DUPONT Tyvek IsoClean

Cleanroom garment validation
Using a risk-based, quality-by-design approach

By: Milenko Pavičić and Thierry Wagner

Introduction

Manufacturing parenteral medicines requires a controlled and validated clean production environment. If terminal sterilization of the final product is not possible, aseptic manufacturing is the only alternative. In aseptic production, exposure of the sterile product to the environment may take place during different stages of the manufacturing process. Aseptic manufacturing of sterile products requires a high level of contamination control.
According to current Good Manufacturing Practices (GMP) guidelines, processes, equipment, facilities and manufacturing activities should be managed by applying Quality Risk Management (QRM) principles[1] that provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality.
An important risk factor in sterile manufacturing is personnel. Contamination from people mainly consists of hair, skin cells, saliva, sebaceous matter, sweat, particles from clothing and exogenous particles and substances picked up in the environment. Adequate cleanroom garments, as well as undergarments, are critically important to minimize the risk of contaminating the environment or products.

Other important risk factors related to cleanroom garments include gowning procedures and processes, as well as laundering, packing, sterilization, repairs, storage, handling and logistics.

Because many factors contribute to the overall quality and suitability of cleanroom garment systems, a risk- and science-based validation of cleanroom garment systems is very important. In this article, cleanroom garment systems are viewed as a process which will be validated in the frame of the overall aseptic process. The term "validation" is used to aggregate the various qualification steps that are required to demonstrate that a cleanroom garment system is suitable for its intended use in a given aseptic process. In this holistic innovative approach, aligned with quality-by-design principles[2], more effort is spent at the front-end in the design phase and during design qualification. This will lead to designed-in risk reductions; better understanding of key aspects, limitations and residual risks; and fewer issues during final simulation runs and routine operations. The article is based on a more extensive paper by the same authors published in the *Journal of Validation Technology*[3].

Regulatory guidance

Depending on the jurisdiction, aseptic production of sterile medicines must meet various regulatory requirements such as those set out in: Annex 1 of the EU Guidelines to Good Manufacturing Practice; U.S. Food and Drug Administration (FDA) Guidance for Industry on sterile drug production; or Japanese Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing.

Current EU-GMP guidelines require use of sterilized or adequately sanitized garments for grade A/B areas and a written procedure for changing and washing that is designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas. Reusable garments are required to be cleaned and handled in a way that the garment does not gather additional contaminants that can be shed later.

The current EU-GMP Annex 1 for the Manufacture of Sterile Medicinal Products includes little guidance on cleanroom garment qualification except that it needs to be "appropriate." In contrast, the new draft EU-GMP

Annex 1[4] published for consultation in December 2017 explicitly introduces the application of QRM principles and provides more details on gowning, including the requirement that gowning is part of a holistic contamination control strategy.
This new draft EU-GMP Annex 1[4] also requires that garments must be sterile and visually checked for cleanliness and integrity. Another key addition is the requirement that "reusable garments should be replaced based at a set frequency determined by qualification or if damage is identified." This requires manufacturers to produce data regarding the effect of reprocessing on the fabric and the overall garments.

ISO 14644-5: 2004 Annex B on cleanroom clothing requirements provides guidance that can be used to establish the user requirements specification (URS).

ISO 13408-1: 2008 includes some general requirements on cleanroom garments for aseptic processing but does not provide much guidance on cleanroom garment system qualifications.

IEST-RP-CC003.4: 2013 provides guidance on design, selection, specification, maintenance and testing of garment systems. Appendix B proposes tests for assessments of particle penetration and garment cleanliness. It is the most useful document to support qualifications of cleanroom garment systems.

Validation approach

The four stages used for validation of equipment, facilities, utilities and systems can be applied to the validation of cleanroom garments. Some stages will focus on the quality of the cleanroom garment, but others must include additional components of the cleanroom garment system. Packaging of the cleanroom garments should be part of the validation. Figure 1 provides an overview of the validation stages for cleanroom garments. Each validation stage must be formally finalized before progressing to the next stage.

