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Validierung von Reinraumschutzkleidung nach einem risikobasierten, qualitätsorientierten Designansatz

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Einleitung

Die Herstellung parenteraler Medikamente erfordert eine kontrollierte und validierte saubere Produktionsumgebung. Wenn eine endständige Sterilisation des Endprodukts nicht möglich ist, ist die keimfreie Produktion die einzige Alternative. In der keimfreien Produktion kann die Exposition des sterilen Produkts gegenüber der Umgebung in verschiedenen Phasen des Herstellungsprozesses erfolgen. Die keimfreie Herstellung von sterilen Produkten erfordert ein hohes Maß an Kontaminationskontrolle.
Gemäß den aktuellen Richtlinien der Good Manufacturing Practices (GMP) sollten Prozesse, Ausrüstungen, Anlagen und Fertigungsaktivitäten unter Anwendung der Prinzipien des Qualitäts-Risikomanagements (QRM)[1] gesteuert werden, die ein proaktives Mittel zur Identifizierung, wissenschaftlichen Bewertung und Kontrolle potenzieller Qualitätsrisiken darstellen
Ein wichtiger Risikofaktor in der sterilen Produktion ist das Personal. Die Kontamination durch Menschen umfasst hauptsächlich Haare, Hautzellen, Speichel, Talg, Schweiß, Partikel aus der Kleidung sowie körperfremde Partikel und Stoffe, die in der Umwelt aufgenommen werden. Angemessene Reinraumschutzkleidung sowie Unterbekleidung sind von entscheidender Bedeutung, um das Risiko einer Kontamination der Umwelt oder der Produkte zu minimieren.

Weitere wichtige Risikofaktoren im Zusammenhang mit Reinraumschutzkleidung sind Ankleideverfahren und -prozesse sowie Waschen, Verpacken, Sterilisieren, Reparieren, Lagern, Handhaben und Logistik.

Da viele Faktoren zur Gesamtqualität und Eignung von Reinraumschutzkleidungssystemen beitragen, ist eine risiko- und wissenschaftsbasierte Validierung von Reinraumschutzkleidungssystemen sehr wichtig. In diesem Artikel werden Reinraumschutzkleidungssysteme als ein Prozess betrachtet, der im Rahmen des gesamten keimfreien Prozesses validiert wird. Unter dem Begriff „Validierung“ werden die verschiedenen Qualifikationsschritte zusammengefasst, die erforderlich sind, um nachzuweisen, dass ein Reinraumschutzkleidungssystem für den vorgesehenen Einsatz in einem gegebenen keimfreien Prozess geeignet ist. In diesem ganzheitlichen innovativen Ansatz, der sich an den Prinzipien des qualitätsorientierten Designs[2] ausrichtet, wird mehr Aufwand im Vorfeld in der Designphase und bei der Designqualifizierung betrieben. Dies führt zu einer Reduzierung der eingeplanten Risiken, zu einem besseren Verständnis der wichtigsten Aspekte, Einschränkungen und Restrisiken sowie zu weniger Problemen bei abschließenden Simulationsläufen und im Routinebetrieb. Der Artikel basiert auf einem umfangreicheren Beitrag derselben Autoren, der im *Journal of Validation Technology* veröffentlicht wurde[3].

Regulatorische Leitlinien

Je nach Rechtsprechung muss die keimfreie Produktion von sterilen Arzneimitteln verschiedene regulatorische Anforderungen erfüllen, wie beispielsweise die im Anhang 1 der EU-Richtlinien für gute Herstellungspraxis, in den Leitlinien der US Food and Drug Administration (FDA) für die Industrie zur Herstellung steriler Arzneimittel oder in den japanischen Leitlinien für die Herstellung steriler pharmazeutischer Produkte durch aseptische Verarbeitung erwähnten Anforderungen.
Die aktuellen EU-GMP-Richtlinien verlangen die Verwendung von sterilisierter oder ausreichend desinfizierter Kleidung für Bereiche der Klasse A/B und ein schriftliches Verfahren für den Wechsel und das Waschen, um die Kontamination von Reinraumschutzkleidung oder das Verschleppen von Kontaminationen in die Reinräume zu minimieren. Wiederverwendbare Schutzkleidung muss so gereinigt und behandelt werden, dass das Bekleidungsstück keine zusätzlichen Verunreinigungen aufnimmt, die später wieder abgegeben werden können.

Der aktuelle EU-GMP-Anhang 1 für die Herstellung steriler Arzneimittel enthält wenig Hinweise zur Qualifizierung von Reinraumschutzkleidung, außer dass sie „angemessen" sein muss. Im Gegensatz dazu führt der im Dezember 2017 zur Prüfung veröffentlichte neue Entwurf des EU-GMP-Anhangs 1[4] ausdrücklich die Anwendung der QRM-Grundsätze ein und enthält weitere Einzelheiten zur Bekleidung, einschließlich der Anforderung, dass die Bekleidung Teil einer ganzheitlichen Kontaminationskontrollstrategie ist.
Dieser neue Entwurf des EU-GMP Anhangs 1[4] verlangt auch, dass die Bekleidung steril sein und visuell auf Sauberkeit und Integrität überprüft werden muss. Eine weitere wichtige Ergänzung ist die Anforderung, dass „wiederverwendbare Schutzkleidung in einer durch die Qualifikation festgelegten Häufigkeit ersetzt werden sollte oder wenn Schäden festgestellt werden." Dies erfordert von den Herstellern, dass sie validierte Daten über die Wirkung
der Wiederaufbereitung auf das Gewebe und die Schutzkleidung liefern.

ISO 14644-5: 2004 Anhang B zu den Anforderungen an Reinraumschutzkleidung enthält Leitlinien, die zur Erstellung der Benutzeranforderungsspezifikation (User Requirements Specification, URS) verwendet werden können.

ISO 13408-1: 2008 enthält einige allgemeine Anforderungen an Reinraumschutzkleidung für die keimfreie Produktion, gibt aber nicht viele Hinweise auf die Qualifizierung von Reinraumschutzkleidungssystemen.

IEST-RP-CC003.4: 2013 bietet Leitlinien für Design, Auswahl, Spezifikation, Wartung und Prüfung von Schutzkleidungssystemen. Anhang B schlägt Tests zur Beurteilung der Partikeldurchdringung und der Sauberkeit der Schutzkleidung vor. Es ist das nützlichste Dokument zur Unterstützung der Qualifizierung von Reinraumschutzkleidungssystemen.

Validierungsansatz

Die vier Stufen, die für die Validierung von Geräten, Einrichtungen, Versorgungseinrichtungen und Systemen verwendet werden, können auch für die Validierung von Reinraumschutzkleidung verwendet werden.
Einige Stufen konzentrieren sich auf die Qualität der Reinraumschutzkleidung, andere müssen jedoch zusätzliche Komponenten des Reinraumschutzkleidungssystems beinhalten. Die Verpackung der Reinraumschutzkleidung sollte Teil der Validierung sein. Abbildung 1 gibt einen Überblick über die Validierungsstufen für Reinraumschutzkleidung. Jede Validierungsstufe muss formal abgeschlossen sein, bevor die nächste Stufe eingeleitet wird.

Abbildung 1. Überblick über die Validierungsstufen für Reinraumschutzkleidung, die in Reinräumen der EU-GMP-Klasse A/B verwendet wird.

Zuerst muss ein URS eingerichtet werden. Es handelt sich um ein Dokument, das die Anforderungen festlegt, die notwendig sind, um ein umsetzbares Design zu erstellen, das dem Zweck der Reinraumschutzkleidung entspricht. Sie kann zusätzliche Anforderungen enthalten, wie beispielsweise den Schutz von Personen vor chemischen und/oder biologischen Stoffen.

Stufe 1—Designqualifikation (DQ)

Während der DQ muss die Konformität des Designs der Reinraumschutzkleidung mit cGMP nachgewiesen und dokumentiert werden, und die Anforderungen der URS müssen überprüft werden, um zu bestätigen, dass die ausgewählte Reinraumschutzkleidung für den vorgesehenen Einsatzzweck geeignet ist. Die DQ muss von qualifizierten, sachkundigen Personen durchgeführt und autorisiert werden, die den vorgeschlagenen Entwurf und seine Ausführung hinterfragen können.

Nach dem Modell der Designvalidierung von sterilen Barrieresystemen, beschrieben in ISO 11607-1: 2019 - Verpackung für terminal sterilisierte Medizinprodukte, wird empfohlen, die DQ in vier Schlüsselbereiche aufzuteilen. Relevante Punkte für jeden dieser Bereiche sind in Tabelle I dargestellt.

1. **Materialqualifikation**—beinhaltet die Qualifizierung der wichtigsten Eigenschaften der verwendeten Materialien und Gewebe, der Reinraumschutzkleidung und der Verpackung.
2. **Leistungstest**—beinhaltet die Prüfung der Reinraumschutzkleidung und -verpackung unter simulierten und standardisierten Bedingungen mit standardisierten Testmethoden.
3. **Stabilitätstest**—wird durchgeführt, um sicherzustellen, dass die wichtigsten Eigenschaften des Materials während der Lebensdauer ausreichend konstant bleiben. Merkmale und Eigenschaften, die sich im Laufe der

Zeit ändern, sollten unter Worst-Case-Bedingungen validiert werden.
Informationen für diese drei Bereiche werden in der Regel vom Lieferanten zur Verfügung gestellt; es ist jedoch wichtig zu überprüfen, ob die Daten mit validierten und soliden wissenschaftlichen Methoden erzeugt wurden.

4. **Evaluation der Verwendbarkeit**—wird vom Endverbraucher durchgeführt, um sicherzustellen, dass die Reinraumschutzkleidung mit akzeptabler Restkontamination und akzeptablen Sicherheitsrisiken verwendet werden kann. Lieferanten können ihre Kleidung auch für den vorgesehenen Verwendungszweck bewerten und diese Daten an die Endverbraucher zur Überprüfung und weiteren Minderung der identifizierten Risiken während des Ankleidens und der Verwendung liefern.

Eignung des Materials	Leistungstest	Stabilitätstest	Evaluierung der Verwendbarkeit
Reinraumschutzkleidung • Freisetzung von Fasern und Partikeln • Sterilisationsverträglichkeit • Sterility Assurance Level (Sterilisierungsvertrauensgrad) • Pyrogene Wirkung • Effizienz der Partikelfiltration • Effizienz der Bakterienfiltration • Porosität • Oberflächenwiderstand • Perforationsbeständigkeit • Mechanische Reißfestigkeit • Chemische Beständigkeit • Schutz vor biologischen Stoffen	***Reinraumschutzkleidung*** • Bodybox-Test • Helmke-Drum-Test	***Einweg-Schutzkleidung*** • Eigenschaften und Merkmale am Ende der Lebensdauer ***Wiederverwendbare Schutzkleidung*** • Eigenschaften und Merkmale nach der maximalen Anzahl von Wasch- und Sterilisationszyklen	***Verwendungsszenarien*** • Überführung in den klassifizierten Lagerbereich • Lesbarkeit des Etikettsl • Einfaches Öffnen der Verpackung • Keimfreies Entfalten der Schutzkleidung • Ankleiden • Anlegen von zusätzlicher Schutzausrüstung (z.B. sterile Handschuhe, Gesichtsmaske, Schutzbrille) • Arbeitssituationen • Sicherheit, Biosicherheit • Auskleiden
Verpackung • Freisetzung von Fasern und Partikeln • Biobelastung • Eindringen von häufig verwendeten Desinfektionsmitteln ***Sterile Verpackun*** • ISO 11607-1	***Sterile Verpackung*** • Einfluss des Transports auf die Integrität/Sterilität (ISO 11607-1)	***Sterile Verpackung*** • Verpackungsintegrität/ Sterilität am Ende der Lebensdauer (ISO 11607-1)	**Verpackung** • Keimfreie Präsentation der Schutzkleidung (mehrere Schichten)

Tabelle I. Die vier Kernbereiche der Designqualifizierung (DQ) für Reinraumschutzkleidung zur Verwendung in Reinräumen der Stufe A/B nach EU-GMP.

