DUPONT™

PERSONAL PROTECTION

Garment selection criteria for the safe handling of HPAPI

• Introduction

At your company, what is the OEL for HPAPI's?
a) ≤ 10 µg/m³
b) > 10 µg/m³

Defining the personnel and environmental potential exposure is required for the safe handling of high potency active pharmaceutical ingredients (HPAPIs). The selection of the most appropriate strategies is required for the containment assurance.

In Europe, HPAPIs have an occupational exposure limit (OEL) of ≤ 10 µg/m³ (micrograms per cubic meter of air). The lower the value, the more potent the compound; and the greater need for a higher level of containment is required. Globally, OEL bands will vary based on the company.

• HPAPI Containment strategy

Engineering controls are the primary source of containment and isolation of potent compounds. There are five stages in the hierarchy of controls that define the best level of protection :

1) Product isolation: closed-system glassware and reactors

2) Containment equipment: isolators, ventilated laminar flow enclosures, rapid-transfer ports, closed-system cleaning via clean-in-place

3) Facility design: air pressurization, high number of air changes, single-pass air, restricted access, airlocks, safe-change filters

4) PPE: chemical suits needed for solvents and reagents, coveralls and hoods, powered air-purifying respirator (PAPR), gloves

5) Personnel: proper training, procedures and policies, education, health monitoring

Correct protective solutions should be selected as a result of a risk assessment and must be part of the contamination control strategy.

Specific for individual end-user and cleanroom application, to protect the products/processes and the operators and avoid cross-contamination.

Risk Assessment – DuPont 9-step guide

Step 1 Hazard identification

Step 2 Determine minimum levels of protection needed

Step 3 Access hazard toxicity

Warning

Step 4 Determine protective perfomance requirements of the fabric and seam

Step 5 Determine mechanical performance requirements

Step 6 Comfort considerations

Step 7 Supplier selection

APPROVE

Step 8 Identify the correct usage of the product

Step 9 Wear test

TRY IT!

DUPONT Kevlar | Nomex | Tyvek | Tychem

Hazard Identification

Questions to be asked

- In what physical state do the HPAPI exist (solid, liquid, waxy, gas)?

- How can they enter the body systems (inhalation, accidental injection, dermal absorption, ingestion of contaminated foodstuffs or mouth contact with contaminated hands)?

- How could they pass through the PPE?

CHEMICAL PROTECTION

In order to provide appropriate protection against a specific chemical, performance properties of the fabric such as **PENETRATION & PERMEATION DATA** need to be consulted.

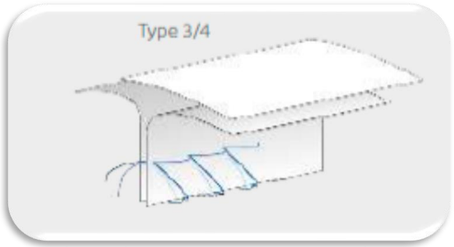
Garment type and design are equally important

Determine protective performance requirements of the fabric and seams

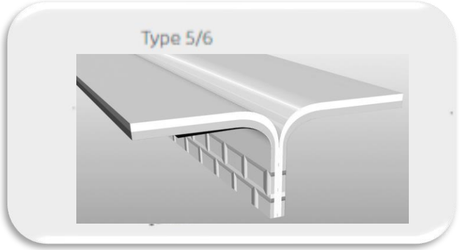
Not all fabrics used in chemical protective garments are the same.

There are a variety of fabrics available with different levels of comfort, durability, breathability and protection to meet your specific needs.

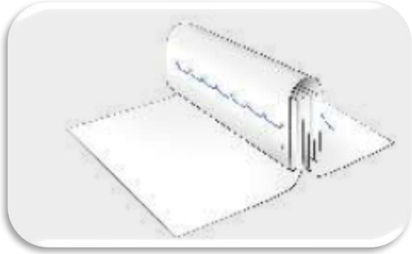
Seams are a critical component of the overall barrier protection provided by a chemical protective garment.
It is vital to select the appropriate seam configuration for your application needs and to know that the garment will be constructed with strong, tight seams.



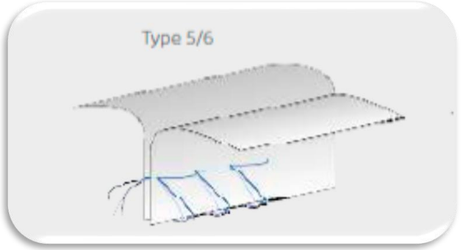
Stitched & Overtaped seams



Welded seams



Bound seams



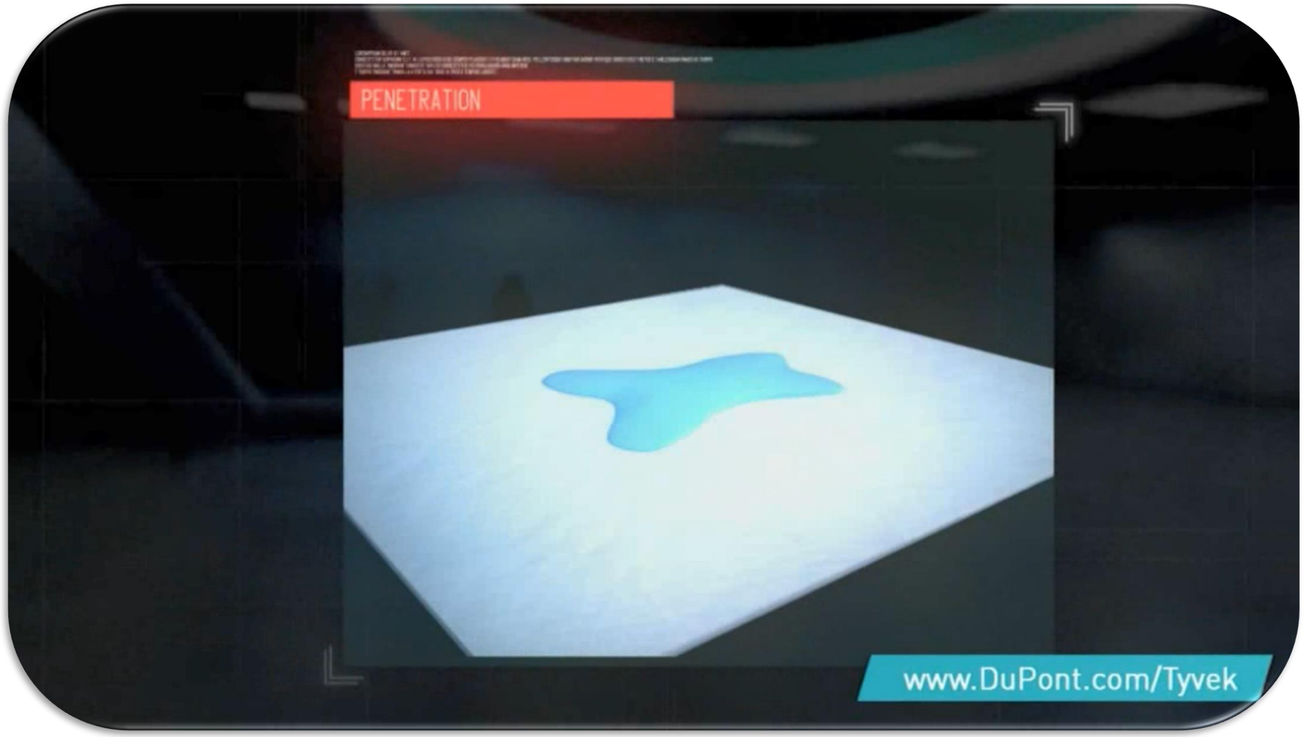
Stitched seams


DUPONT
GET the
FACTS
1 min video
Know More About Personal Protection

Understanding Penetration

- **Penetration:** Process whereby liquid, gaseous or solid substances penetrate a fabric by **passing through the pores or holes.** It may be a **visual process**.

