DuPont Personal Protection

The HSE Manager's Guide to Cleanroom Garments for HPAPI Manufacturing

How to Protect Workers and Prevent Contamination According to GMP Annex 1

Introduction

Highly Potent Active Pharmaceutical Ingredients (HPAPI) are enabling unprecedented progress in the medical field. Yet, these substances can be harmful to workers throughout the manufacturing process. Personal Protective Equipment (PPE) like coveralls is critical to keeping workers safe while preventing contamination that can compromise the quality and safety of HPAPI-based drugs. This e-guide looks at the key factors that Health, Safety, and Environment (HSE) managers, together with the Quality Control (QC) managers in the HPAPI manufacturing sector should consider when selecting protective garments for their workers.

The guide analyses the primary worker safety and contamination risks and the specific requirements of Good Manufacturing Practice (GMP) Annex 1. It examines how to protect workers and prevent contamination, focusing on the role of protective garments in meeting various cleanroom requirements. The concluding section explores other factors to consider when selecting protective coveralls, including fabric structure and garment design.

Content overview

HPAPI definition and market trends

HPAPI are the backbone of medical innovation. They are highly effective, even at low doses, by targeting cells selectively. This selectivity enables researchers to develop tailored, patient-centred care that maximises efficacy with minimum side effects. Given these characteristics, oncology is currently one of the primary applications for HPAPI. Research shows that the HPAPI market is experiencing a compound annual growth rate (CAGR) of more than 10%, with forecasts predicting a market size of just under US$40 billion by 2027.

HPAPI risks

There are two main risks associated with HPAPI manufacture. The first is potential harm to workers, and the second is contamination of pharmaceutical products. Both risks can have severe consequences, which places an onus on manufacturers to mitigate against them.

Safety risks of HPAPI manufacture

Pharmaceutical manufacturers ensure worker safety by limiting their exposure to hazardous substances. Regulators specify occupational exposure limits (OELs), which represent safe levels of exposure (health-based) for a chemical substance in the air of a workplace. The most predominant risk of exposure in pharmaceutical manufacturing is inhalation, with the next most likely source being dermal exposure. By definition, HPAPI compounds meet the criteria of having an OEL of <= 10 µg/m3 or a therapeutic dose of <10 mg. OELs may vary across regions, and regulators may include different substances in this category.

Pharmaceutical workers perform various tasks that may result in exposure to HPAPI, including preparation of ingredients, formulation, fill and finish, and cleaning and disinfecting. Cleaning and disinfecting is one of the most hazardous tasks requiring the highest levels of PPE protection. Aseptic filling carry a lower risk, and packaging has the least stringent PPE requirements.

Contamination risks of HPAPI manufacture

The latest revision of the EU GMP Annex 1, first published in 2022, came into effect on 25th August 2023. The new guidance places the onus of responsibility on pharmaceutical manufacturers to manage quality proactively. The Annex classifies cleanrooms into four grades, defined by the maximum allowable number of airborne particles per cubic meter (m^3) of air and the maximum limits for microbial contamination during qualification as shown in the tables below.

Grade	Maximum limits for total particle ≥ 0.5 µm/m^3		Maximum limits for total particle ≥ 5 µm/m^3	
	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 Contamination Control Strategy (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 on routine data, where applicable.

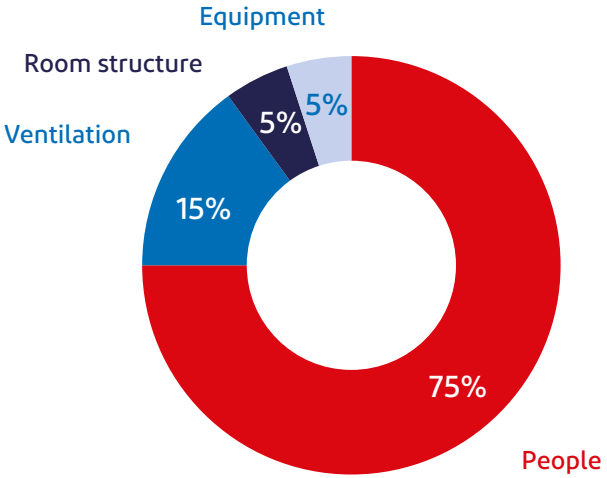
Grade	Air sample CFU /m³	Settle plates (diam. 90 mm) CFU /4 hours[a]	Contact plates (diam. 55mm), CFU / plate[b]	Glove print, Including 5 fingers on both hands CFU / glove
A	No growth[c]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

(a) Settle plates should be exposed in grade A and B areas for the duration of operations (including equipment set-up) and changed as required after a maximum of 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used).
- For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency should be based on QRM.
- Individual settle plates may be exposed for less than 4 hours.