Es ist wichtig zu beachten, dass die Validierung von wiederverwendbarer Reinraumschutzkleidung komplexer ist als bei Einmal-Reinraumschutzkleidung. Wiederholtes Waschen, wiederholte Sterilisation, Mehrfachverwendung und Reparatur beeinflussen die Qualität von wiederverwendbarer Reinraumschutzkleidung. Der Einfluss dieser Faktoren muss über den gesamten Lebenszyklus validiert werden. Darüber hinaus muss nicht nur der Bekleidungslieferant qualifiziert sein, sondern auch die Reinraum-Wäscherei, die Sterilisationseinrichtungen und der Reparaturservice. Die Wiederaufbereitung sollte Gegenstand einer separaten DQ durch den Hersteller und IQ-OQ-PQ durch den Lieferanten sein.

Stufe 2—Installationsqualifizierung (IQ)

Die IQ ist eine formale Prüfung, um zu überprüfen, ob alle erforderlichen Elemente vorhanden sind, einschließlich: Einrichtungen und Standardbetriebsverfahren für das An- und Auskleiden, Konformitäts- und/oder Analysezertifikate sowie dem Schulungs- und Qualifizierungsplan für das Bedienpersonal. Die im Rahmen der DQ durchgeführten Risikobewertungen sollten abgeschlossen und die Risikokontrollen durchgeführt werden. Siehe Abbildung 1 für eine Zusammenfassung der Elemente, die in die IQ aufgenommen werden sollen.

Stufe 3—Betriebsqualifizierung (Operational qualification, OQ)

Alle relevanten Schritte des Be- und Entkleidungsprozesses sowie der keimfreien Präsentation der Kleidungsstücke sollten während der OQ qualifiziert werden (siehe Abbildung 1). Es sollten mindestens drei unabhängige, aufeinanderfolgende visuelle und mikrobiologische Bewertungen für mindestens eine Person durchgeführt werden, die für keimfreies Anziehen ausgebildet ist. Die OQ sollte auch eine formelle Bewertung unter Verwendung aller verfügbaren Größen der Reinraumschutzkleidung und mit Personen unterschiedlicher Körperform beinhalten, um sicherzustellen, dass Bewegungen wie Bücken, Strecken und Heben ordnungsgemäß ausgeführt werden können.

Stufe 4—Leistungsqualifizierung (Performance Qualification, PQ)

Das Ziel der Leistungsqualifizierung ist es, die Leistung des verwendeten Reinraumschutzkleidungssystems zu validieren. Die Leistungsqualifizierung erfolgt typischerweise unter Worst-Case-Bedingungen, die auf der Grundlage einer Risikobewertung ermittelt werden. Vor der Durchführung der Leistungsqualifizierung ist es notwendig, die Maßnahmen zu definieren, die ergriffen werden sollten, wenn festgelegte Kriterien nicht erfüllt sind.

In der ersten Phase sollte die Einhaltung der keimfreien Ankleidevorschriften sowohl durch eine visuelle als auch durch eine mikrobiologische Beurteilung bestätigt werden. Jede Person, die Zugang zu einer EU-GMP-gerechten A/B-Umgebung hat, muss eine Ankleidequalifikation vorweisen. Nur ausreichend geschultes Personal sollte die Leistungsqualifizierung durchführen, um Fehler auszuschließen, die auf andere Ursachen als Qualitätsprobleme mit der Reinraumschutzkleidung zurückzuführen sind.

Die zweite Phase konzentriert sich auf die Validierung der mikrobiologischen Qualität des gekleideten Personals bei der Durchführung von Arbeitsaufgaben (z.B. keimfreie Herstellung, Reinigung und Desinfektion etc.). Diese Phase umfasst auch die Validierung der mikrobiologischen und partikulären Qualität der Arbeitsumgebung und die Durchführung der Validierung keimfreier Prozesse.

Neuvalidierung und Änderungsmanagement

Um zu bestätigen, dass das Reinraumschutzkleidungssystem überwacht wird, sollte es in einer angemessenen Häufigkeit (z.B. jährlich oder alle zwei Jahre) überprüft werden. Die Qualifikation zum Ankleiden sollte mindestens einmal im Jahr wiederholt werden, oder häufiger, wenn Zweifel an der Qualität des Ankleideprozesses oder den Fähigkeiten bestimmter Personen bestehen.

Änderungen müssen kritisch hinterfragt werden und können zu Revalidierungen führen. Gut dokumentierte DQs sowie IQ-OQ-PQ sind die Grundlage für erfolgreiches Änderungsmanagement.

Schlussfolgerung

Ein wissenschafts- und risikobasierter Quality-by-Design-Ansatz bietet viele Vorteile bei der Gestaltung, Auswahl und Implementierung von Reinraumschutzkleidung. Es ist nicht nur der richtige Ansatz zur wirksamen Kontrolle der Kontaminationsrisiken für den Menschen, sondern auch eine angemessene Antwort auf die neuesten regulatorischen Anforderungen, wie etwa dem Entwurf des neuen EU-GMP Anhang 1[4], der auf QRM-Prinzipien basiert. Er führt das Konzept einer ganzheitlichen Kontaminationskontrollstrategie ein, die alle Aspekte der Kontaminationskontrolle während der gesamten Lebensdauer berücksichtigt und auf fundiertem technischem Wissen und solidem Prozesswissen basiert. Dieser Ansatz schafft auch die Grundlage für eine ordnungsgemäße Ursachenanalyse bei Unregelmäßigkeiten und für ein risikobasiertes Change Management.

Referenz

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.

Über die Autoren

Milenko Pavičić begann seine Karriere 1994 als Mikrobiologe in der pharmazeutischen Industrie. Er war in verschiedenen Funktionen in Forschung und Entwicklung, Qualitätskontrolle und Produktion tätig. Seine Spezialisierungen liegen im Bereich der Kontaminationskontrolle im Zusammenhang mit der aseptischen und sterilen Produktion, der mikrobiologischen Qualitätskontrolle und der (praktischen) Ausbildung. 2003 gründete er Pavičić Pharmaceutical Microbiology (PPM). PPM unterstützt Pharmaunternehmen und Krankenhausapotheken in beratender Funktion oder durch die Teilnahme an bzw. das Management von Projekten. PPM hat sich auch auf praktische Schulungen, Kurse und die Entwicklung von maßgeschneiderten E-Learning-Modulen im Bereich der aseptischen und sterilen pharmazeutischen Produktion spezialisiert.

Thierry Wagner, MSc, war in den letzten 30 Jahren für DuPont in den Bereichen Polyesterfolien und Vliesstoffe tätig. Derzeit ist er Regulatory Affairs Director für Europa, den Nahen Osten und Afrika bei DuPont Medical and Pharmaceutical Protection. Er ist Moderator der ISO TC198 / WG7 „Sterilisation von Produkten für die Gesundheitsfürsorge - Verpackung“ (ISO 11607), Vorsitzender der Sterile Barrier Association (SBA), Mitglied der Parenteral Drug Association (PDA) und aktiv an verschiedenen technischen Fragen der ISO und des CEN beteiligt Ausschüsse für medizinische und pharmazeutische Verpackungen wie CEN TC102 „Sterilisatoren für medizinische Zwecke - Verpackung“ (EN868) und ISO TC76 „Transfusions-, Infusions- und Injektionsgeräte für medizinische und pharmazeutische Zwecke“. Thierry ist auch Mitglied der ISO / TC 210, zuständig für ISO 13485, Symbole für Medizinprodukte, ASTM-Ausschuss F02 und des CEN-Beirats für Gesundheitsstandards-Europa (CEN ABHS).

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Risk and science-based validation of cleanroom garments

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Abstract

Important quality attributes of cleanroom garments that to worn during the manufacture of sterile medicines include: cleanliness; sterility; particle and microbial filtration efficiency; durability; usability; and comfort. Important risk factors related to cleanroom garment systems include gowning processes and related activities, such as laundering, packing, sterilization, repairs, storage, handling and logistics, as well as change management. Because many factors contribute to the overall quality, adequacy and suitability of cleanroom garment systems, a thorough and focused validation of cleanroom garments is critically important.

After providing a review of current and emerging regulations and standards, this article proposes a risk- and science-based quality-by-design approach for the development, implementation and validation of sterile cleanroom garment systems. With this approach, more effort is spent at the front-end during the design phase as well as during design qualification. This will lead to designed-in risk reductions; enhanced scientific knowledge on selected technical solutions; and better awareness of limitations and residual risks. As a result, there should be fewer issues during cleanroom qualifications and process validations, leading to more effective routine operations as well as improved patient safety. The proposed approach, if implemented correctly, is not only the correct strategy to effectively control contamination risks related to people, but also an adequate response to the latest regulatory requirements.

Introduction

Parenteral medicines are administered through injection, infusion or implantation, and must be sterile and pure to assure product safety. Therefore, the manufacture of parenteral medicines requires a controlled and validated clean production environment. Sterile medicines can be manufactured by terminal sterilization. In this case, the product is sterilized in its final packaging, resulting in a sterility assurance level (SAL) of at least 10^{-6}. 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 (i.e., from preparation of the product using sterile ingredients to filling the product in its final container). In Europe, exposure of sterile products to the environment is only allowed in EU GMP grade A zones placed in a grade B cleanroom or in an isolator.[1]

Aseptic manufacturing of sterile products requires a high level of contamination control. Figure 1 shows the important elements that must be addressed in a contamination control strategy to assure purity of the products, sterility of sterile products and good microbiological quality of non-sterile products.

According to current Good Manufacturing Practices (GMP) guidelines, (EU,[2] US,[3] Japan,[4] WHO[5,6]), processes, equipment, facilities and manufacturing activities should be managed in accordance with Quality Risk Management (QRM) principles[7] that provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. A quality-by-design approach,[8] combined with effective risk management, should be applied to ensure the safety, quality and efficacy of sterile products. This comes from the belief that quality cannot be tested into the product, it can only be built into the design of products and the processes used to produce them. Risk assessments must be performed to identify, assess, eliminate and control

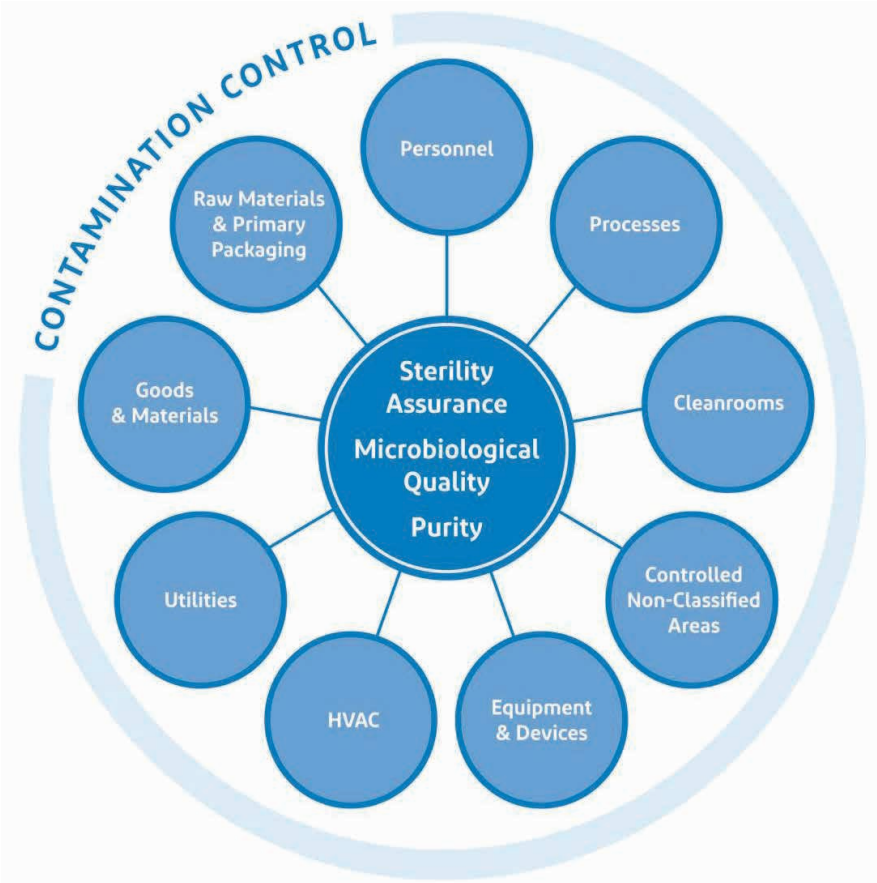

Figure 1: Important elements of a contamination control strategy for sterile manufacturing

contamination risks from the design phase of an aseptic process; to monitor and detect contamination; and to establish process requirements and acceptance criteria for all elements of a sterile manufacturing process. Risk assessments should be documented as well as maintained and should include the rationale for decisions taken in relation to mitigating risks, discounting of potential risks and residual risk.