(ASTM F903)

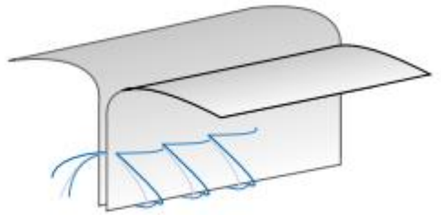


Penetration, pore size & seams

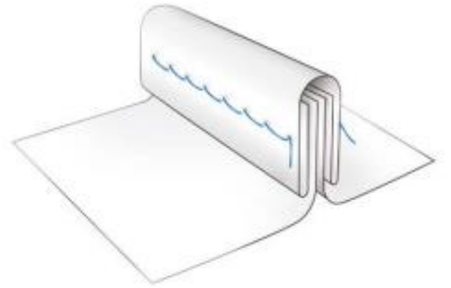
The larger the pore size, the higher the comfort, but the higher the risk of penetration

Tyvek® structure

Reusable cleanroom garment fabric

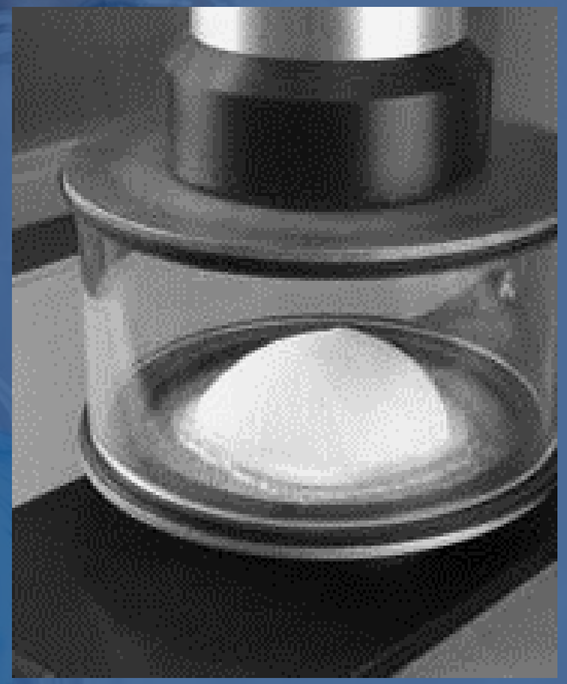


Stitched seams



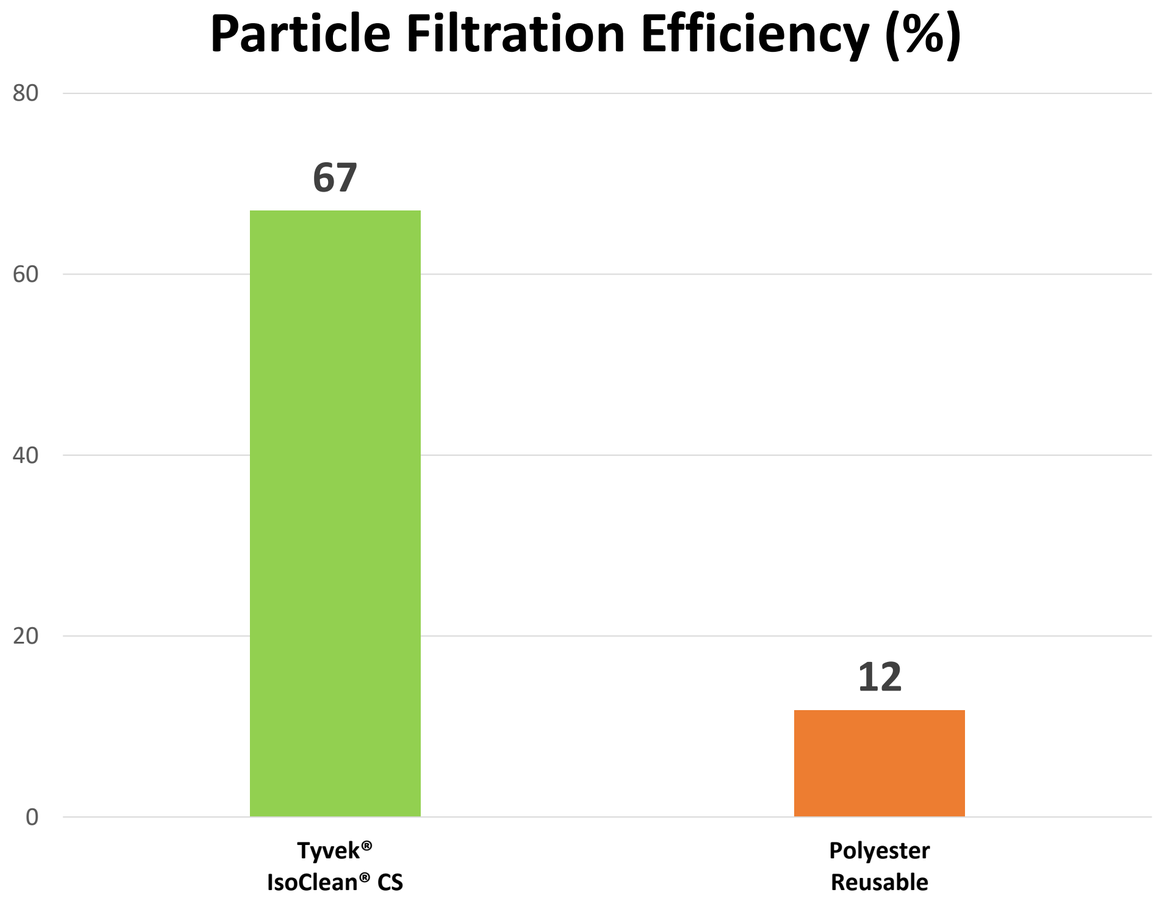
Bound seams

Filtration efficiency verification



- Particles: Sodium chloride (NaCl)
- Flow rate: 2.3 liter per minute
- Particle size: 0.3 µm