(b) Contact plate limits apply to equipment, room and gown surfaces within the grade A and grade B areas. Routine gown monitoring is not normally required for grade C and D areas. depending on their function.

(c) It should be noted that for grade A, any growth should result in an investigation.

For pharmaceutical companies, ensuring product quality by preventing contamination from foreign particles is critical. People are the primary contributor to contamination, responsible for 75% of the risk. The next highest risk factor is ventilation at 15%.



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

People contribute to contamination in two ways. Firstly, skin flakes and bacteria are shed from the human body continuously. Protective garments are designed to prevent this but have risks of their own. Fabric fibres or particles could be shed from clothing and contaminate the product.

Key steps to protecting workers and preventing contamination in HPAPI manufacturing

Mitigating the risks of HPAPI manufacture begins with a containment strategy, including complete isolation from the hazardous substance using closed-system glassware and reactors. On the other end of the scale, PPE provides the final barrier that prevents workers from coming into contact with hazardous substances.

DuPont recommends a thorough an assessment process to identify the risks and select the most appropriate protective garments. The process is illustrated by the flow chart below.

The 9-step guide from DuPont to garment selection

STEP 1
Hazard identification

STEP 2
Determine minimum levels of protection needed

STEP 3
Assess hazard toxicity

STEP 4
Determine protective performance requirements of the fabric and seam

STEP 5
Determine mechanical performance requirements

STEP 6
Comfort considerations

STEP 7
Supplier selection

STEP 8
Identify the correct usage of the product

STEP 9
Wear test

Tyvek® IsoClean® CS fabric performs exceptionally well with a PFE of 67% PFE compared to reusable polyester cleanroom fabric with a PFE of only 12%.

Identifying the hazard involves an assessment of the HPAPI and worker risk by asking questions like:

- In what physical state do the HPAPI exist (solid, liquid, waxy, gas)?
- How can they enter the body systems (inhalation, accidental injection, dermal absorption, etc.)?
- How could they pass through the PPE?

The purpose of PPE is to keep the hazardous substance from migrating through the garment to the worker. There are different tests to verify the performance of the fabric depending on the physical state of the hazardous substance. Liquid penetration can be tested using the gutter test (EN ISO 6530) or the type 6 cabin test used for testing the tightness of chemical protective clothing (EN ISO 17491-4). Solid particle penetration can be tested using the type 5 cabin test (EN ISO 13982-2). For testing the permeation of liquids and gases, EN ISO 6529 or ASTM F739 can be used.

On the one hand, the manufactured drugs also risk getting contaminated by the particles, droplets or skin flakes generated by the operator when they penetrate through the pores of the fabric out of which the protective coveralls are made. On the other hand, penetration occurs when liquid, gaseous, or solid substances or skin flakes shed by the wearer penetrate a fabric by passing through the pores. This risk can be assessed by measuring the Particle Filtration Efficiency test (EN 143) and the Bacterial Filtration Efficiency test (ASTM F2101).

GMP Annex 1 specifies the garment requirements for each cleanroom class based on activity type and contamination risk, while the European regulation 425/2016 covers the requirements for the personal protective equipment (PPE).

Grade A and B cleanrooms are often located next to each other. Personnel must don protective clothing before entering a grade A/B cleanroom for activities like aseptic filling. Grade C cleanrooms are typically used for cleaning and disinfecting or the synthesis of the HPAPI, while Grade D cleanrooms are generally used for packaging.

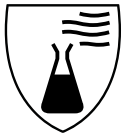
Grade A/B
garment requirements

In grade A and B cleanrooms the protective garments must be sterile and together with the gloves, facemask and goggles make sure that no skin of the operators is apparent.

Grade A and B cleanroom personnel require coveralls with a bound neck or attached hood. Seams must be internal, bound, and covered with garment fabric to reinforce seam protection and reduce the potential for liquid and particle penetration. Front zippers must be closed with a storm flap. Grade A/B coveralls must be fitted with covered elastic thumb loops and tunnelled elastication at wrists and ankles. While the risk of contamination for the operators is much lower than in grade C/D, the cleanliness of the products is significantly more critical. Therefore, it is critical to protect the finished products from contamination by the operators*. Nevertheless it is still necessary to protect the operator from the residual risk of exposure to the finished dosis HPAPI. The grade A/B protective garments should therefore meet both the GMP Annex 1 requirements and the PPE classification as chemical & biological protective garments.

*Grade A/B garments must be clean-processed (washed in a cleanroom laundry and folded & packed in an ISO Class 4 cleanroom), and sterilised according to a validated sterilisation process with special folding for aseptic gowning. They must have a dual barrier validated packaging system for contamination control and sterility risk management. These garments must meet the criteria for Helmke Drum category 1 for cleanliness and a Sterility Assurance Level (SAL) of 10^{-6} (ISO 11137).