An important risk factor in sterile manufacturing is personnel. People can cause contamination of the production environment and products in many ways.[9] Contamination from people mainly consists of hair, skin cells, skin flakes, saliva, sebaceous matter, sweat, particles from clothing and many different exogenous particles and substances picked up in the environment. These contamination sources mostly contain different endogenous (i.e., commensal) and exogenous microorganisms present in numbers which vary from a few (e.g., skin cell) to thousands (e.g., sweat) or even millions e.g., saliva). Therefore, it is important that people working in an environment, where sterile products are manufactured, wear adequate cleanroom garments.

Contamination control related to people starts with good personal hygiene based on adequate hygienic procedures, such as hand washing and hand disinfection; aseptic behavior; aseptic skills; and a good working discipline. Adequate cleanroom garments, as well as undergarments are critically important to minimize the risk of contaminating the environment or products with contamination generated by people. Cleanroom undergarments[10] serve as a first barrier against contamination from people. The cleanroom garments must form a very robust barrier between the person and the environment.

Additional protective measures, such as adequate cleanroom footwear, cleanroom socks, head coverings, face masks, eye coverings and (sterile) gloves, may be necessary or required from a regulatory point of view, to minimize the contamination risk.

Important quality attributes of cleanroom garments are cleanliness (free from chemicals, particles, pyrogens, fibers); sterility; particulate and microbial filtration efficiency; durability (tear, puncture, seam strength, abrasion); and comfort. Personal protection against chemical or biological agents may also be a relevant quality attribute. A quality-by-design approach[8] combined with effective risk management,[7] should also be applied to the design, selection and implementation of adequate cleanroom garments.

With the quality-by-design approach, more effort is spent at the front-end, in the design phase as well as in the design qualification, leading to designed-in risk reductions; better understanding of key aspects, limitations and residual risks; and fewer issues during final simulation runs and routine operations. This approach also creates the basis for proper root cause analysis (in case of issues) and adequate change management.

Other important risk factors related to cleanroom garments include gowning procedures and processes and activities related to cleanroom garments, such as laundering, packing, sterilization, repairs, storage, handling and logistics. Because many factors contribute to the overall quality, adequacy and suitability of cleanroom garment systems, a risk- and science-based validation of cleanroom garment systems is very important.

This article provides an overview of the various qualification, validation and monitoring aspects of cleanroom garments.

Current regulatory guidance for validation of cleanroom garments

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[1] or in the U. S. Food and Drug Administration (FDA) Guidance for Industry on sterile drug production[3].

The FDA guidance outlines various recommendations for gowns, such as proper gown control; no unreasonable contamination risk to the gown; providing a barrier between the body and exposed sterilized materials; and preventing contamination from particles generated by, and microorganisms shed from the body. Gowns should be sterilized and non-shedding. Methods used to don each gown component in an aseptic manner should be detailed. Manufacturers should implement an aseptic gowning qualification program to assess the ability of a cleanroom operator to maintain the quality of the gown after performance of gowning procedures, including periodic requalification and microbiological monitoring of strategically selected locations on the gown.

The current EU GMP guidelines require sterile (sterilized or adequately sanitized) garments to be provided for grade A/B areas and changing and washing to follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas. It further requires that clothing and its quality be "appropriate" without defining what would be considered appropriate. It also requires clothing to "be worn in such a way as to protect the product from contamination". In terms of attributes, "protective clothing should shed virtually no fibers or particulate matter and retain particles shed by the body". Reusable garments are required to be cleaned and handled in such 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[11] includes little guidance on cleanroom garment qualification except that it needs to be "appropriate".

The new draft EU GMP Annex 1[12] 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. It further requires that:

- Personnel are trained on gowning practices, which must be assessed
- Personnel are qualified through a successful aseptic process simulation test
- Microbial monitoring of personnel is performed

In addition, this new draft EU GMP Annex 1[12] requires that garments are visually checked for cleanliness and integrity. It also provides several new requirements regarding clothing of grade A/B; body parts that should be covered; the prevention of droplets, particles and fibers; and the folding of packaged garments to make sure that "contact to the outer surfaces of the garment is reduced to a minimum".

A key addition is the requirement that "reusable garments should be

replaced 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.

However, there is little guidance on how to qualify those garments other than stating in subclause 4.11 that "clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination".

The Japanese Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing,[4] developed by a task force of Japanese experts, is an extensive document covering all areas of aseptic processing. It includes recommendations on gowning, operations, monitoring and controls that are comparable to other standards. It provides some interesting design recommendations on gowning and de-gowning areas and highlights the need to establish appropriate control procedures, including visual inspection. It also defines maximum allowable frequency of steam sterilization for reusable materials, such as aseptic gowns, to "ensure maintenance of specifications, safety, and intended functions after repeated exposure to steam at its maximum intensity".

ISO 14644-5[13] includes an informative annex B on cleanroom clothing requirements that provides some useful guidance on aspects to consider during qualification of such clothing. It provides guidance on barrier properties; evaluation of electrostatic properties; some guidance on fit and function; and helpful guidance on construction, finishing of seams and general design criteria that can be used to establish URS. It proposes use of the dispersal chamber or body box[14] as a simulation procedure to evaluate performance; recommends that shelf life of sterile packaging be determined; and includes considerations on thermal comfort and some guidance on cleaning, referring to IEST-RP-CC003.4.[14]

ISO 13408-1[15] on general requirements of aseptic processing includes some general requirements on cleanroom garments but does not provide much guidance on cleanroom garment system qualifications.

IEST-RP-CC003.4 "Garment Systems Considerations for Cleanrooms and Other Controlled Environments"[14] provides guidance on design, selection, specification, maintenance and testing of garment systems. It includes useful guidance on material qualification attributes, considerations on processing (cleaning, re-sterilization, etc.), gowning system specifications and quality management. Appendix B proposes various tests for assessments of particle penetration and garment cleanliness, which includes the well-known and very useful body box test,[16,17] that allows simulation of the actual use of the garment, as well as the Helmke drum test.[18] Overall, IEST-RP-CC003.4[14] is the most useful document to support qualifications of cleanroom garment systems.

The EU general guidance on validation (GMP Annex 15[19]) provides the general framework that we will apply to the qualification of cleanroom garment systems.

Validation approach for cleanroom garments

The main stages of validation of equipment, facilities, utilities or systems are:

- Definition of User Requirements Specification (URS)
- Design Qualification (DQ)

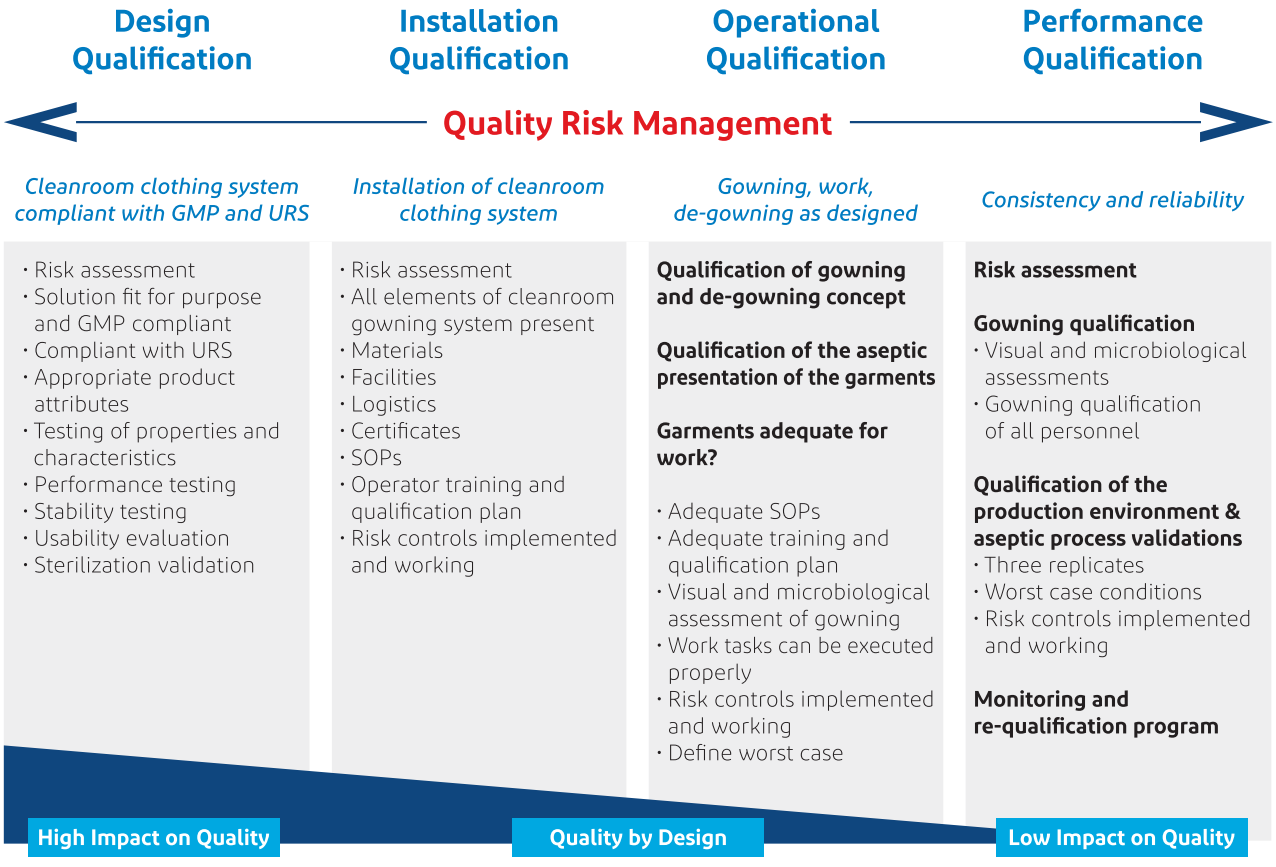

Figure 2: Overview of the different validation stages for cleanroom garments used in EU GMP grade A/B cleanrooms

- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

This approach is also appropriate for cleanroom garments. Some stages of the validation can focus mainly on the quality of the cleanroom garment itself, but in other stages, the other items of the cleanroom clothing system (i.e., cleanroom undergarments, footwear, socks, head coverings, face masks, eye coverings, gloves and other accessories) must be included. The packaging (sterile and non-sterile barriers) of the cleanroom garments should be part of the validation. An overview of the different validation stages and validation items for cleanroom garments is given in Figure 2. Each validation stage must be formally finalized before progressing to the next stage.

The GMP (EU, US, Japan) guidelines state that QRM7 should be used for qualification and validation activities. If changes occur during the project phase or during commercial production (e.g., change of garment design, fabric, zipper type, packaging, laundering process or sterilization process), the risk assessments must be repeated to determine if additional validation must be performed. The way in which risk assessments are used to support qualification and validation activities should be clearly documented.