Particle Filtration Efficiency
EN 143

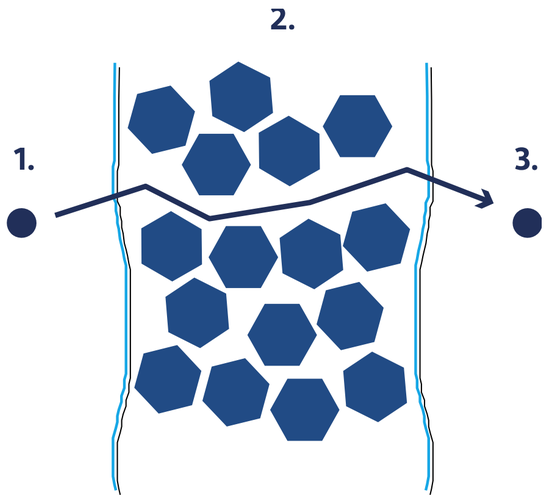


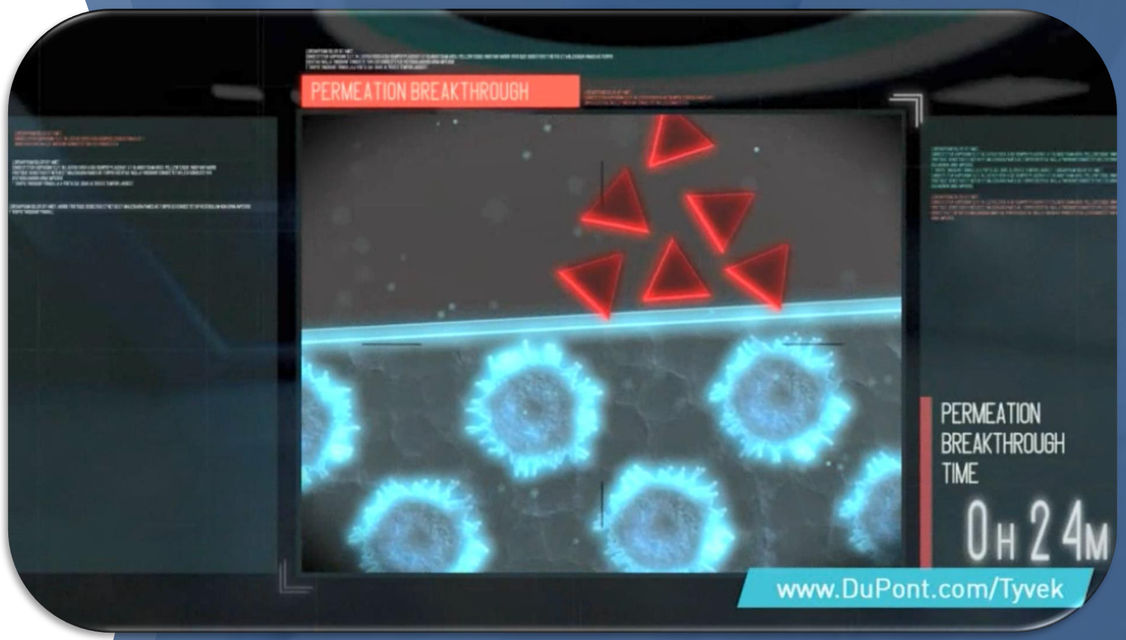
Understanding Permeation?

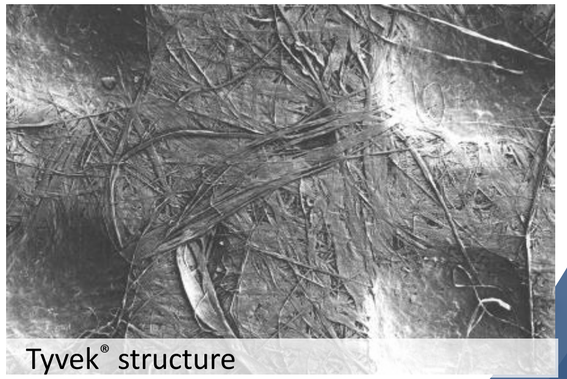
Permeation: Process in which – on a molecular level – **molecules** of a hazard **pass through** a fabric. This is **NOT a visual process**.

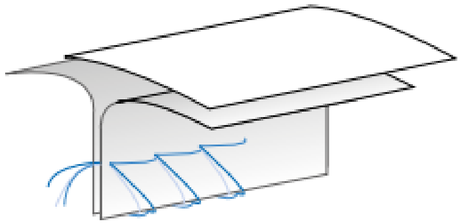
Permeation process

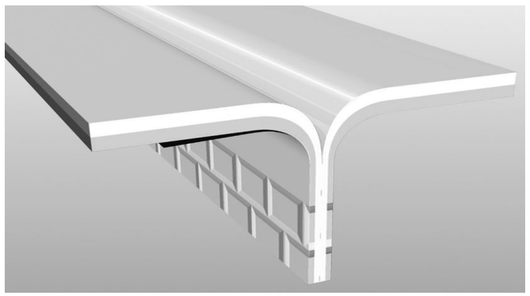
1. Absorption of molecules of liquids on to contact surface
2. Diffusion of the absorbed molecules through material
3. Desorption of the molecules from the opposite surface