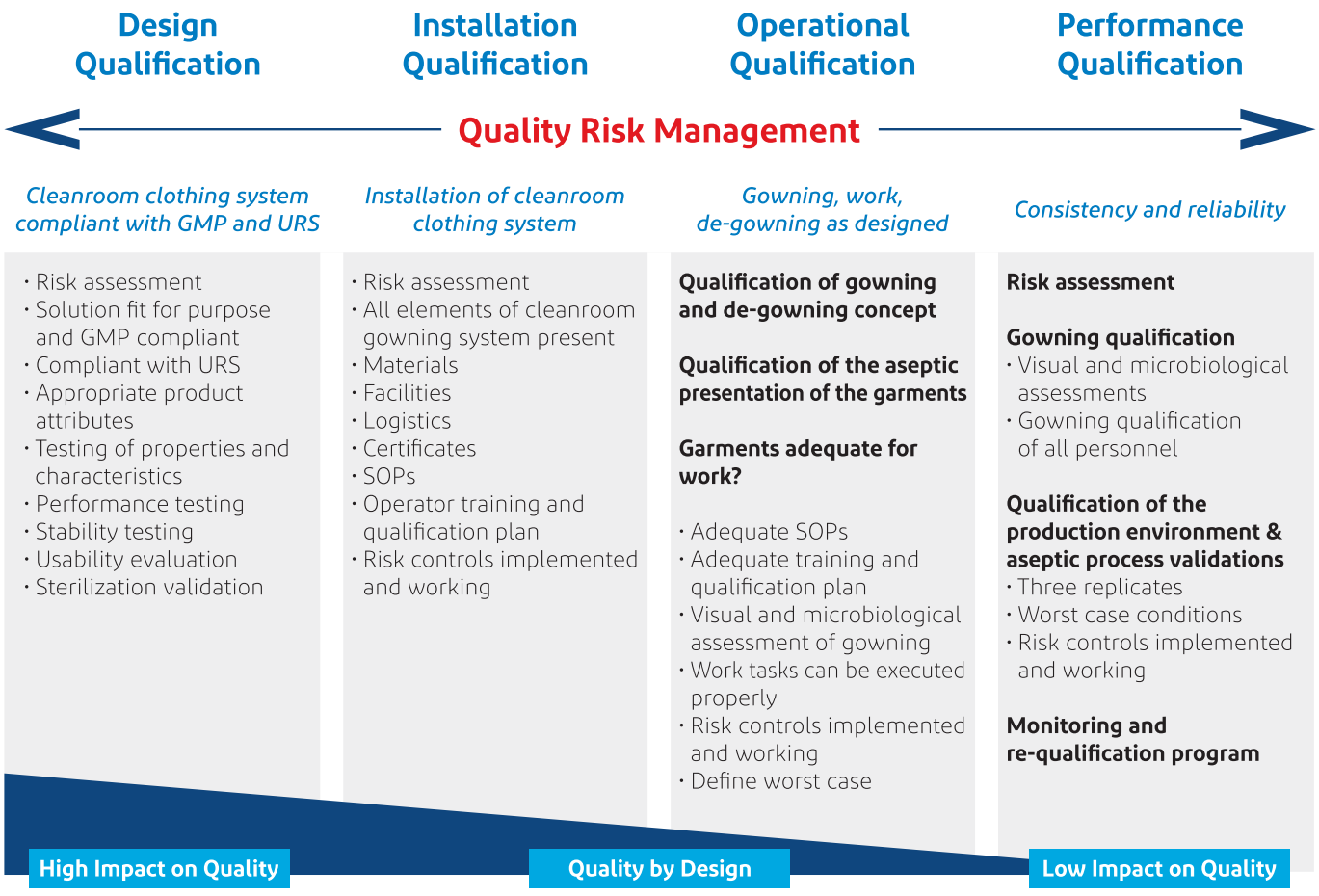

Figure 1. Overview of the validation stages for cleanroom garments used in EU-GMP grade A/B cleanrooms.