For critical goods and materials, such as cleanroom garments, it is also important to qualify the supplier. This qualification should provide an appropriate level of confidence that the supplier is able to supply cleanroom garments with consistent quality and acts in compliance with regulatory requirements. A supplier qualification should also include qualification of subcontractors, suppliers of base materials (e.g., fabric and garment accessories) and outsourced service providers (e.g., laundries and sterilization facilities).

User Requirements Specification (URS)

The specification for cleanroom garments should be defined in a User Requirements Specification (URS). The URS is a document that specifies requirements necessary and sufficient to create a feasible design, meeting the intended purpose of the material, equipment, utility or system. The URS may also include additional requirements, such as protection of people against chemical and/or biological agents.

An example of a URS for cleanroom garments is given in Table 1.

Cleanroom garments for use in EU GMP grade A/B cleanrooms should

Table 1: Example of a URS for cleanroom garments used in EU GMP grade A/B cleanrooms

General
1. The clothing must consist of a suit or coverall; a hood that can be firmly and reliably tucked into the neck of the suit; and boots. The hood may also be attached to the suit. It must be possible to tuck the trouser legs firmly and reliably into the boots. Boots shall have an anti-slip sole.
2. The garments may be reusable or single-use.
3. Unpacking and gowning must be conducted in an aseptic manner.
4. The garments must fit well and be available in different sizes (e.g. XS to XXL).
5. The clothing must be comfortable to wear (e.g., ease of movement, thermal, tactility).
6. Garments must be traceable, including number of laundering and sterilization cycles.
Cleanliness and sterility
1. The garments should be clean (low levels of ions and organic extractables).
2. The garments shall not shed fibers, including filaments of the fabric and thread.
3. The garments shall not shed too many particles (≥ 0.5µm and ≥ 5µm). Maximum number of particles (≥0.5µm and ≥ 5µm) must be specified.
4. The garments shall be sterile (sterility assurance level ≤ 10^{-6}).
5. The garments shall have a low pyrogenicity.
Barrier properties
1. The garments shall have a good particulate and bacterial filtration efficiency.
Packaging
1. The garments shall be double or triple sterile packed.
2. The sterile packaging must be robust and should endure common manipulations without jeopardizing the integrity of the packaging.
3. The sterile packaging shall be clean.
4. The sterile packaging shall not shed too many particles (≥ 0.5µm and ≥ 5µm) and shall not shed fibers. Maximum number of particles (≥ 0.5µm and ≥ 5µm) must be specified.
5. The space between the sterile packaging shall not contain too many particles (≥ 0.5µm and ≥ 5µm) and should not contain fibers. Maximum number of particles (≥ 0.5µm and ≥ 5µm) must be specified.
6. The sterile packed garments must be packed into a clean, low bioburden bag that is present in a firmly closed clean box.
7. The box and the last sterile packaging of the garments must be labeled with a clear description of the manufacturer, content, size, batch number, production date, expiry date, storage conditions and indicator that the sterilization was done.
Identification
1. Each garment must have an unique identification number.
2. Labels must be firmly attached to the packaging or exist as an integral part of the packaging.
3. Labels must be clean and should not shed too many particles (≥ 0.5µm and ≥ 5µm) and should shed no fibers. Maximum number of particles (≥ 0.5µm and ≥ 5µm) must be specified.
4. Labels and printed text must be resistant to disinfectants that are commonly used (e.g., 70% alcohol, 6% hydrogen peroxide solution or a 600-ppm hydrogen peroxide vapor, 1000 ppm active chlorine).

adequately protect the environment and products against contamination from people. A trained and qualified operator, wearing a nonwoven polypropylene head cover, clean polyester two-piece undergarment, clean dedicated socks, double sterile gloves, a sterile face mask and sterile goggles, must be able to work at least three hours in the same set of cleanroom garments without causing unacceptable (cGMP) levels of contamination of the garments and the aseptic working environment.

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. The purpose of the DQ is to confirm that the selected cleanroom garment is qualified for the intended use. Therefore, it should also include tests to simulate the intended use. The DQ must be executed and authorized by suitably qualified persons who are knowledgeable enough to challenge the proposed design and its performance.

Following the model of design validations of sterile barrier systems described in ISO 11607-1,[20] it is recommended to split the DQ into four key areas: material qualification, performance testing, stability testing and usability evaluation. For reusable garments, reprocessing should be the subject of a separate DQ by the manufacturer and IQ-OQ-PQ by the supplier.

The material qualification includes the qualification of key characteristics and key properties of the materials and fabrics used, the cleanroom garments and the packaging.

Performance testing includes testing of the cleanroom garments and the packaging under simulated and standardized conditions using standardized test methods.

Stability testing must be performed to assure that key material characteristics and properties remain sufficiently stable during the life cycle. Characteristics and properties that change over time (e.g., deterioration of filtration efficiency of garments due to repeated laundering and sterilization; wear of the garments due to multiple use; and changes to the integrity of the sterile packaging during storage due to long-term effects of gamma irradiation) should be validated under worst-case conditions. Information for material qualification, performance testing and stability testing normally should be provided by the supplier. It is important to verify that the data has been generated using validated and sound scientific methods.

The purpose of the usability evaluation is to assure that the cleanroom garments can be used with acceptable remaining contamination and safety risks due to the design of the garments and the established gowning, working and de-gowning procedures. The usability evaluation is typically done by the end-user. However suppliers can also evaluate their garments for the intended use and supply that data to users for verification and further mitigation of identified risks during gowning and operations. The concept of usability engineering and testing has developed into a well-accepted way to successfully reduce use-related risks by reviewing these risks during the design phase and systematically reviewing the design and use of the product against those identified risks (see also IEC 62366-1 on usability engineering of medical devices[21]).

Relevant items to be covered for each of the four areas are presented in Table 2. A summary is given in Figure 2.

Reusable versus single-use cleanroom garments.

The validation of reusable cleanroom garments is more complex and more extensive compared to single-use cleanroom garments. Repeated laundering, repeated sterilization, multiple use and repairs influence the quality of reusable cleanroom garments. This also means that the influence of these factors must be validated throughout the entire

Table 2: The four key areas of the Design Qualification (DQ) for cleanroom garments used in EU GMP grade A/B cleanrooms

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)

life cycle in the frame of the stability testing and the performance testing at the end of the life cycle. In addition, not only the supplier of the garments but also the cleanroom laundry, sterilization facilities and repair service must be qualified. Reprocessing should be the subject of a separate DQ by the manufacturer and IQ-OQ-PQ by the supplier.

Installation Qualification (IQ)

The IQ for cleanroom garments is a formal check to verify if all required elements of the cleanroom gowning system are present. These include the gowning and de-gowning facilities; certificates of conformance and/or analysis; implementation of instructions from the supplier; standard operating procedures for gowning and de-gowning; logistical processes for the cleanroom garments and related accessories; and the operator training and qualification plan. Risk assessments that were executed as part of the DQ of the cleanroom garments should be finalized and risk controls should be implemented.

In addition, it is important to verify that the correct materials have been received for performing the OQ and PQ (i.e., the correct cleanroom garments, correctly folded, in the correct packaging and correctly labeled). A summary of items to be included in the IQ is given in Figure 2.

Operational Qualification (OQ)

During the OQ, the objective is to qualify the gowning and de-gowning concept. For this purpose, all relevant steps of the gowning and de-gowning process, including logistics, should be qualified. In addition, the aseptic presentation of the garments should be qualified. To validate the aseptic gowning procedure, at least three independent, consecutive, successful 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 to verify that different work tasks can be executed properly from a practical point of view (e.g., moving, bending, stretching and lifting). It is recommended to perform this assessment with all available sizes of the cleanroom garments and with people of different body shapes. A summary of items to be included in the OQ is given in Figure 2.

Performance Qualification (PQ)

During PQ, the objective is to validate the performance of the cleanroom garment system when it is actually in use. The requirements specified in the URS must be complied with fully.

The PQ of cleanroom garments consists of two stages. In the first stage of the PQ, compliance with aseptic gowning procedures should be assessed and confirmed. This gowning qualification must involve both a visual and microbiological assessment. The visual assessment is to qualify that people don the cleanroom garments in a correct and aseptic manner, which shall be described in detail in a gowning procedure. After gowning, the microbiological quality shall be assessed by taking surface samples from several locations on the cleanroom garments, gloves, goggles and face mask. Locations must be determined based on a risk assessment.

Each person accessing an EU GMP grade A/B environment must perform a gowning qualification. For the PQ, it is important to determine how many gowning qualifications are required to demonstrate compliance with the requirements. Typically, initial gowning qualification is performed three times for each person. It is important that adequately trained, qualified and experienced persons execute the PQ to exclude failures due to causes other than quality issues with the cleanroom garments.

The second stage of the PQ focuses on the validation of the microbiological quality of the gowned personnel with the garments and other accessories (e.g., gloves, face mask, goggles) during the actual work (e.g., aseptic compounding, aseptic filling, cleaning and disinfection, and other activities).

The second stage of the PQ also includes validation of the microbiological and particulate quality of the environment people are working in and the execution of aseptic process validations (i.e., media simulations or media fills). The number of runs for these validations must be determined based on a risk assessment. Typically, these validations are performed three times. To exclude failures due to causes other than quality issues with the cleanroom garments, it is important that adequately trained, qualified and experienced personnel execute the PQ in areas with an excellent quality history.

The PQ is typically done under worst-case conditions. These worst-case conditions must be determined based on a risk assessment. Also, the actions that should be taken if established criteria are not met during the PQ, must be defined before executing the PQ. Only after a successful PQ can the cleanroom clothing system be formally implemented. A summary of items to be included in the PQ is given in Figure 2.

Revalidation and change management

The cleanroom clothing system should be evaluated at an appropriate frequency (e.g., annually or biennially) to confirm that it remains in a state of control. Gowning qualifications shall be repeated at least annually and even more frequently in cases where there is doubt about the quality of the aseptic gowning process or aseptic gowning skills of specific persons. The cleanroom clothing system is included in validations which must be performed periodically (i.e., cleanroom qualifications under dynamic conditions and aseptic process validations).

Changes must be reviewed critically and may lead to revalidations that are more or less extensive, depending on the type of change. Properly and well documented DQs, as well as IQ-OQ-PQ, are the basis for successful change management.

Monitoring

Personnel monitoring must be part of the environmental monitoring program[1, 3, 22]. The microbiological quality of cleanroom garments for persons working in a grade A/B environment must comply with the EU GMP1 grade B limit for surface samples (i.e., the action limit is 5 CFU/contact plate). Alert limits are usually lower (e.g., 2 or 3 CFU/contact plate). Cleanroom garments, face masks, goggles and gloves are typically sampled at the conclusion of activities in a grade A/B area, but just before leaving the area. For this "exit monitoring," contact samples are taken from different locations. Sample locations must be determined based on a risk assessment. After sampling, the person must leave the area to prevent spreading contamination due to medium residues present on the cleanroom garments.

Gloves should be sampled after performing activities in a grade A environment to verify the quality of the aseptic conditions and aseptic handling. Gloves of operators working in a grade B environment should also be monitored during each work shift. Gloves are typically sampled with a frequency ranging from once to multiple times per work shift.

In addition to personnel monitoring, samples from several locations in the cleanroom should be taken to determine if the production environment and processes are in control. Sampling is typically performed during (passive and active microbiological air sampling and particle counting) or at the conclusion (surface sampling) of operations but may also be performed under static conditions (i.e., in the at-rest state of an area), to verify cleanliness.

In the case of non-conformities, assessments must be done to determine root causes. The cleanroom clothing system as a potential root cause should be included in these assessments.

It is also recommended to assess if gowning procedures, cleanroom behavior guidelines and aseptic procedures are followed correctly. These visual assessments should be done on a regular basis.