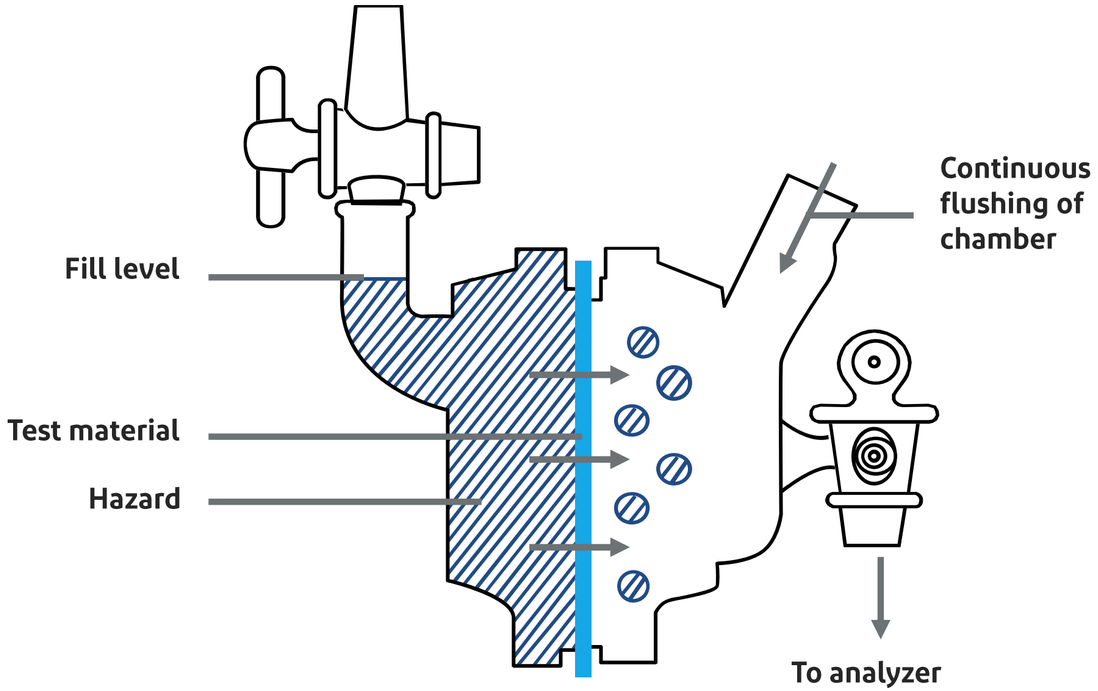

Tyvek® structure


Stitched & Overtaped seams


Welded seams

Gas and liquid permeation: test cell

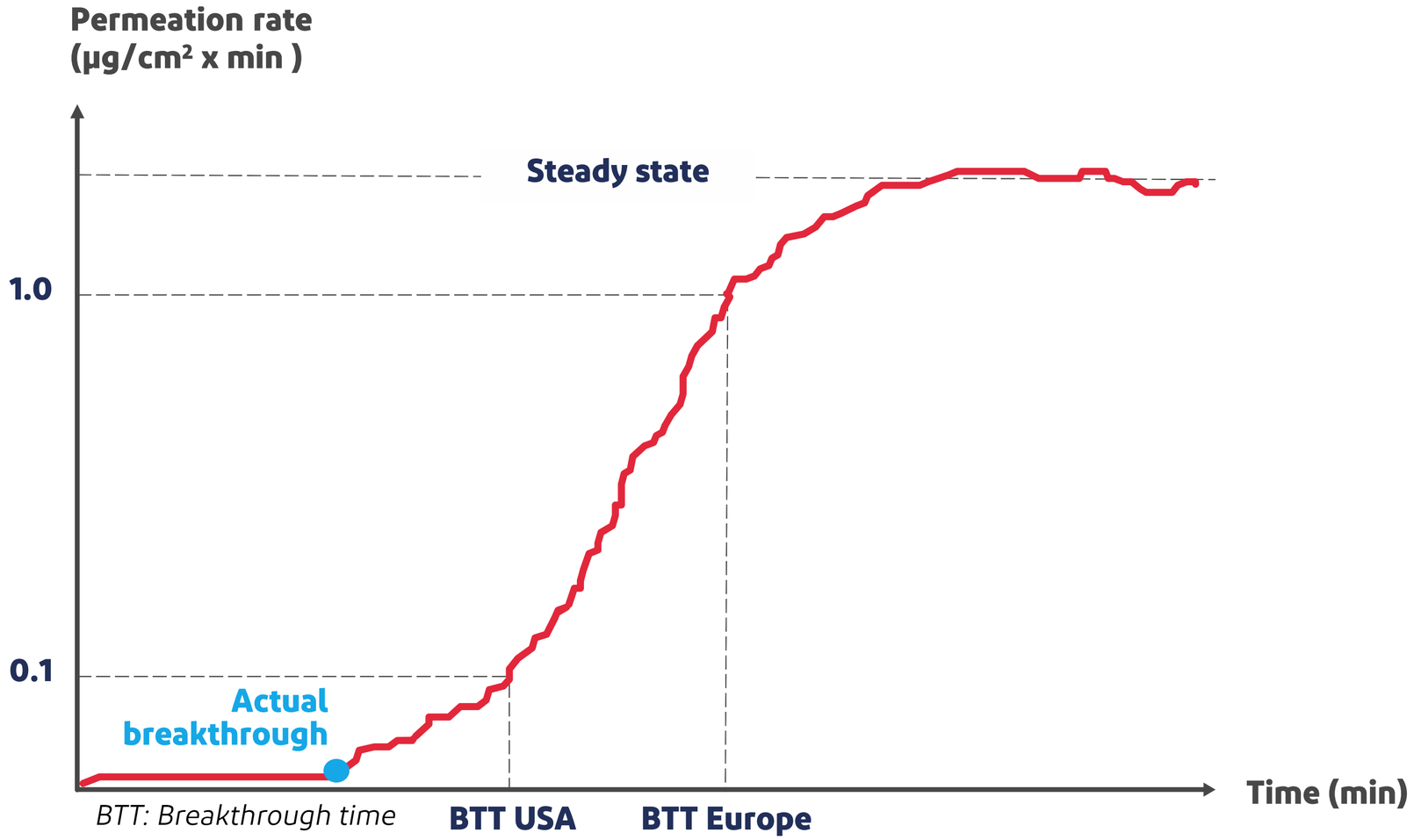
- Test according to **EN 16523-1 / ASTM F739**
- Duration: **up to 480 minutes**
- Procedure: **A test substance** (at 23°C / 27°C ± 1°C) **permeates a barrier** between chambers. It is **then dissolved in a detector beaker** and measured.
- Result: **Determining the resistance of the material to permeation**
- Unit: **Permeation rate =** mass / area x time; **µg/cm² x min**



How to interpret Permeation results

Invisible but gradual process which increases over time until it reaches the upper limit

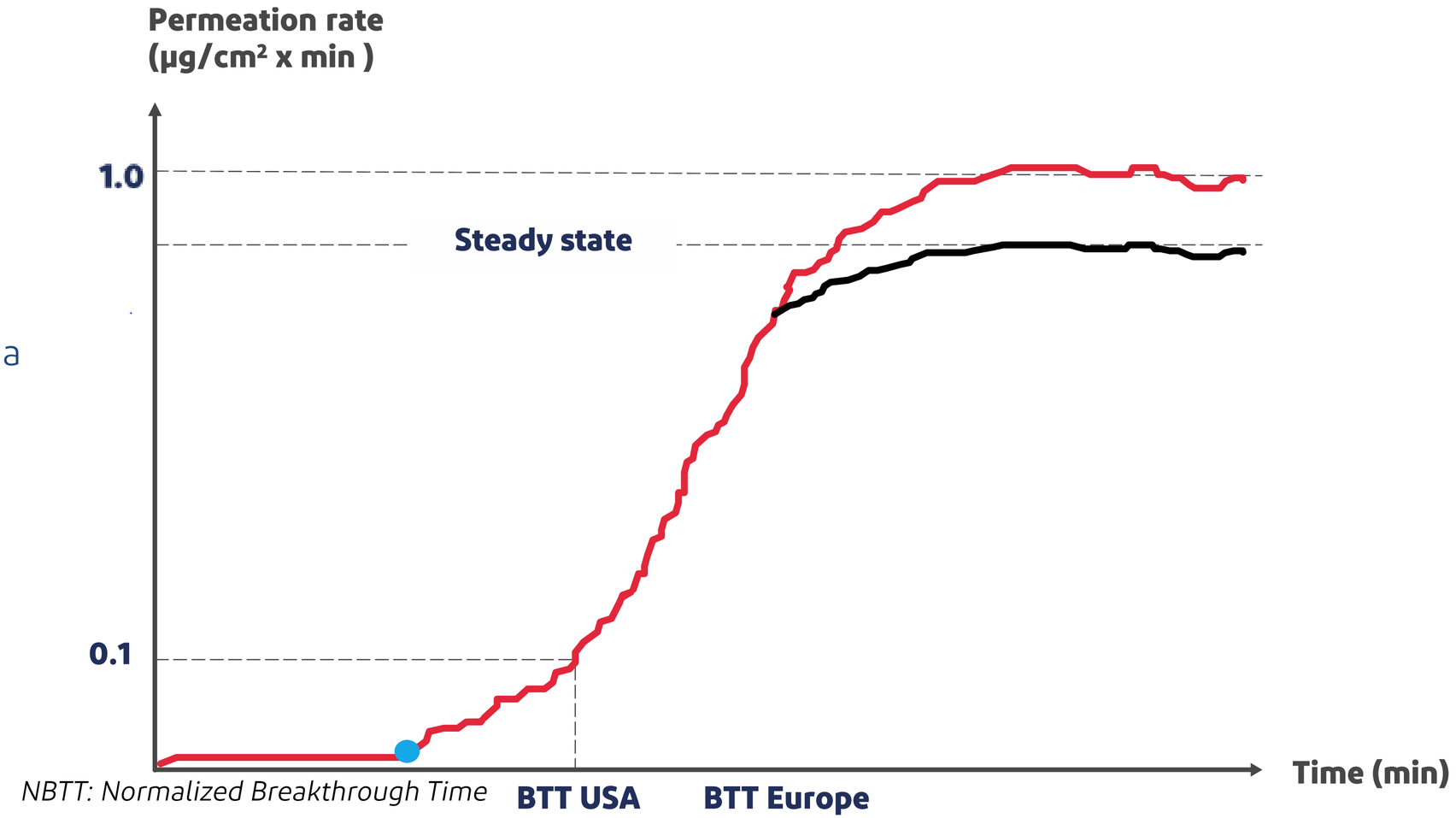
2 different measures: US (0.1) & European (1.0) standards



Permeation Tests - Different Endpoint Impact

As the European norm is set at 1.0 µg, a breakthrough may have happened without being detected at this threshold!