First a URS must be established. It is a document that specifies the requirements necessary to create a feasible design that meets the intended purpose of the cleanroom garment. It may include additional requirements, such as protection of people against chemical and/or biological agents.

Stage 1—Design qualification (DQ)

During DQ, compliance of the cleanroom garment design with cGMP must be demonstrated and documented, and the requirements of the URS must be verified to confirm that the selected cleanroom garment is qualified for the intended use. The DQ must be executed and authorized by qualified, knowledgeable persons who can challenge the proposed design and its performance.

Following the model of design validations of sterile barrier systems described in ISO 11607-1: 2019 - Packaging for terminally sterilized medical devices , it is recommended to split the DQ into four key areas. Relevant items for each of these areas are presented in Table I.

1. **Material qualification**—includes the qualification of key characteristics and properties of the materials and fabrics used, the cleanroom garments and the packaging.
2. **Performance testing**—includes testing the cleanroom garments and packaging under simulated and standardized conditions using standardized test methods.
3. **Stability testing**—performed to assure that key material characteristics and properties remain sufficiently stable during the life cycle. Characteristics and properties that change over time should be validated under worst-case conditions.

Information for these three areas is normally provided by the supplier; however, it is important to verify that the data has been generated using validated and sound scientific methods.

4. **Usability evaluation**—performed by the end-user to assure that the cleanroom garments can be used with acceptable remaining contamination and safety risks. Suppliers can also evaluate their garments for the intended use and supply that data to end-users for verification and further mitigation of identified risks during gowning and operations.

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

Table I. The four key areas of the design qualification (DQ) for cleanroom garments used in EU-GMP grade A/B cleanrooms.

It is important to note that the validation of reusable cleanroom garments is more complex compared to single-use cleanroom garments. Repeated laundering, repeated sterilization, multiple uses and repairs influence the quality of reusable cleanroom garments. The influence of these factors must be validated throughout the entire life cycle. In addition, not only the garment supplier must be qualified, but also the cleanroom laundry, sterilization facilities and repair service. Reprocessing should be the subject of a separate DQ by the manufacturer and IQ-OQ-PQ by the supplier.

Stage 2—Installation qualification (IQ)

The IQ is a formal check to verify if all required elements are present, including: facilities and standard operating procedures for gowning and de-gowning; certificates of conformance and/or analysis; and the operator training and qualification plan. Risk assessments executed as part of the DQ should be finalized and risk controls should be implemented. Refer to Figure 1 for a summary of items to be included in the IQ.

Stage 3—Operational qualification (OQ)

All relevant steps of the gowning and de-gowning process, as well as the aseptic presentation of the garments should be qualified during the OQ (refer to Figure 1). At least three independent, consecutive visual and microbiological assessments for at least one person who is trained for aseptic gowning should be performed.
The OQ should also include a formal assessment, using all available sizes of the cleanroom garments and with people of different body shapes, to verify that movements such as bending, stretching and lifting can be executed properly.

Stage 4—Performance qualification (PQ)

The objective of the PQ is to validate the performance of the cleanroom garment system in use. The PQ is typically performed under worst-case conditions, which are determined based on a risk assessment. Prior to performing the PQ, it is necessary to define the actions that should be taken if established criteria are not met.
During the first phase, compliance with aseptic gowning procedures should be confirmed using both a visual and microbiological assessment. Each person accessing an EU-GMP grade A/B environment must perform a gowning qualification. Only adequately trained persons should execute the PQ to exclude failures due to causes other than quality issues with the cleanroom garments.
The second phase focuses on validation of the microbiological quality of the gowned personnel while performing work tasks (e.g., aseptic compounding, cleaning and disinfecting, etc.). This phase also includes validation of the microbiological and particulate quality of the work environment and the execution of aseptic process validations.