Conclusion

A science- and risk-based quality-by-design approach for the development, implementation and validation of sterile garment systems for EU GMP grade A/B aseptic processing areas is not only the correct approach to effectively control contamination risks related to people, but also an adequate response to the latest regulatory requirements. The new EU GMP Annex 1 draft is based on QRM principles and introduces the concept of a holistic contamination control strategy that considers all aspects of contamination control over the entire life cycle based on thorough technical knowledge and sound process know-how. Considerable efforts will be required by manufacturers to update their technical files, with cleanroom garments being just one of the many aspects.

With a risk-based quality-by-design approach applied to cleanroom garment systems, more effort is spent at the front-end, in the design phase, as well as in the design qualification. This will lead to designed-in risk reductions; better scientific knowledge of key aspects, attributes, limitations and residual risks of the selected technical solutions; and fewer issues during cleanroom qualifications, process validations and routine operations. In case of failures, it can be difficult to determine the root cause or the elements that have failed. That's why a quality-by-design approach, with focused and extensive design qualifications for each element, is the only way to successfully and systematically reduce the risk of failure. This approach also creates the foundation for adequate and risk-based change management.

References

1. European Commission. Eudralex - Volume 4 - EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use - Annex 1: Manufacture of Sterile Medicinal Products (corrected version 1. March 2010). In: Commission E, ed. Brussels2008:16.
2. European Commission. EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines - Chapter 1 Pharmaceutical Quality System. In. Vol SANCO/AM/sl/ddg1.d.6(2012)8603622013.
3. U.S. Food & Drug Administration (FDA). Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. In: FDA, CDER, CBER, ORA, eds. Rockville: FDA; 2004.
4. Task Force on Sterile Pharmaceutical Products by Aseptic Processing. Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing (1st revision of original version). In. Japan2006.
5. World Health Organization (WHO). WHO Technical Report No. 986 - Annex 2 -WHO good manufacturing practices for pharmaceutical products: main principles. In:2014:60.
6. World Health Organization (WHO). WHO Technical Report No. 996 - Annex 6 -WHO Good trade and distribution practices for pharmaceutical starting materials. In:2016:16.
7. International Council for Harmonisation (ICH). ICH Q9 - Quality risk management. In:2005.
8. 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.
9. Reinmüller B, Ljungqvist B. Modern Cleanroom Clothing Systems: People as a Contamination Source. PDA Journal of Pharmaceutical Science and Technology. 2003;57(2):114-125.
10. Moschner C. Cleanroom Undergarments. Cleanroom Technology,. 2002.
11. Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-Operation Scheme. Guide To Good Manufacturing Practice For Medicinal Products - Annexes. In. Guide To Good Manufacturing Practice For Medicinal Products. Geneva: PIC/S Secretariat; 2017.
12. European Medicine Agency (EMA). Annex 1 - Manufacture of Sterile Medicinal Products. In: European Medicine Agency (EMA), ed2017.
13. International Organization for Standardization. ISO 14644-5: 2004 - Cleanrooms and associated controlled environments - Part 5: Operations. In. Geneva2004.
14. Institute of Environmental Sciences and Technology (IEST). IEST-RP-CC003.4:2011 - Garment system considerations in cleanrooms and other controlled environments. In. Rolling Meadows, Illinois: IEST; 2011.
15. International Organization for Standardization. ISO 13408-1:2008 - Aseptic processing of health care products — Part 1: General requirements. In. Geneva2008.
16. Institute of Environmental Sciences and Technology (IEST). IEST-RP-CC003.4:2011 - Garment system considerations in cleanrooms and other controlled environments - B2.4 Particle Dispersion Test (Body Box) Test Method. In. Rolling Meadows, Illinois: IEST; 2011.

17. Hu SC, Shiue A. Validation and application of the personnel factor for the garment used in cleanrooms. Data Brief. 2016;6:750-757.

18. Institute of Environmental Sciences and Technology (IEST). IEST-RP-CC003.4:2011 - Garment system considerations in cleanrooms and other controlled environments - B2.5 Helmke Drum Test Method. In. Rolling Meadows, Illinois: IEST; 2011.

19. European Commission. EudraLex - Volume 4 - EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use - Annex 15: Qualification and Validation. In: DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY, ed. Brussels2015.

20. International Organization for Standardization. ISO 11607-1:2019 Packaging for terminally sterilized medical devices -- Part 1: Requirements for materials, sterile barrier systems and packaging systems. In. Geneva: ISO; 2019.

21. International Electrotechnical Commission (IEC). IEC 62366-1:2015 Medical devices -- Part 1: Application of usability engineering to medical devices. In: International Organization for Standardization.

22. United States Pharmacopoeia (USP/NF). USP 41 <1116> Microbiological Control and Monitoring of Aseptic Processing Environments. In: USP, ed.

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Thierry Wagner has spent over 30 years working for DuPont in its polyester films and nonwovens businesses and from the 1st of October 2019 as Global Director, Regulatory & Standards – Healthcare, DuPont – Safety & Construction. He is convenor of ISO TC198/WG7 "Sterilization of Health Care Products—Packaging", 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" 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 and 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.

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® 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, significantly reducing the risk of contamination. Most reusable garments are packed in a bag with a six-month shelf life and then in a reusable crate.

Working in the cleanroom

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. Tyvek® IsoClean® provides a consistent barrier against dry particles and microorganisms, delivering the ideal balance of protection, durability and comfort.

Washing & sterilizing the garments

Tyvek® IsoClean® 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.

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 increased permeability. Requalifying repaired garments can also be expensive and disruptive.

Tyvek® IsoClean®

Sterile single-use garment & accessory options*

Coverall

IC253BWHXX0025CS

Bound seams
Bound neck
Dolman sleeve
Elastic wrists
Elastic ankles
Zipper closure
25/cs
SM–4X

Bouffant

IC729SWH000250CS

Serged seams
Elastic headband
21.5" diameter
250/cs
Universal sizing (00)

Sleeves

IC501BWH000100CS

Bound seams
Covered elastic wrists, bicep
18" length
100/cs
Universal sizing (00)

Coverall

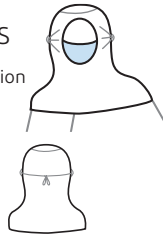
IC105SWHXX0025CS

Serged seams
Standard hood
Elastic hood opening
Set sleeve
Elastic wrists
Elastic ankles
Attached thumb loops
Zipper closure
Attached boots with PVC soles
25/cs
MD–4X

Hood/mask

IC669BWH0001000S

Integrated hood/mask combination
Bound seams
Bound head opening
Ties with loops for fit
White hood
Blue face mask
Pleated polyethylene outer
7" wide mask
Individually packaged
100/cs
Universal sizing (00)



Boot cover

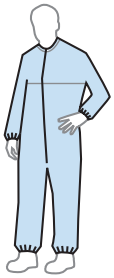
IC447SWHXX0100CS

Serged seams
Elastic opening
Elastic ankles
Gripper™ sole
18" high
100/cs
MD–2X

Coverall

CC252BBUXX00250S

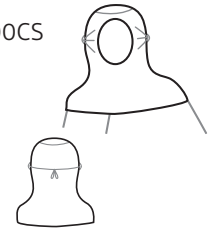
Bound seams
Bound neck with loop at center back
Dolman sleeve
Elastic wrists
Elastic ankles
Zipper closure
25/cs
SM–5X



Hood

IC668BWH000100CS

Bound seams
Full face opening
Bound hood opening
Ties with loops for fit
100/cs
Universal sizing (00)



Boot cover

IC457SWHXX01000S

Serged seams
Covered elastic opening
Ties at ankles
PVC sole
18" high
100/cs
SM–XL

Frock

IC264SWHXX0030CS

Serged seams
Bound neck
Raglan sleeve
Elastic wrists
Zipper closure
A-line
30/cs
SM–4X

Mask

ML7360WH0002500S

9" size
Bound Tyvek® ties
Pleated
Rayon outer facing
Metal nose piece
250/cs
Universal sizing (00)

Boot cover

IC458BWHXX0100CS

Bound seams
Covered elastic opening
Ties at ankles
Gripper™ sole
18" high
100/cs
SM–XL

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A global study of the performance of cleanroom garments over their life cycle

Matheus Barbosa, Jean-François Teneul

Abstract

Sterile garments for cleanroom use often present a variable performance over their entire life cycle as they are vulnerable to damage from laundering and sterilization methods. A study was conducted to understand how reusable garments perform when subjected to multiple laundering and irradiation cycles – tear strength, particle shedding, permeability, etc.. The study enables a cost comparison with single use garments.

Introduction and key concepts

In the context of a global business with ever-increasing quality standards and effectiveness requirements as well as the latest draft review of the Good Manufacturing Practice (GMP) Annex 1 of December 2017, one of the main technical areas explored is related to studying and mitigating potential process/product contamination risks against biological bodies, particulates and pyrogen agents. One key strategy for cleanroom supervisors should be to carry out complete Risk Assessments in order to map, classify, and then reduce contamination risks.

Humans are the main source of potential contamination inside cleanrooms (more than 70%), as shown by several past global studies (Akers, J. *et al*., 2004; Ramstorp M, 2000 and Whyte and Hejab, 2007). Hence, cleanroom garments serve as the last protection barrier against controlled environment contamination by the thousands of human particles (potentially carrying microorganisms) that are shed every minute. In terms of contamination risk management, it is critical to evaluate the variables related to human contamination and cleanroom garment barrier performance besides HEPA filtering, process air flow velocity and other factors. This study aims to explore several important technical aspects of cleanroom garments that should be considered when evaluating contamination risks.

The process of wearing, laundering and sterilizing reusable cleanroom garments can impact their physical properties and change their functionality. Laundering and wearing abrades garment fibers. Simultaneously, changes to the polymers that make up the garments can occur at the molecular level. Although routine visual inspection is often part of garment quality evaluation programmes, non-visible properties also change with time.

When selecting reusable garments for use in cleanroom environments, it is important to understand how they will perform over their intended life cycle. Consideration of all the degradation aspects should be part of the decision process for when to take reusable garments out of service, or alternatively to change to a single-use garment system. Several factors should also be considered when evaluating intrinsic risks generated by cleanroom garments, such as: particle shedding, biological/particle barrier, worker comfort and protection, durability, packaging, sterilization continuous validation – besides process and supply factors: logistics chain reliability, damages and repairs, shrinking and ergonomic fit, among others.

Physical property data are often available for new cleanroom garments; however, there are less physical property data for the remainder of the garment life cycle. To aid in garment choice, DuPont conducted a study, led by Jennifer Galvin PhD, DuPont Principal Investigator, of the physical properties of reusable cleanroom garments after a set number of laundering and gamma radiation exposure (sterilization) cycles.

Methodology

Two sets of commercially branded, reusable coveralls were purchased for testing and designated as Garment A and Garment B. Garments were made of woven polyester with integral carbon fiber for electrostatic decay properties. Garments were laundered under standard industrial settings and subsequently exposed to gamma radiation; this was considered one cycle. Garments were removed for testing after pre-determined numbers of cycles until a total of 30 cycles had been completed.

Not all properties were tested at the same frequency. Initial properties of the garments were either measured on "as-received" garments or garments that had been laundered one time, but not exposed to gamma radiation. Parameters for garment laundering and gamma exposure were consistent throughout the study.

Garments were not worn or exposed to simulated work scenarios between cycles and the effect of routine garment "wear and tear" was not part of this study.

A summary of the garment testing methods is shown in Table I, according to IEST (Institute of Environmental Sciences and Technology), ASTM (American Society for Testing and Materials) and AATCC (American Association of Textile Colorists and Chemists) standards. Most of testing was done at third-party laboratories. Results for property testing are shown with the average and the Bonferroni confidence interval on the mean. Changes in both absolute performance and variability within the garment population may factor into formulation of end-of-life criteria.