Result as per norm is > 480 minutes



Example of permeation data for cytostatic drugs

Results from permeation tests on Tyvek® and Tychem® products with typical cytostatic drugs

Hazard name	Tyvek® 600	Tyvek® 800	Tychem® 2000
Carmustine (3.3 mg/ml, 10% ethanol)	imm.*	>240**	>240**
Cyclophosphamide (20 mg/ml)	>240	>240	>240
Doxorubicin HCl (2 mg/ml)	>240	>240	>240
Etoposide (20 mg/ml, 33.2% [v/v] ethanol)	>240	>240	>240
Fluorouracil, 5- (50 mg/ml)	imm.*	>240	>240
Paclitaxel (6 mg/ml, 49.7% [v/v] ethanol)	>240	>240	>240
Thiotepa (10 mg/ml)	imm.*	>240**	>240**

*imm=immediate (<10 minutes)
**Under the conditions of the test, an actual breakthrough time of <60 minutes.
For additional permeation test details, please refer to the footnote at the end of this document.

Suitable for the job ?

Duration

Risk of contamination

Required PPE

Standard manufacturing

Sample analysis

R&D

Cleaning operations

Maintenance & repair

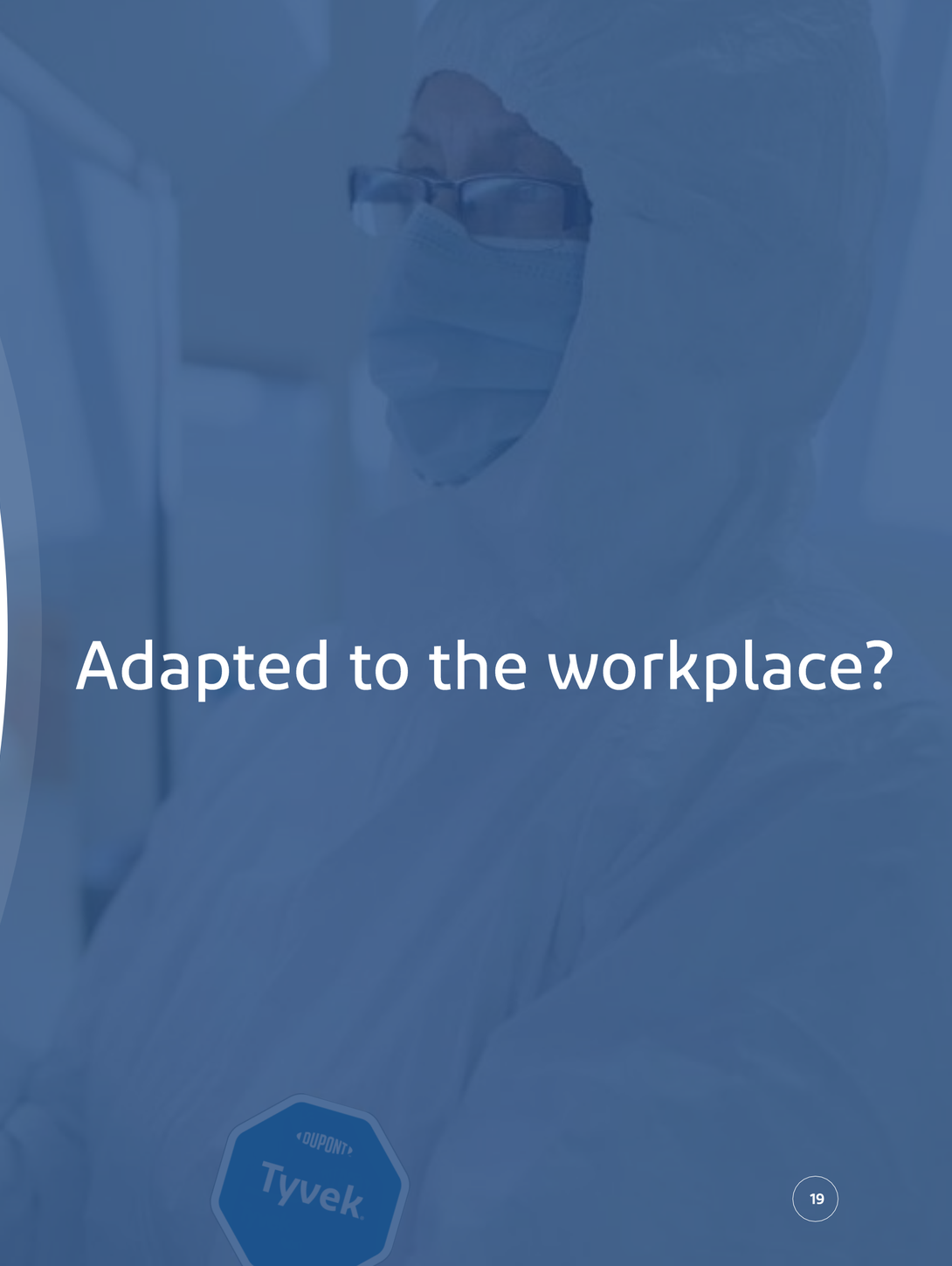
Hazardous waste handling

Emergency interventions

Configuration of the production area

Residual risk for operators

Decontamination equipment (misting shower or emergency shower)



Adapted to the workplace?

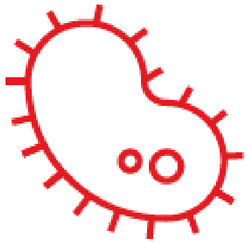
• Requirements for grade A-D environments

"Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. (...) Exclusively monitoring or testing does not give assurance of sterility."

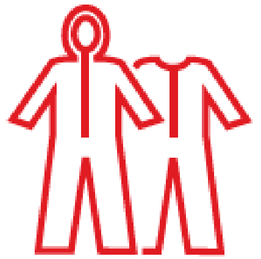
New EU GMP Annex 1 (published 25th of August 2022)

Contamination risks for operators wearing cleanroom garments

In high hazardous processes cleanroom operators may run the risk of getting exposed and/or being contaminated with dangerous substances.



The risk of human contamination (skin flakes, bacteria).



The cleanroom garments themselves as a risk of contamination (fibers, particles).

Classifications

In Europe, the GMPs (Good Manufacturing Practice) utilize Grades A through D (see Table 1) classifications. It also defines the limits for microbial contamination (see Table 2).

Corresponding classifications exist in ISO 14644-1.