Revalidation and change management

To confirm that the cleanroom garment system remains in a state of control, it should be evaluated at an appropriate frequency (e.g., annually or biennially). Gowning qualifications should be repeated at least once a year, or more frequently if there is doubt about the quality of the gowning process or skills of specific persons.
Changes must be reviewed critically and may lead to revalidations. Well-documented DQs, as well as IQ-OQ-PQ, are the basis for successful change management.

Conclusion

A science- and risk-based, quality-by-design approach offers many benefits when applied to the design, selection and implementation of cleanroom garments. It is not only the correct approach to effectively control contamination risks related to people, it is an appropriate response to the latest regulatory requirements, such as the new EU-GMP Annex 1 draft[4] that is based on QRM principles and introduces the concept of a holistic contamination control strategy that considers all aspects of contamination control during the entire life cycle based on thorough technical knowledge and sound process know-how. This approach also creates a foundation for proper root cause analysis in case of deviations, and for risk-based change management.

References

1. International Council for Harmonisation (ICH). ICH Q9 - Quality risk management. In:2005.
2. International Council for Harmonisation (ICH). PHARMACEUTICAL DEVELOPMENT Q8(R2). In: INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, ed2009.
3. Pavičić M, Wagner T. Risk & Science-Based Validation of Cleanroom Garments (http://www.ivtnetwork.com/article/risk-science-based-validation-cleanroom-garments). Journal of GXP Compliance (IVT Network). 2019;23(4).
4. European Medicine Agency (EMA). Annex 1 - Manufacture of Sterile Medicinal Products - draft for public consulation. In: European Medicine Agency (EMA), ed. Brussels: Directorate-General for Health and Food Safety, Unit SANTE B/4, BE-1049 Brussels; 2017.

About the authors

Milenko Pavičić, PhD started his career as a microbiologist in the pharmaceutical industry in 1994. He occupied several functions in R&D, QC and production. His specializations are in the field of contamination control related to aseptic and sterile production, microbiological quality control and (practical) training. In 2003 he founded Pavičić Pharmaceutical Microbiology (PPM). PPM supports pharmaceutical companies and hospital pharmacies in an advisory role, or by participating in or managing projects. PPM is also specialized in practical training, courses and development of tailor made e-learning modules in the field of aseptic and sterile pharmaceutical production.

Thierry Wagner, MSc has spent the past 30 years working for DuPont in its polyester films and nonwovens businesses currently as Regulatory Affairs Director, Europe, Middle-East & Africa in DuPont Medical and Pharmaceutical Protection. He is convener of ISO TC198/WG7 “Sterilization of Health Care Products—Packaging” (ISO 11607), chairman of the Sterile Barrier Association (SBA), member of the Parenteral Drug Association (PDA) and actively involved in various ISO and CEN technical committees on medical and pharmaceutical packaging like CEN TC102 “Sterilizers for Medical Purposes—Packaging” (EN868) and ISO TC76 “Transfusion, infusion and injection equipment for medical and pharmaceutical use”. Thierry is also a member of ISO/TC 210 in charge of ISO 13485, medical device symbols, ASTM Committee F02 and of the CEN Advisory Board for Healthcare Standards-Europe (CEN ABHS).
Thierry Wagner earned a master’s degree in mechanical and process engineering from ETH Zürich in Switzerland. He is a featured speaker at international conferences and seminars on medical and pharmaceutical packaging regulatory aspects.

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DUPONT Tyvek IsoClean

Annex 1 revision — Contamination risk factors

Advantages of Tyvek® IsoClean® single-use garments over reusable garments

Manufacturing of the garments

For DuPont™ Tyvek® IsoClean®, the production of raw materials is well controlled by DuPont as the sole manufacturer.