Table 1: Test Method Summary

Test	Test Method
Particle shedding via Helmke Drum	IEST RP-CC003.4
Particle dispersion (Body Box)	IEST RP-CC003.4
Hydrostatic head	AATCC TM127
Trapezoidal tear strength	ASTM D5587

Results and discussion

3.1 Studied parameters

Based on all experimental parameters listed above, a number of results were obtained. The object was to analyze critical limits of cleanroom garment performance in order to help end users

a. evaluate which garment system solution to choose (single-use or reusable),

or

b. after how many cycles reusable garments become non-performing and have to be replaced.

The properties studied reflected key features including process protection, people protection (when needed), comfort and durability.

3.2 Polyester reaction mechanism after gamma exposure

The impact of gamma radiation exposure on a variety of polymers is well studied (Skiens, W. E, 1980). Although multiple reaction mechanisms can occur simultaneously, there is typically a predominating reaction type. The extent and type of each reaction depend on many factors and combinations of factors, including:

- Polymer composition (different polymers behave differently)
- Presence or absence of air during irradiation
- Crystallinity of the polymer and changes in crystallinity
- Physical configuration (e.g., fibre, film or tubing)
- Additional processing (e.g., laundering, calendaring or surface treatment)
- Presence of antioxidants or other additives in the polymers
- Cumulative radiation dose

The two primary reaction mechanisms that occur in polyester (PET) after exposure to gamma radiation are chain scission and cross linking (Potnis, S. P., Shetty, S. M., Rao, K. N, Prakash, J, 1969; Nair, P. D., Sreenivasan, K., and Jayabalan, M, 1988). Changes in the polymer makeup can result in changes to a garment's physical properties. To better understand which mechanism predominated under the conditions of this study, PET molecular weight was measured by size exclusion chromatography (SEC) using hexa-fluoro-isopropanol (HFIP) as the solvent.

Results for Garments A and B overlapped, so the data was grouped (Figure 1). Because the molecular weight of the PET decreased with laundering and exposure to gamma radiation, chain scission was the predominant mechanism. As garments were both laundered and exposed to gamma radiation (but not used by operators), this data includes the combined simultaneous impact of both factors.

This initial result indicates that reusable textile garments suffer degradation throughout their life cycle. As mentioned before, the polymer molecular weight decrease effect is a result of laundering and irradiation processes, but in actual use there are other additional effects. Repeatedly wearing and submitting garments to physical stress (standard operation moves), as well as transportation/manipulation, donning/doffing or the exposure of chemical/biological compounds could also impact and intensify degradation effects.

In order to analyze garment performance that result from the PET degradation process, other important physical properties were tested. These are categorized under: Process Protection, People Protection and Durability.

3.3 Process protection

The primary function of cleanroom garments is to protect a product or a process against contamination from humans (particle shedding and biological exposure) or from the garment itself (particle or linen shedding). To represent process protection, particle shedding was measured via the Helmke Drum method (Figure 2), and particle dispersion via the Body Box method (Figure 3).

3.3.1 Helmke Drum test

The best known measurable parameter for cleanroom garment cleanliness is particle shedding. This is tested in accordance with the Helmke Drum testing standard. Garments or fabric swatches are tumbled for determined cycles inside a rotating drum equipped with a standardized particle counter. The final measurement defines the shedding rate (particles/minute). Seeking to normalize test results, fabric swatches were tested, and swatch data can be evaluated for performance trends. The results show that particle shedding increased after 25 cycles or exposure to a cumulative mid-dose of 754kGy units of ionising radiation, but was fairly consistent until that point (Figure 4).

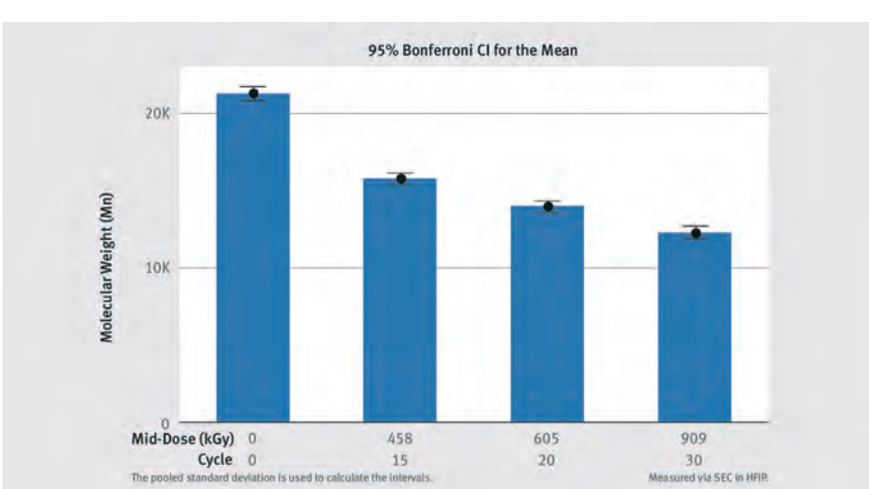


Figure 1: Number average polymer molecular weight (Daltons) for garments A and B

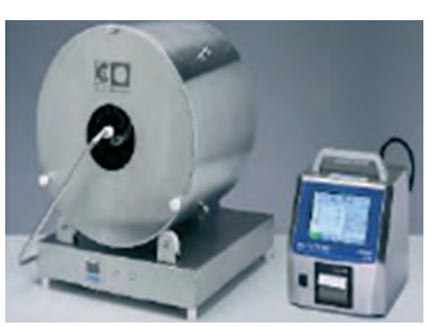


Figure 2: Helmke drum

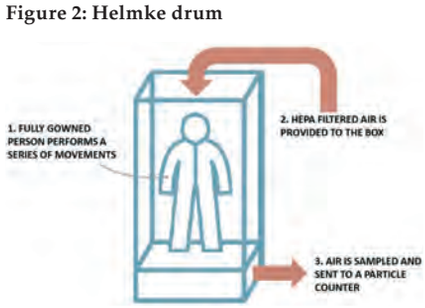


Figure 3: Body box

The key preliminary conclusion for these results indicates that cleanrooms that are sensitive to particle shedding should establish a monitoring program to better understand when their garments are no longer performing as required for cleanroom compliance. As observed above, after a determined number of laundering and sterilization cycles, reusable polyester materials will not only increase their magnitude of particle shedding, but also the variability of the same property. This effect can also generate an extra layer of unpredictability when determining contamination control standards and procedures – especially because the garment's "performance breaking point" may vary based on specific application, physical stress and size fit for the operators.

A final point to consider is that the Helmke Drum test is a well-known and effective method to evaluate garment cleanliness and particle shedding from its material (polyester), but it does not indicate garment particle/bacterial barrier performance against human shedding – which is the main source of contamination for cleanrooms. In that matter, complementary tests were conducted according to the Body Box method.

3.3.2 Body Box test

Body Box testing measures not only particle generation from the garment, but can also indicate its function as a particle barrier. The method is described in the same standard as the Helmke Drum (IEST-RP-CC003.4). In this test, a fully garbed trial subject conducts a series of movements inside a box supplied with HEPA-filtered air. Air in the box is sampled by a particle counter and shedding rate is reported as a function of activity as well as a total rate for all activities conducted during the test. This data also showed a shift in performance and variability after increased cycles of laundering and gamma radiation exposure (Figure 5).

Both the Helmke and Body Box data show an increase in both amount and variability of shedding. Cleanroom operators who are particularly prone to particle shedding should consider establishing a monitoring programme to determine when garment performance no longer meets requirements. Particle sizes typically monitored in a cleanroom are too small to be visible to the naked eye, so visual inspection alone cannot indicate an increase in garment shedding. Other potential contamination factors related to the garments should also be studied and considered, such as the intrinsic abrasion effects of wear and tear and sterile packaging.

3.4 People protection

It is not uncommon to identify chemical and biological hazards in controlled environments or cleanrooms. In these instances, the garments not only need to perform as a process contamination barrier, but also serve as a PPE (Personal Protective Equipment) to guarantee the health and safety of the operators. Several applications and common activities may present a potential risk to workers in cleanrooms, among them:

- Oncology drugs compounding and manipulation (cytotoxic handling)
- HPAPI (High Potent Active Pharmaceutical Ingredient) manufacturing
- Hormones handling and production
- Activities with different Biosafety levels (bacteria or virus manipulation)
- Chemical products manipulation (solutions preparation, cleanroom sanitizing)
- Infectious residues (animal, human)

Several standards exist to certify chemical and biological protective garments, such as the ISO 16602 (for chemical risks) and ISO 16603/EN 14126 (for biological hazards).

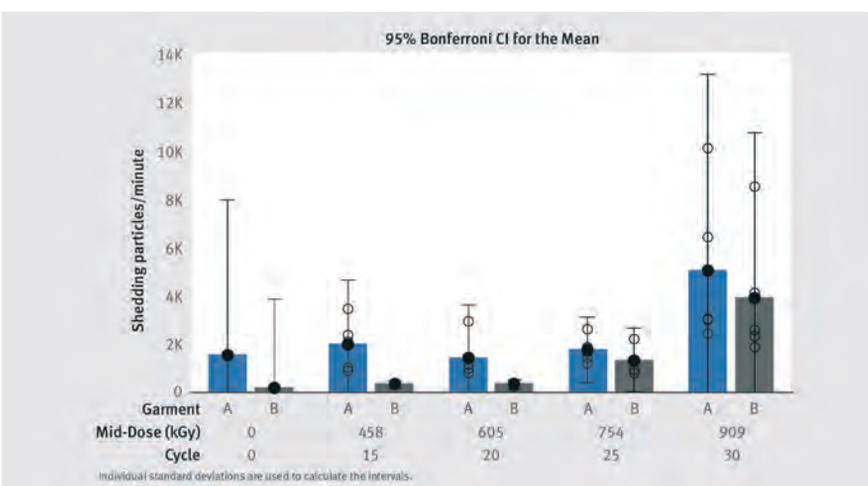


Figure 4: Helmke Drum particle (greater than 0.5 microns) shedding of swatches

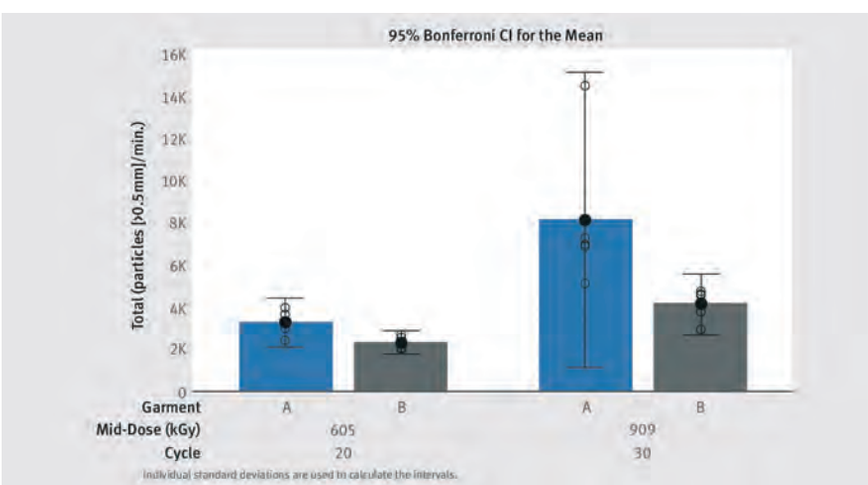


Figure 5: Body Box valuation by the sum of shedding for all activities

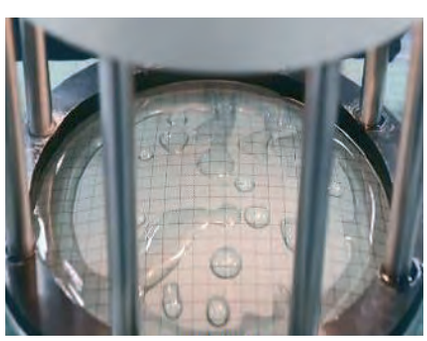


Figure 6: Hydrostatic head test

Properties such as permeation and repellency should also be considered for significant chemical/biological risks.

