upon as a covering barrier concept, and to be used in various grades of coverage depending on the cleanliness demands and requirements of the cleanroom.

The very best garment material, from a contamination control perspective, is a totally impermeable material that in fact do not allow anything to pass, particles, air, or water vapour. However, this is contradictory to the comfort needs of the personnel.

Other aspects to consider are the cleanliness of the garment, its integrity, as well as the garments lifespan and finally if the cleanroom garment can, in one way or the other, be controlled and validated.

Grade B cleanroom garment system

As stated in Annex 1 the overall purpose of the garment used in Grade B cleanrooms is to cover the operator to such an extent that no naked skin is to be exposed to the surrounding air. Further to this, the garment should be sterile when put on, and it should be put on in such a manner not to compromise the cleanliness of the garment.

Two different types of cleanroom garments are available today; single use garments that often are pre-sterilised, and reusable

> **The overall demands stated in Annex 1 is that everything must be in accordance with QRM**

garments that are to be repeatable washed and sterilised before use. It is well known that washing and sterilisation of reusable textile garments has a negative impact on the lifespan of the garment, but this has not been emphasised in previous versions of Annex 1 until the version published in 2022.

Annex 1 – Need for scientific evidence

The overall demands stated in Annex 1 is that everything must be in accordance with QRM – "Quality Risk Management" principles to, in a proactive way, identifying, scientifically evaluating, and controlling potential risks to quality.

In other words, it is not sufficient to rely on general subjective opinions nor poorly verified recommendations, but to rely only on scientifically justified facts.

In the Nordic countries it has been recommended by laundry and lease companies that textile cleanroom garments can be washed 150 times, and washed and sterilised 50 times. Scientific evidence for these recommendation has not been available for many years.

Different tests conducted

Many different tests have been conducted, including body box testing and more traditional textile fabric tests. The result from these tests shows that washing and sterilisation will have a major negative impact in the performance and strength of the fabric, but unfortunately, these results cannot be translated into maximum washing and sterilisation cycles.

Need for a garment integrity test

As for microbiologically rated process filters, there is a need for some sort of garment integrity test. At the University of Lund such an integrity test was developed, based on integrity testing of sterilising grade filters. Unfortunately, the test did not work practical on textile cleanroom garments due to the volatile structure of the weave. However, the test worked fine on single-use, non-woven cleanroom garments.

Cleanroom gloves – Integrity test

Cleanroom gloves is an important part of the cleanroom garment system. Gloves play a crucial role, especially since operator gloved hands are used in different operations. Operator hands are important work tools and need to be covered with a clean enough barrier in order not to contaminate what is being handled.

Barrier gloves have been discussed for many years. Mainly because gloves are regularly disinfected, which has a negative impact on the strength of the gloves. Therefore, gloves are exchanged after a specified period, a period that often is not based on scientific evidence but merely on subjective considerations.

However, as stated in Annex 1, there is a need for some sort of integrity test or indicative method on cleanroom garments. On the body covering parts, there is no methods presently available, but on gloves the use of indicator gloves offers one solution.

Indicator gloves comprise of a set of two gloves, a coloured inner dressing glove, onto which a traditional wheat coloured working glove is worn. If damaged on the outer most critical working glove occurs, applying disinfectant on the gloves will result in a coloured spot on the glove, indicating nonconformities and thus time to change gloves.

Summary and thoughts

Annex 1 states, from a quality risk management point of view, that there is a need for scientifically based validation and test data on reusable cleanroom garments including gloves.

The maximum number of washing and sterilisation cycles of reusable cleanroom garments must be qualified, and this is in many cases the responsibility of the end-user, not the laundry-lease company.

Of all the papers published on cleanroom garments effectiveness, non can be used in practice since it is impossible to translate the results into garment integrity and effectiveness to filter out particles generated by the operator.

Cleanroom garment, including gloves, needs to be integrity tested. Indicator gloves make it easy to check gloves for integrity when entering and leaving as well during cleanroom use.

The operators are by far our most important assets. It is essential to provide them with the best filtration efficient, comfortable and protective cleanroom garments!

For more information
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