ISO 14644-1 air cleanliness classes for cleanrooms and clean zones

ISO classification number	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1.0 µm	5.0 µm	SI	English former FED-STD-209E
ISO Class 1	10							
ISO Class 2	100	24	10					
ISO Class 3	1,000	237	102	35			M 1.5	1
ISO Class 4	10,000	2,370	1,020	352	83		M 2.5	10
ISO Class 5	100,000	23,700	10,200	3,520	832		M 3.5	100
ISO Class 6	1,000,000	237,000	102,000	35,200	8,320	293	M 4.5	1,000
ISO Class 7				352,000	83,200	2,930	M 5.5	10,000
ISO Class 8				3,520,000	832,000	29,300	M 6.5	100,000
ISO Class 9				35,200,000	8,320,000	293,000		

Grade	Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total particle ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not specified [a]	Not specified [a]
B	3 520	352 000	Not specified [a]	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined [b]	29 300	Not predetermined [b]

[a] Classification including 5µm particles may be considered where indicated by the CCS or historical trends.
[b] For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.

Table 1: GMP Annex 1

Grade	Air sample CFU/m³	Settle plates (diameter 90 mm) CFU/4 hours [a]	Contact plates (diameter 55 mm) CFU/plate
A	No growth		
B	10	5	5
C	100	50	25
D	200	100	50

(a) Settle plates should be exposed for the duration of operations and changed as required after a maximum of 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.

Table 2: Limits for microbial contamination during qualification

Gowning requirements

Based on the cleanroom classification, the GMP Annex 1 has also defined the gowning requirements

- Grade B (including access / interventions into grade A): appropriate garments that are dedicated for use under a sterilised suit should be worn before gowning. Appropriately sterilized, non-powdered, rubber or plastic gloves should be worn while donning the sterilised garments. Sterile headgear should enclose all hair (including facial hair) and where separate from the rest of the gown, it should be tucked into the neck of the sterile suit. A sterile facemask and sterile eye coverings (e.g. goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particles. Appropriate sterilized footwear (e.g. over-boots) should be worn. Trouser legs should be tucked inside the footwear. Garment sleeves should be tucked into a second pair of sterile gloves worn over the pair worn while donning the gown. The protective clothing should minimize shedding of fibers or particles and retain particles shed by the body. The particle shedding and the particle retention efficiencies of the garments should be assessed during the garment qualification. Garments should be packed and folded in such a way as to allow operators to don the gown without contacting the outer surface of the garment and to prevent the garment from touching the floor.

- Grade C: Hair, beards and moustaches should be covered. A single or two-piece trouser suit gathered at the wrists and with high neck and appropriately disinfected shoes or overshoes should be worn. They should minimize the shedding of fibers and particles.

- Grade D: Hair, beards and moustaches should be covered. A general protective suit and appropriately disinfected shoes or overshoes should be worn. Appropriate measures should be taken to avoid any ingress of contaminants from outside the clean area.

- Additional gowning including gloves and facemask may be required in grade C and D areas when performing activities considered to be a contamination risk as defined by the CCS.

Source: GMP Annex 1 (25th of August 2022)

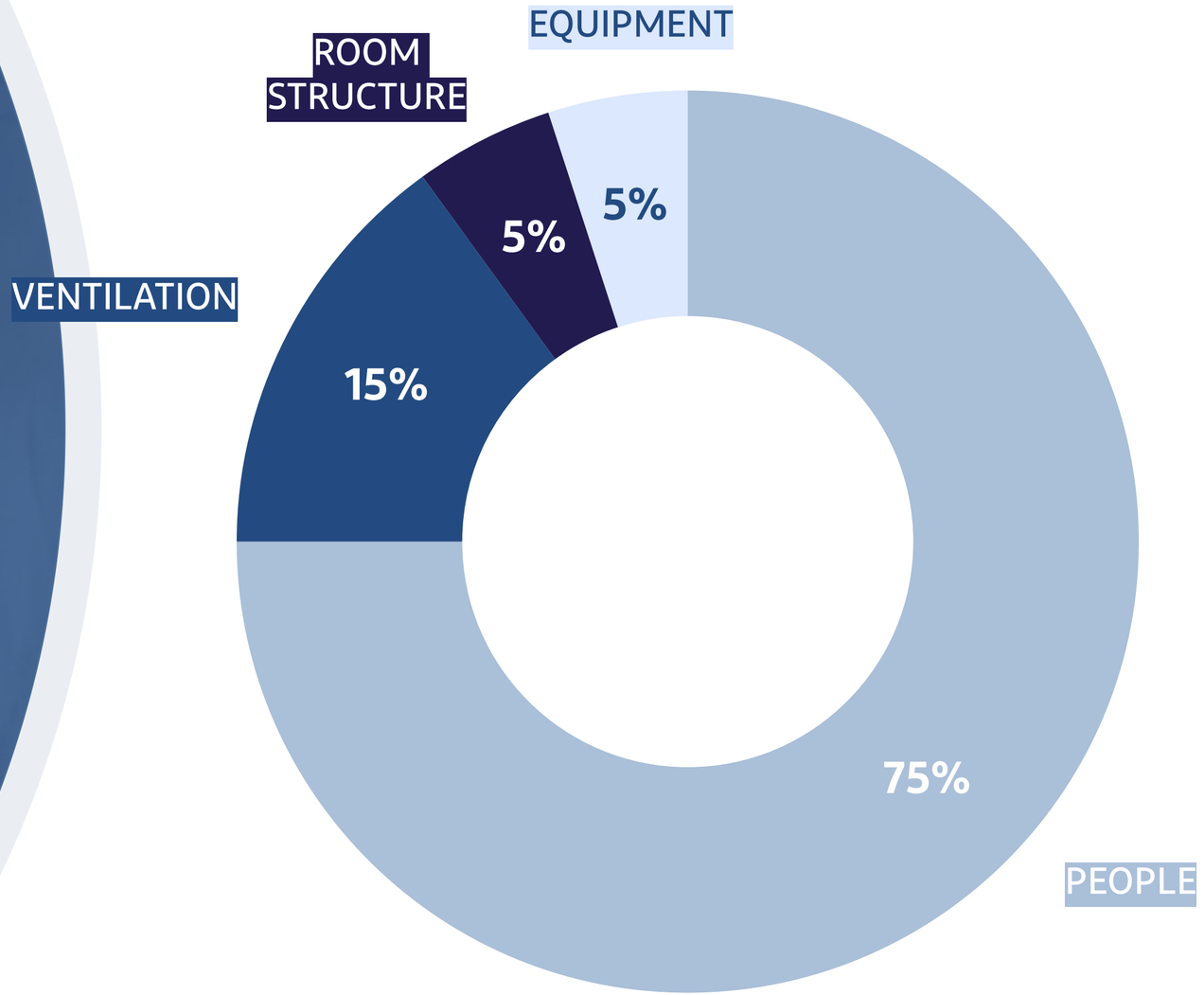
23

Contamination sources

People remain the biggest contamination risk in a cleanroom environment

75%
People

15%
Ventilation



Source: Ramstorp M., "*Introduction to Contamination Control and Cleanroom Technology*", Wiley VCH, 2000, Weinheim (Germany)

The cleanroom garments must also offer chemical protection

ISO 16602

Type indication doesn't tell you the performances of the garment. It only tells that it meets the minimum requirements of type certification.