The hydrostatic head test (Figure 6) was used to evaluate fabric performance against an aqueous challenge. Fabric was subjected to a water column of increasing pressure until three drops penetrated the fabric. The data show a significant drop in performance as a function of exposure to laundering and gamma radiation (Figure 7). If garments are considered for incidental, light aqueous splash protection, understanding the degradation per cycle is important.

Many potential hazards are found in liquid form, so partial impermeability of the garment fabric should be considered and/or studied when selecting cleanroom equipment for applications with an exposure risk level. Part of the health and safety procedure could include establishing the garment's worker protection performance over its life cycle. As mentioned before, other international standards and certifications may assist companies to verify the chemical/biological barrier effectiveness for cleanroom garments, such as the CE Category III PPE certification and specific permeation data.

3.5 Durability

The length of a garment life cycle is also affected by the last performance parameter studied: durability. Garments should withstand normal wear and tear. Without adequate durability, garment breach is possible. Besides significant process contamination, extra costs could be generated as the repair of polyester garments is often a complicated and costly activity, sometimes not included within a company's budget or laundering contract service.

To understand the impact of laundering and exposure to gamma radiation on garment durability, trapezoidal tear strength was measured (Figure 8). Cross direction (CD) tear strength is shown in Figure 9 while machine direction (MD) tear strength is shown in Figure 10. Often in woven garments, there are different constructions in the two directions, so differences in tear values between MD and CD are expected.

Testing showed that garment durability decreases with increasing cycles of laundering and exposure to gamma radiation. Reducing potential impact from garment tearing is important, especially in cleanrooms and controlled environments where workers may have physical activities such as climbing stairs or bending to monitor or adjust equipment. In terms of contamination control procedures, the decay of mechanical resistance for cleanroom garments adds an extra layer of

Figure 8: Tear strength test

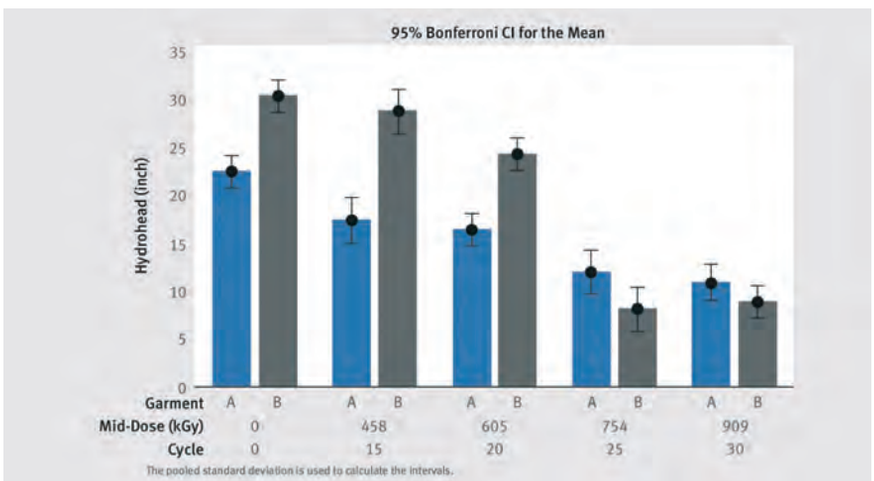


Figure 7: Interval plot of Hydrohead (inches)

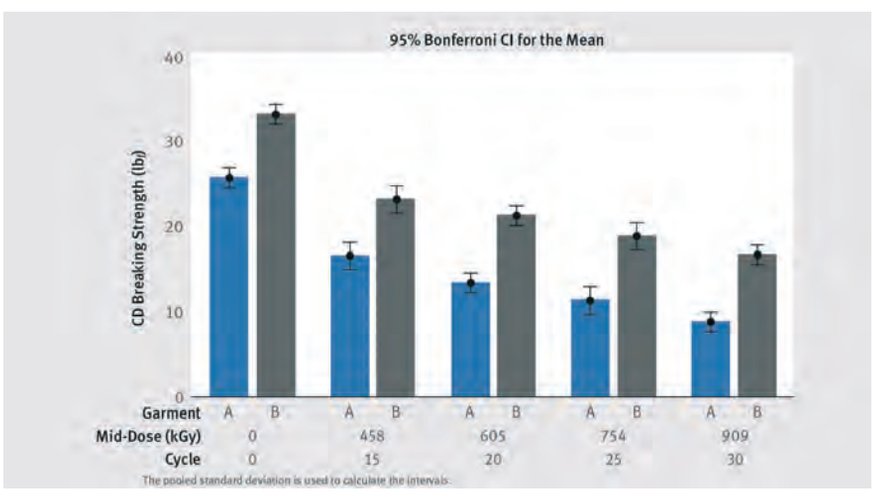


Figure 9: CD Trapezoidal tear strength (lbf – Pound-force)

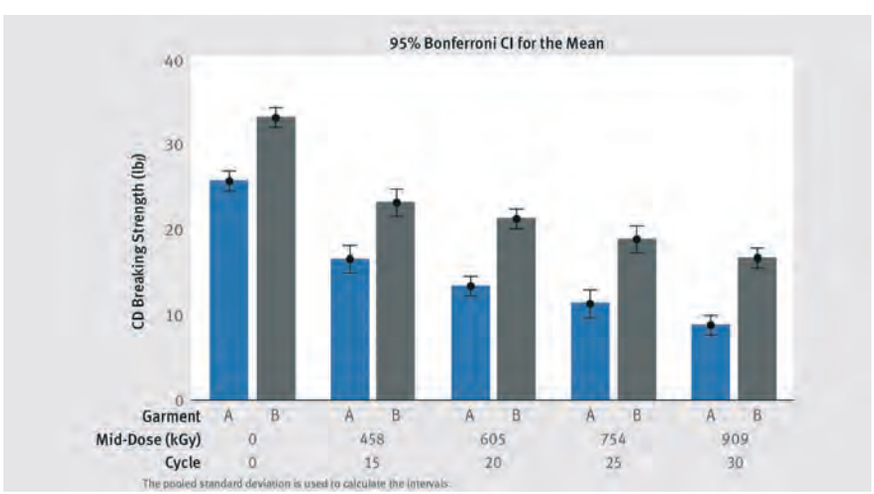


Figure 10: MD Trapezoidal tear strength (lbf)

complexity on establishing a monitoring standard to determine each garment's life cycle end point; variables such as workers' activities and potential external abrasion factors also need to be considered.

Conclusions

People are the main source of contamination in controlled environments, and cleanroom garments are the main and last barrier to protect critical processes and products. The data outlined here demonstrate that garment properties do change after several laundering and gamma exposure cycles. These changes are not always visible to the naked eye, so visual garment inspection alone may not be sufficient to understand garment performance. Based on these findings, the following guidelines are recommended:

- Even though tests were conducted with sterilization via gamma irradiation, several studies show that other sterilization methods also present abrasion and degradation effects over the garment's life cycle. Autoclaving, for example, uses a physical process that may degrade polyester composition after several utilization cycles (Nair, P. D., Sreenivasan, K, 1984). It is important to consider that continuous laundering (shrinking & expanding), and wearing of cleanroom garments also play a considerable part in the structure degradation of fabrics.
- Consider performance data over the entire garment life cycle. If not available, question your cleanroom garment provider or assess the risk of not having control of your garments' system in place;
- When cleanroom garments also need to perform as Personal Protective Equipment, companies should consider looking for specific technical data and certifications that would enhance worker safety and protection. Asking garment providers for permeation data for specific risks or barrier technical claims might be an effective strategy;
- Enact testing protocols to monitor the performance of garments as they age, based on the risk assessments and needs of each individual cleanroom. Parameters should not only consider particle shedding and cleanliness of the garment itself, but also its barrier effectiveness against human contamination (particle shedding and biological filtering) and sterility validation assurance. Then, establish criteria for taking garments out of service when they no longer meet functionality requirements;
- It is also important to continuously map, evaluate and control the risk of the entire garments system value-chain: from the fabric weaving and sourcing, garment assembly, packaging and sterilization and, if applicable, the laundry process as well.

It ought to be noted that since garment requirements vary by cleanroom operation, establishing initial and ongoing fitness for use is the responsibility of the end user. Garment assessment may require evaluation of additional information beyond what is presented here. For example, seams and closures may have lower barrier properties than fabric. Properties of garments and fabrics subjected to other conditions, including different sterilization methods, may also vary.

In conclusion, when assessing risks related to potential contamination in controlled environments, cleanroom companies should question and require their suppliers to support their quality claims with continuous technical data, risk mitigation and process control.

References

Akers, J. *et al*., Development of a Highly Automated PAT- Compatible Aseptic Processing System, paper presented at the A3P congress, Biarritz, France, 2004.

Galvin, J (DuPont de Nemours). A Life Cycle Assessment of Reusable Garment Properties, Cleanroom Technology, June 2017

Skiens, W. E. Radiat. Sterilizing radiation effects on selected polymers. Phys. Chem., 1980, 15, p. 47-57

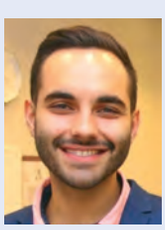
Potnis, S. P., Shetty, S. M., Rao, K. N. and Prakash, J. Die Angew. Effect of γ-radiation on synthetic fibres – II irradiation in the presence of chemicals. Markromol. Chemie, 1969, 6, p. 127-135

Nair, P. D., Morphological changes of poly(ethylene terephthalate) on multiple steam sterilization. Clinical Materials, 1990, 5, p. 43

Nair, P. D., Sreenivasan, K. Effect of steam sterilization on polyethylene terephthalate. Biomaterials, 1984, 5, p. 305

Nair, P. D., Sreenivasan, K., and Jayabalan, M. Multiple gamma radiation sterilization of polyester fibres. Biomaterials, 1988, 9, p. 335-338

Whyte, W. and Hejab, M., Particle and microbial airborne dispersion from people, European Journal of Parenteral and Pharmaceutical Sciences, 12 (2). pp. 39-46. ISSN 0964-4679, 2007



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DUPONT™ TYVEK® ISOCLEAN®

FRAGEN UND ANTWORTEN

Was ist Tyvek®?

Tyvek® ist ein per Flash-Spinning-Verfahren hergestelltes Polyethylen-Material mit hoher Dichte, das nur von DuPont angeboten wird. Tyvek® bietet eine inhärente, atmungsaktive Barriere mit hoher Verschleiß- und Abriebfestigkeit. Diese inhärente Barriere von Tyvek® ist nicht von einem dünnen Film oder einer dünnen Schicht kleiner Fasern abhängig – bei Tyvek® erfüllt jeder Teil des Materials eine Barrierefunktion. Diese einzigartige Materialstruktur bildet somit eine wirksame, atmungsaktive Barriere für Partikel.

Für welche Reinraumklasse eignet sich die Tyvek® IsoClean® Schutzkleidung?

Tyvek® IsoClean® Schutzkleidung (Optionscode CS, DS und MS) ist in der Regel für den Einsatz in Reinraumumgebungen der GMP-Klassen A-D, ISO-Klassen 5-8 (ehemals Federal Standard 209E-Klassen 100-100.000) vorgesehen. Allerdings kann je nach den Anforderungen einer bestimmten Anwendung auch die Verwendung in den ISO-Klassen 4 und 9 erwogen werden. In allen Fällen hängt die Wahl der Schutzkleidung von einer Bewertung ab, u. a. von Merkmalen, Schutzkleidungsdesign und -verarbeitung, sowie von den Anforderungen einer konkreten Anwendung. Unter Reinraumbedingungen verarbeitete Kleidung mit eingefassten Nähten bietet die höchste Kontaminationskontrolle und sollte in kritischeren Anwendungen verwendet werden. Sterile Kleidung ist erhältlich, falls erforderlich. Es liegt in der Verantwortung des Trägers, die geeignete Kleidung für eine bestimmte Anwendung zu bestimmen.

Wie wird Schutzkleidung für kontrollierte Umgebungen verarbeitet und verpackt?