Grade C/D
garment requirements



Protective garment requirements for Grade C/D cleanrooms vary widely, with different categories of garments representing different levels of protection and the GMP Annex 1 allows a range of options. While the cleanliness requirements are less stringent than in grade A/B cleanrooms, the risk of contamination for the operators is significantly higher, because the quantities of HPAPI being handled are larger and their potency much higher. The protection of the operators therefore takes priority above the cleanliness requirements. These operators must wear a CE certified chemical & biological protective garment (Cat III) which should also meet the cleanliness requirements of a grade C/D cleanroom (see GMP Annex 1 for further details). The table below highlights some key features for different levels of protection (referred to as "Types") within Category III Chemical Protective Clothing and the common practices in HPAPI manufacturing:

Type	Chemical hazard	Definition	PPE recommendations
3	Liquids under pressure	Liquid HPAPI	Type 3 chemical protective coverall with liquid tight seams together with a full face mask, ventilated hood, airline, or Powered Air Purifying Respirator (PAPR) , chemical protective gloves and eye protection.
4	High level spray	Aerosolised HPAPI	Type 4 chemical protective coverall with particle tight seams together with a full face mask or PAPR , chemical protective gloves and eye protection.
5	Particle aerosol and type	Solid HPAPI or finished dosis HPAPI	Type 5 & 6 chemical protective coverall with stitched (grade C/D) or bound (grade A/B) seams together with a FFP2/3 mask (grade C/D) or sterile clean-room mask (grade A/B), chemical protective gloves (non-sterile for grade C/D and sterile for grade A/B) and suitable eye protection (depending on clean-room class).
6	Low level spray		

Other selection considerations

Besides the type certification, several other factors should be considered when comparing protective garments for HPAPI manufacturing.

Fabric structure

A non-woven material, such as DuPont™ Tyvek® which is made out of continuous HDPE filaments, offers breathability and excellent type 5 & 6 protection against solid or finished-dose liquid HPAPI while being low-linting and being available in clean & sterile, sterile only and non-sterile garment options.

On the other hand, coated or laminated Chemical Protective material such as DuPont™ Tychem® fabric have higher chemical barriers (type 3 and type 1) specifically engineered to help protect workers against highly concentrated hazardous substances like HPAPI, but they are not breathable.

Garment design

Design can play a significant role in performance and comfort. Several different garments may meet the regulatory requirements for an application, but thoughtful design features make some garments stand out from others. For example, zippers on DuPont™ Tyvek® garments that have adhesive flaps offer optimum protection to workers, and integrated chin flaps offer increased liquid protection.

DuPont™ Tychem® 6000 AL garment is a ventilated coverall designed for handling HPAPI with several design features : the hood allows freedom of movement, a >180° panoramic view, in-suit lighting and above vision make a significant difference in comfort, along with elasticated thumb loops, cuffs, ankles, and waist. Simplified closures make the donning procedure easier, while egress strips help enable workers to doff their suits quickly during an emergency.

Air pressure and ventilation

Air pressure is an important consideration when selecting ventilated suits for HPAPI manufacturing environments requiring high protection against hazardous chemicals in liquid, spray aerosol, and mist form (Category III - Type 3-B, 4-B, and 6-B). A suit's internal air pressure should be significantly higher than in the surrounding environment, preventing hazardous particles and droplets from entering.

A suit's ventilation system can help improve the wearer's comfort. The Tychem® 6000 AL ventilated suit, for example, has three exhaust valves, two at the hips and one at the back of the hood, and a fabric air plenum which helps distribute cooling and breathing air effectively, reducing heat and ensuring a safe air supply.

The air belt location is another factor to consider. Air belts inside the coverall are protected against contaminants, preventing workers from inhaling harmful substances. In addition, these air belt are reusable, helping reduce cost.

Conclusion

The rapid expansion of HPAPI manufacturing to meet the demand for targeted therapeutic action means that many pharmaceutical workers may be exposed to the risks of these hazardous substances. Regulations like GMP Annex 1 specify stringent requirements for protective clothing used in each cleanroom grade classification. Protective garments have the dual role of protecting workers and preventing contamination, which may compromise the quality and safety of medicinal products. Global suppliers like DuPont Personal Protection have the expertise and technology to enable HPAPI manufacturers to take health and safety to the next level without having to choose between product protection or operator's protection.

For more information on DuPont™ Tyvek® solutions for the pharmaceutical industry, visit: https://www.dupont.co.uk/personal-protection/pharmaceutical-industries-ppe.html.

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