ISO 16602

Type 1

EN 943-1/
EN 943-2

Gas-tight protection against chemicals and vapors and toxic particles

Leak Tight

Type 2

Non-gas-tight protection

Type 3

EN 14605

Protection against pressurized liquid chemicals

Jet

Type 4

EN 14605

Protection against liquid aerosols

Spray

Type 5

EN ISO 13982-1

Protection against airborne solid particulate chemicals

Particle inward leakage

Type 6

EN 13034

Limited protection against liquid mist

Low level spray

GMP Annex 1 requirements on grade B (A) cleanroom garments

"The protective clothing should minimize shedding of fibres or particulate matter and retain particulates shed by the body. The particle shedding and the particle retention efficiencies of the garments should be assessed during the garment qualification. "

"7.15 Every operator entering grade B or A areas should gown into clean, sterilised protective garments "

"8.10 BFS used for aseptic processing (...) The equipment should be installed in at least a grade C environment, provided that grade A/B clothing is used. "

New GMP Annex 1 (2022)

Example grade B (A)/ISO Class 5
Ensemble options

Features
✓ Sterility Assurance Level (SAL) of 10^{-6} (ISO 11137)
✓ Helmke Drum category 1
✓ Dual barrier validated packaging system for contamination control and sterility risk management
✓ Packed in an ISO Class 4 Certified Cleanroom
✓ Special folding for aseptic gowning
✓ Internal taped or bound seams covered with garment fabric to reinforce seam protection and reduce potential for liquid and particle penetration

Description
Coverall with bound neck or attached hood. Clean-processed and gamma sterilized. Bound seams (internal). Covered elasticated thumb loops. Tunneled elastication at wrists and ankles. Front zipper closure with storm flap.

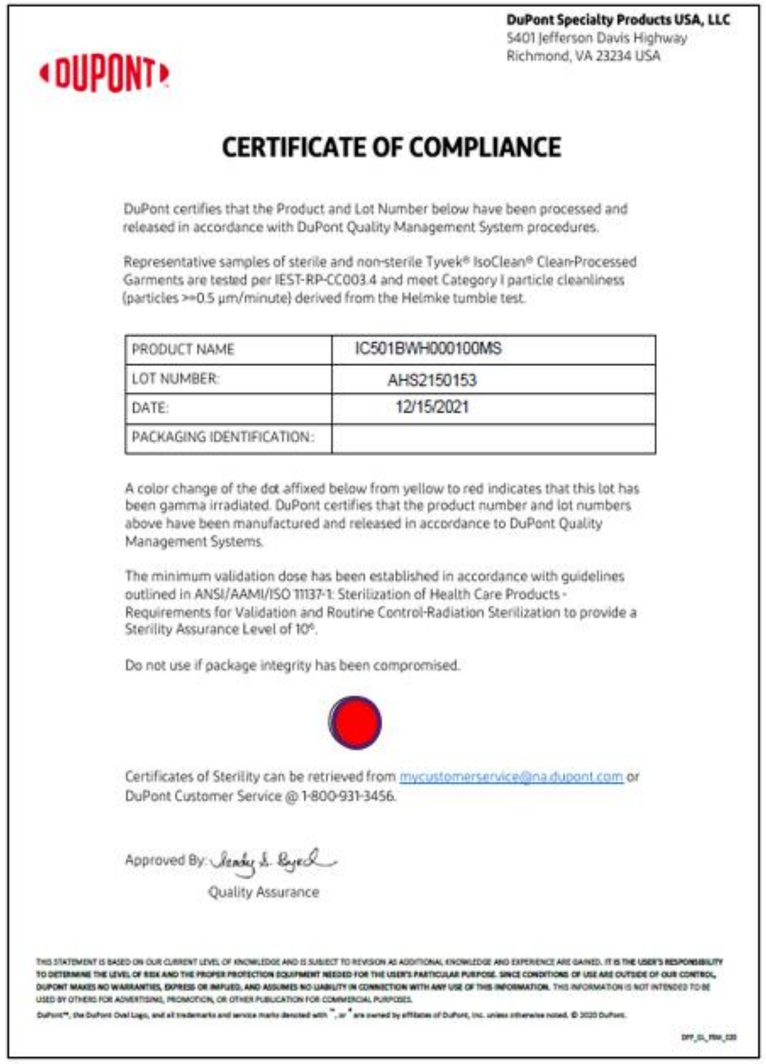
Hood & mask

Hood

Boot cover

Key requirement

Certified Cleanliness



DuPont Specialty Products USA, LLC
5401 Jefferson Davis Highway
Richmond, VA 23234 USA

DUPONT

CERTIFICATE OF COMPLIANCE

DuPont certifies that the Product and Lot Number below have been processed and released in accordance with DuPont Quality Management System procedures.

Representative samples of sterile and non-sterile Tyvek® IsoClean® Clean-Processed Garments are tested per IEST-RP-CC003.4 and meet Category I particle cleanliness (particles >=0.5 µm/minute) derived from the Helmke tumble test.

PRODUCT NAME	IC501BWH000100MS
LOT NUMBER:	AHS2150153
DATE:	12/15/2021
PACKAGING IDENTIFICATION:	

A color change of the dot affixed below from yellow to red indicates that this lot has been gamma irradiated. DuPont certifies that the product number and lot numbers above have been manufactured and released in accordance to DuPont Quality Management Systems.

The minimum validation dose has been established in accordance with guidelines outlined in ANSI/AAMI/ISO 11137-1: Sterilization of Health Care Products - Requirements for Validation and Routine Control-Radiation Sterilization to provide a Sterility Assurance Level of 10^6.

Do not use if package integrity has been compromised.

Certificates of Sterility can be retrieved from mycustomerservice@na.dupont.com or DuPont Customer Service @ 1-800-931-3456.

Approved By: Stanley S. Byrd
Quality Assurance

DPP_SL_RW_020

- ✓ A Certificate of Compliance should come with every shipment.

Key requirement

Certified Sterility

DuPont Specialty Products USA, LLC
5401 Jefferson Davis Highway
Richmond, VA 23234 USA

CERTIFICATE OF STERILITY

PRODUCT NAME:	DUPONT ™ TYVEK ® ISOCLEAN® COVERALL
PRODUCT RELEASE DATE:	10/11/2021 12:00 AM
STERILIZATION RUN NUMBER:	M2102457B
EXPIRATION DATE:	OCT-2026
PART NUMBER:	**IC183BWH2X0025DS**
SIZE:	2X
STERILE LOT NUMBER:	AHS2139165

GAMMA IRRADIATION STERILIZATION:

VALIDATED DOSE (KGY):	30.0
MINIMUM SPECIFIED DOSE (KGY):	31.0
MAXIMUM SPECIFIED DOSE (KGY):	55.0
MINIMUM DELIVERED DOSE (KGY):	34.2
MAXIMUM DELIVERED DOSE (KGY):	52.5

DUPONT CERTIFIES THAT THE LOT NUMBER ABOVE HAS BEEN RELEASED ACCORDING TO DUPONT INTERNAL SPECIFICATIONS. THE STERILITY ASSURANCE LEVEL (SAL) 10^{-6} WAS ESTABLISHED IN ACCORDANCE TO GUIDELINES OUTLINED IN ANSI/AAMI/ISO 11137.