Nicht sterile Schutzkleidung ist folgendermaßen erhältlich:

- **Lose verpackt (Optionscode 0B oder 00):** Die Artikel werden in der entsprechenden Menge in einem Karton unter zwei Polyethylen-Schichten verpackt.

Sterile Schutzkleidung ist folgendermaßen erhältlich:

- **Unter Reinraumbedingungen verarbeitet und steril (Optionscode CS, DS und MS):** Die Schutzkleidung wird speziell verarbeitet, um die Partikelabgabe zu minimieren, anschließend zur Unterstützung des sterilen Anziehens zusammengelegt und in einem Reinraum der ISO-Klasse 4 einzeln verpackt. Die Artikel werden in der entsprechenden Menge in einem Karton unter zwei Polyethylen-Schichten verpackt. Die Sterilität wird durch Gammabestrahlung gewährleistet. Die Bestrahlungsdosis wird nach ISO 11137 für einen SAL-Wert (Sterilitätssicherheitsniveau) von 10^{-6} validiert. Alle unter Reinraumbedingungen verarbeiteten und sterilen DuPont™ Tyvek® IsoClean® Zubehörartikel (Optionscode MS und DS) werden in einem Verpackungssystem mit doppelter Barriere verpackt, das aus einem inneren und äußeren einfach aufreißbaren, validierten Reinraumbeutel besteht. Das System dient sowohl als zusätzliche Sterilitätsrisikomanagementkomponente als auch als wesentliches Element zur Verringerung des Kontaminationsrisikos beim Transport von Bekleidung in Reinbereiche.
- **Steril (Optionscode 0S):** Die Schutzkleidung wird für steriles Anlegen zusammengelegt und einzeln verpackt. Die Artikel werden in der entsprechenden Menge in einem Karton unter zwei Polyethylen-Schichten verpackt. Einige sterile Artikel werden zusammengelegt und in einem Reinraum der ISO-Klasse 5 einzeln verpackt. Die Sterilität wird durch Gammabestrahlung gewährleistet. Die Bestrahlungsdosis wird nach ISO 11137 für einen SAL-Wert (Sterilitätssicherheitsniveau) von 10^{-6} validiert.

Welches Mindesthaltbarkeitsdatum hat die sterile Schutzkleidung?

Sterile Artikel bleiben generell steril, solange die Verpackung nicht beschädigt wurde (kein Bruch der Verpackung oder der Versiegelung). Untersuchungen zur Lebensdauer zeigen, dass Tyvek® IsoClean® Schutzkleidung mindestens 5 Jahre steril bleiben, wenn sie in der Originalverpackung und bei korrekten Lagerbedingungen aufbewahrt werden.

Bei sterilen Tyvek® IsoClean® Produkten befindet sich das Mindesthaltbarkeitsdatum auf dem Etikett des Beutels und des Kartons. DuPont empfiehlt, nicht sterile Tyvek® IsoClean® Schutzkleidung innerhalb von 5 Jahren nach Erhalt zu verwenden.

Sind für die Tyvek® IsoClean®-Schutzkleidung Sterilitätszertifikate erhältlich?

Jeder sterilen Schutzkleidung liegt ein Sterilitätszertifikat bei. Kopien von Sterilitätszertifikaten erhalten Sie auf **www.safespec.dupont.de**

Warum weist Tyvek® IsoClean® Schutzkleidung nach der Gammasterilisation einen Geruch auf?

Tyvek® IsoClean® Schutzkleidung, die mithilfe von Gammastrahlung sterilisiert wurde, verströmt manchmal einen Geruch, vor allem beim erstmaligen Öffnen der Verpackung. Dieser Geruch ist nicht ungewöhnlich und durchaus normal.

Ist Tyvek® IsoClean®-Schutzkleidung antistatisch oder statisch ableitfähig?

Das zur Herstellung von Tyvek® IsoClean® Schutzkleidung verwendete Material wird mit einem topischen Antistatikmittel behandelt, um statisches Aufladen zu minimieren und lästiges Anhaften der Kleidung zu reduzieren. Da das topische Antistatikmittel wasserlöslich ist, wird das antistatische Verhalten bei unter Reinraumbedingungen verarbeiteter Schutzkleidung reduziert.

Auch die Sterilisation kann das antistatische Verhalten beeinträchtigen. Im Falle von Situationen, in denen es unbedingt auf statische Ableitung ankommt, sollten Endnutzer das diesbezügliche Verhalten sämtlicher von ihnen getragener Kleidungsstücke und Ausrüstungsgegenstände bewerten, einschließlich Außenanzüge, Innenanzüge, Fußbekleidung und anderer persönlicher Schutzausrüstung (PSA). Damit die Schutzkleidung statisch ableitfähig ist, muss die entstandene elektrische Ladung über entsprechende Erdungsvorrichtungen abgeleitet werden können, z. B. Erdungsklemmen am Arbeitsplatz oder statisch ableitfähige Fußböden. Wählen Sie für die CE-zertifizierte Tyvek® IsoClean® Schutzkleidung, die EN 1149-5 erfüllt.

Wie sollte Tyvek® IsoClean® Schutzkleidung gelagert werden?

Bewahren Sie die Schutzanzüge im Dunkeln und vor UV-Einstrahlung geschützt (im Karton) bei 15 bis 25 °C auf. DuPont weist darauf hin, dass Tyvek® IsoClean® Schutzanzüge bis zu 5 Jahre lang genutzt werden können, sofern sie richtig aufbewahrt werden und eine vollständige Sichtprüfung bestehen. Hohe Temperaturen, Oxidationsgase, Nässe, Kälte, UV- und ionisierende Strahlung können sich stark auf die Langlebigkeit der Anzüge aus Tyvek® Material auswirken. Siehe Ablaufdatum auf dem Verpackungsetikett.

Ist die Tyvek® IsoClean® Schutzkleidung in anderen Farben als traditionellem Weiß erhältlich?

Derzeit bietet DuPont die Tyvek® IsoClean® Schutzkleidung nur in Weiß an.

Bei welchen Temperaturen würde Tyvek® schmelzen?

Tyvek® schmilzt bei 135 °C. Tyvek® und Tyvek® IsoClean® Schutzkleidung ist nicht flammbeständig und nicht flammhemmend. Die Schutzkleidung nicht in Gegenwart von Hitze, Flammen oder Funken verwenden.

Ist Tyvek® IsoClean® Schutzkleidung wasserabweisend?

Schutzkleidung der Marke Tyvek® IsoClean® bietet begrenzten Spritzwasserschutz, verhindert das Eindringen von Wasser, ist nicht saugfähig und ist im trockenen und nassen Zustand gleichermaßen robust. Tyvek® IsoClean® Schutzkleidung wird nicht für den Schutz vor gefährlichen flüssigen Chemikalien empfohlen. Zum Schutz vor gefährlichen flüssigen Chemikalien eignen sich die DuPont™ Tychem®-Produkte, siehe **www.safespec.dupont.de**

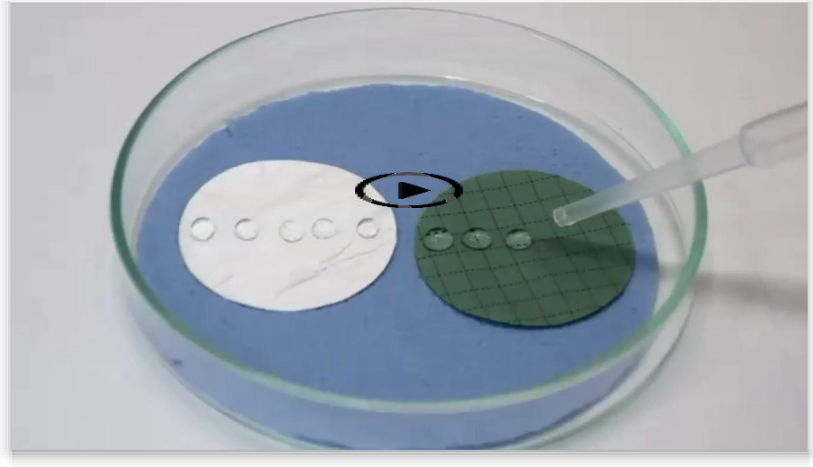
Wie kann Tyvek® Schutzkleidung entsorgt werden?

Die Schutzanzüge können recycelt sowie thermisch oder auf Deponien entsorgt werden. Einschränkungen hinsichtlich der Entsorgung sind von der während der Verwendung anfallenden Kontamination abhängig mit nationalen oder regionalen Rechtsvorschriften.

Ist Tyvek® Schutzkleidung recycelbar?

Ja, nicht kontaminierte Schutzkleidung, die in Reinräumen verwendet wurde, kann für nicht gefährliche Anwendungen recycelt werden.

DuPont™ SafeSPEC™
www.safespec.dupont.de



Tyvek IsoClean vs Reusable Polyester Textile - Droplet Tests.mp4

This slide was originally a mp4 file and could not be converted into PDF.
You can find the original file in the .ZIP that was downloaded.

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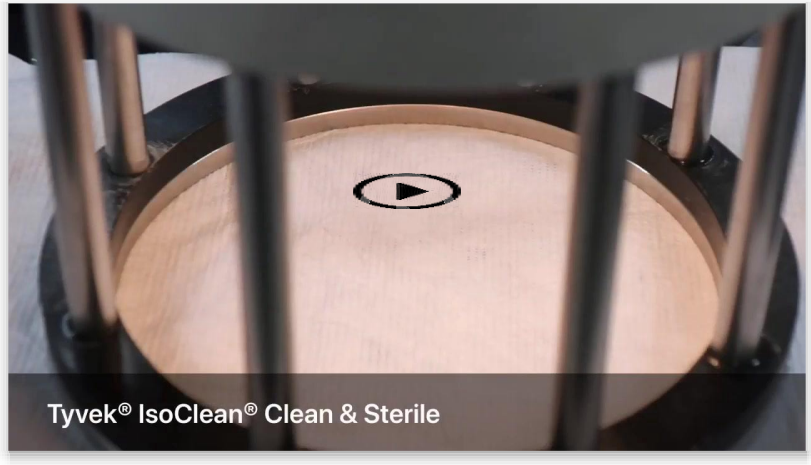

Tyvek IsoClean vs Reusable Polyester Textile - Hydrohead Tests.mp4

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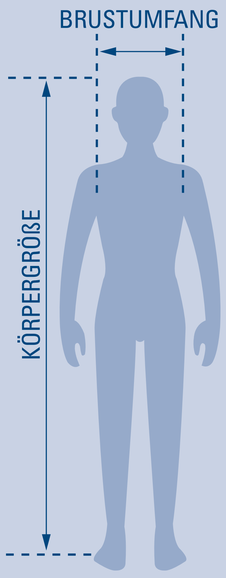
DuPont Personal Protection

Tyvek® IsoClean®

Anzug ohne Kapuze, Modell 183 B DS

GRÖSSENTABELLE

Größe	Brustumfang (cm)	Körpergröße (cm)	Brustumfang (Zoll)	Körpergröße (Fuß /Zoll)
XXS	68 - 76	150 - 158	27 - 30	4’11” - 5’2”
XS	76 - 84	156 - 164	30 - 33	5’1” - 5’5”
S	84 - 92	162 - 170	33 - 36	5’4” - 5’7”
M	92 - 100	168 - 176	36 - 39	5’6” - 5’9”
L	100 - 108	174 - 182	39 - 43	5’8” - 6’0”
XL	108 - 116	180 - 188	43 - 46	5’11” - 6’2”
2XL	116 - 124	186 - 194	46 - 49	6’1” - 6’4”
3XL	124 - 132	192 - 200	49 - 52	6’3” - 6’7”
4XL	132 - 140	200 - 208	52 - 55	6’7” - 6’10”
5XL	140 - 148	208 - 216	55 - 58	6’10” - 7’1”
6XL	148 - 156	208 - 216	58 - 61	6’10” - 7’1”
7XL	156 - 162	208 - 216	61 - 64	6’10” - 7’1”



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