For reusable garments, the risk of garment failure varies considerably across multiple manufacturers within that supply chain.

Packaging & transport of the garments

Tyvek® IsoClean® sterile garments are packaged in a pouch with a five-year shelf life, then in double poly case liners, and finally in a single-use sealed box, which represents 4 layers of protection significantly reducing the risk of contamination.

Most reusable garments, that are autoclaved are packed in a single bag with a six-month shelf life and then in a reusable crate, which can lead to transfer of contamination.

Working in the cleanroom

Tyvek® IsoClean® provides a consistent barrier against dry particles and microorganisms, delivering the ideal balance of protection, durability and comfort. Thanks to excellent fabric properties the coverall and accessories are a barrier that protects both the wearer and the environment.

Reusable polyester garments have a higher risk of contamination in the cleanroom due to their high permeability. Additionally, the frequent washing and sterilization of reusable garments leads to damaged fabric and larger pores, thereby increasing the release of particles and fibers into the environment.

Washing & sterilizing the garments

Tyvek® IsoClean® clean and sterile garments are only washed and sterilized prior to wearing, so there is no risk of ineffective washing or sterilizing of a garment that has already been worn.

Reusable garments are washed and sterilized many times over their lifetime, increasing the risk of contamination. Changes in garment performance can be invisible to the naked eye. Download our study on **www.tyvek.co.uk/invisible** to make informed garment decisions.

Repairing contaminated garments

Tyvek® IsoClean® garments are only worn once, so there is no risk of inadequately repairing damaged garments.

Inadequate repairs on reusable garments can lead to holes and decrease of barrier. Requalifying repaired garments can also be expensive and disruptive.

Tyvek® IsoClean®

Sterile single-use garment & accessory options*

Coverall

Model IC 183 B WH DS

Clean-processed and gamma-sterilized.
Bound internal seams.
Tunnelled elastication at wrists and ankles.
Elasticated waist at back.
Tyvek® covered elasticated thumb loops.
Zipper closure.
Storm flap.
Aseptically folded.
CE-certified. Cat.III, Type 5-B, 6-B.
White.
25/box
SM–3XL

Labcoat

Model IC 270 B WH MS

Clean-processed and gamma-sterilized.
Bound internal seams.
Tunnelled at wrists.
Front snap closure.
Aseptically folded.
CE certified. Cat.I.
White.
30/box
SM-3XL

Hood

Model IC 668 B WH MS

Clean-processed and gamma-sterilized.
Bound internal seams.
Bound hood opening.
Full face opening.
Ties with loops.
Aseptically folded.
CE certified. Cat.III, PB [6].
White.
100/box
Universal sizing (00)

Hood/mask

Model 9820 MS

Clean-processed and gamma-sterilized.
HOOD:
Bound seams.
Bound head opening.
Ties with loops.
White.
MASK:
Pleated Polyethylene outer.
17,5 cm.
Sterile.
CE ceritified.Cat I.
Blue.
100/box
Universal sizing (00)

Bouffant

Model IC 729 S WH MS

Clean-processed and gamma-sterilized.
Elastic headband.
CE certified. Cat. I.
White.
250/box
Universal sizing (00)

Sleeve

Model IC 501 B WH MS

Clean-processed and gamma-sterilized.
Bound internal seams.
Tunnelled elastication at wrist and bicep.
Aseptically folded.
White.
CE certified. Cat.III, PB [6].
100/box
Universal sizing (00)

Overboot

Model IC 458 B WH MS

Clean-processed and gamma-sterilized.
Tunnelled elastication at shin.
Ties.
Elasticated ankle.
Gripper™ sole.
Bound internal seams.
Aseptically folded.
CE certified. Cat.III, PB [6].
White.
100/box
SM-XL

Sierra™ Mask

Model ML7360 WH 0S

Gamma-sterilized.
Bound ties, metal nose piece.
23 cm.
White.
250/box
Universal sizing (00)

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