DO NOT USE IF PACKAGE INTEGRITY HAS BEEN COMPROMISED.

CERTIFICATES OF STERILITY CAN BE RETRIEVED AT MYCUSTOMERSERVICE.NA@DUPONT.COM OR CONTACT DUPONT CUSTOMER SERVICE AT 1-800-931-3456.

APPROVED BY: Sandy S. Byrd
QUALITY ASSURANCE

- ✓ Sterility of the garments and accessories is achieved by gamma irradiation.
- ✓ Irradiation dosage is validated in accordance with ISO 11137 for a Sterility Assurance Level (SAL) of 10^{-6}. Radiation doses are validated in accordance with ANSI/AAMI/ISO 11137 through bio burden and dose verification testing.

Examples for grade C-D / ISO Class 7/8

Type 1 / Level A

Category III

TYPE 1a -ET

Tychem® 10000, type 1a

Respirex GTA, type 1c
Source: www.respirex.co.uk

- ✓ Fully encapsulated
- ✓ With air bottles inside, outside or airline

Examples for grade C-D / ISO Class 7/8

Type 3 / Level B/C

Level C

Tychem® 6000 F FaceSeal

Level B

VenPIPE from TB Safety AG
Picture source: https://tbsafety.ch/

Level C

Venion from TB Safety AG
Picture source: https://tbsafety.ch/

✓ Liquid tight seams

✓ For full face mask, ventilated hood, airline or PAPR

DUPONT
Kevlar | Nomex | Tyvek | Tychem

Examples for grade C-D / ISO Class 7/8

Type 3 / Level C

Picture Source: https://www.biovectra.com/.com

Picture Source: https://www.prnewswire.com/ Merck site

Examples for grade C-D / ISO Class 7/8

Type 4 / Level C

Tyvek® 600 Plus

ProChem III TY from 3S Arbeitsschutz GmbH
Picture source: https://www.3s-arbeitsschutz.de/

- ✓ Particle tight seams
- ✓ For full face mask or PAPR

Examples for grade C-D / ISO Class 7/8

Type 4 / Level B/C

Picture Source: https://www.usinenouvelle.com Lonza site

Picture Source: https://www.farmhispaniagroup.com/

Examples for grade C-D / ISO Class 7/8

Type 5 & 6 / Level C

Picture Source: https://www.biovectra.com/.com

Picture Source: https://www.manufacturingchemist.com/

Examples for grade C-D / ISO Class 7/8

Type 5 & 6 / Level D

Tyvek® 400/500

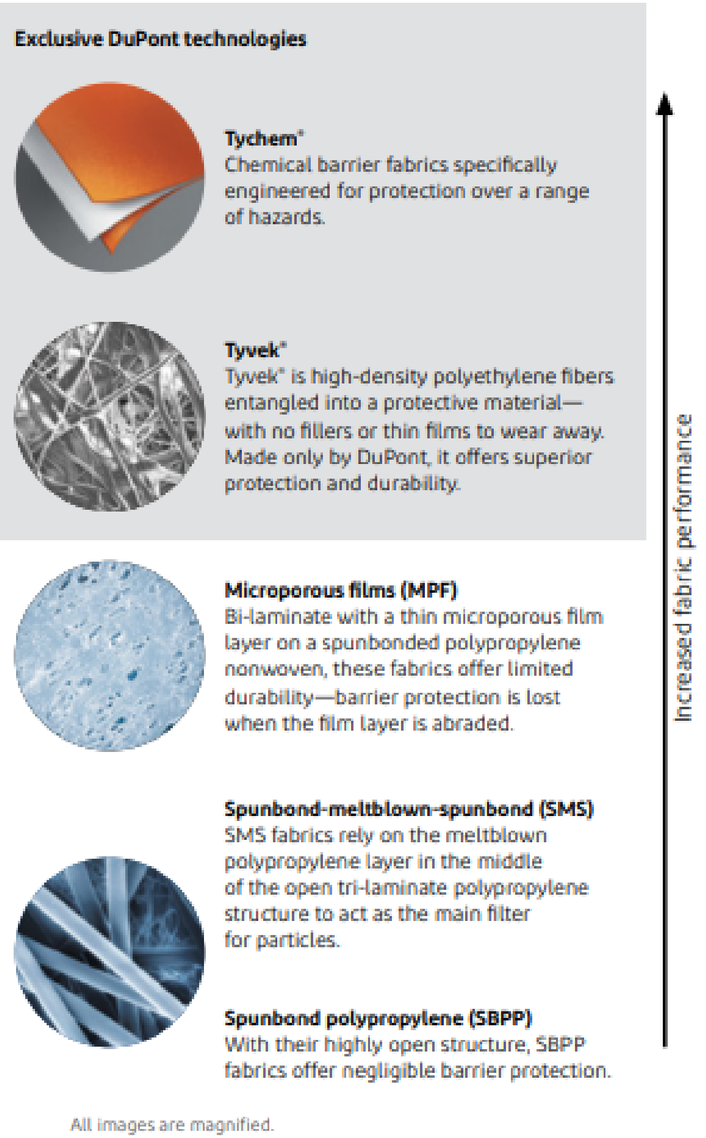
Tyvek® 400/500

✓ **Stitched seams**

Protective Apparel Fabric Comparison

(Single-use Garments)

- **Coated or Laminated Chemical Protective Fabrics (DuPont™ Tychem®)**
- **High Density Polyethylene (DuPont™ Tyvek®)**
  - 100% flashspun polyethylene fibers entangled into a fabric
  - Inherent protection and durability, no fillers or thin films to wear away
- **Microporous Films (MPF)**
  - Bi-laminate fabric with thin microporous film, spun-bond polypropylene non-woven
  - Limited durability protection, once film layer is gone the barrier protection is lost
- **Spunbond/Meltblown/Spunbond (SMS)**
  - Open structure
  - Tri-laminate polypropylene fabric with meltblown polypropylene layer in middle
    - Acts as the main filter for particulates
- **Spunbonded Polypropylene (SBPP)**
  - Highly open fabric offers negligible barrier protection



Ideal Balance of Protection, Durability, & Comfort

Key Fabric Selection Criteria: Protection > Durability > Comfort

- **Protection**
  - Will potentially hazardous materials penetrate through the garment?
  - Does it comply with OSHA requirements?
- **Durability**
  - Will it maintain its protection throughout the task?
  - Will a change out(s) be required during the task?
- **Comfort**
  - Will the garment contribute to heat stress?
  - Will wearing the garment lower worker productivity?

Protective Apparel Considerations

Garment Selection Criteria : Design

- Garment design linked to End-User needs
  - Perceptions of garment comfort
  - Durability in use
  - Hazard Assessment

Apparel Frame of Reference – Clo Values

Clo is a unit of thermal resistance indicating the insulating ability of the test material

Higher clo values provide wearers with more thermal insulation

Clo = 1

Business suit that is comfortable for a person in normal conditions

Clo = 0.5

Summer wear

Clo = 4-5

Outdoor winter clothing

Tyvek® 400 coveralls clo value ~1.

Summary

- When producing or handling HPAPI, both the operators & products must be protected
- PPE is only the last line of defense
- The garments must meet both PPE regulations & cGMP requirements
- The selection of the cleanroom garment systems should be based on risk assessments & other PPE to be worn

Q&A ?