

Annex 3

WHO good manufacturing practices for pharmaceutical products containing hazardous substances

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References

1. Introduction

1.1 These guidelines set out good practices applicable to facilities handling pharmaceutical products (including active pharmaceutical ingredients (APIs)) that contain hazardous substances such as certain hormones, steroids or cytotoxins. They do not replace national legislation for protection of the environment and personnel. Other WHO guides to good manufacturing practices (GMP) and regulations need to be observed in addition to the workers' safety criteria (1–4).

1.2 These guidelines are to be read in conjunction with other WHO GMP guidelines with respect to building finishes and general services installations, among others. See the reference list for relevant publications which serve as additional background material. The primary focus of these guidelines is on the air-conditioning and ventilation systems of the facility; however, the document also provides some guidance on personnel protection.

1.3 The areas to which this document applies include all zones where the handling of products could lead to cross-contamination, exposure of personnel, or discharge to the environment. This includes research and development facilities, and the sites of API manufacturing and storage and of finished product manufacturing.

1.4 Where possible products should be manufactured in closed systems.

2. General

2.1 Facilities should be designed and operated in accordance with the main GMP principles, as follows:

- to ensure quality of product;
- to protect the operators from possible harmful effects of products containing hazardous substances; and
- to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.

2.2 The production of certain products containing hazardous substances should generally be conducted in separate, dedicated, self-contained facilities.

These *self-contained facilities* may be in the same building as another facility but should be separated by a physical barrier and have, e.g. separate entrances, staff facilities and air-handling systems. The extent of the separation from adjacent facilities and sharing of common services should be determined by risk assessment.

2.3 In general these manufacturing facilities should be regarded as containment facilities.

2.4 The effective operation of a facility may require the combination of some or all of the following aspects:

- appropriate facility design and layout, with the emphasis on safely containing the materials being handled. Manufacturing processes using closed systems or barrier technology enhance operator and product protection;
- manufacturing process controls including adherence to standard operating procedures (SOPs);
- appropriately designed environmental control systems (ECS) or heating, ventilation and air-conditioning (HVAC);
- extraction systems;
- personal protective equipment (PPE);
- appropriate degowning and decontamination procedures;
- industrial hygiene (monitoring staff exposure levels);
- medical surveillance (monitoring staff exposure levels); and
- administrative controls.

3. **Glossary**

The definitions given below apply to terms used in these guidelines. They may have a different meaning in other contexts.

action limit

The action limit is reached when the acceptance criteria of a critical parameter have been exceeded. Results outside these limits will require specified action and investigation.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

air-handling unit (AHU)

The air-handling unit serves to condition the air and provide the required air movement within a facility.

airlock

An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of

controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (this can be a personnel airlock (PAL) or a material airlock (MAL)).

alert limit

The alert limit is reached when the normal operating range of a critical parameter has been exceeded, indicating that corrective measures may need to be taken to prevent the action limit being reached.

barrier technology

A system designed to segregate people from the product, contain contaminants or segregate two areas, which could be a barrier isolator (BI) or a restricted access barrier system (RABS):

- A BI is a unit supplied with high-efficiency particulate air (HEPA) filtered air that provides uncompromised continuous isolation of its interior from the external environment, including surrounding clean room air and personnel.
- A RABS is a type of barrier system that reduces or eliminates interventions into the critical zone. In practice, its level of contamination control is less than that of a barrier isolator.

clean room

A room or area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

commissioning

Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation.

containment

A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

contamination

The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or material during production.

design condition

Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

environmental control system (ECS)

Environmental control system, also referred to as heating, ventilation and air-conditioning (HVAC).

facility

The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

hazardous substance or product

A product or substance that may present a substantial risk of injury, to health or to the environment.

heating, ventilation and air-conditioning (HVAC)

Heating, ventilation and air-conditioning, also referred to as environmental control system (ECS).

high efficiency particulate air (HEPA) filter

High efficiency particulate air filter.

ISO 14644

International standard relating to the design, classification and testing of clean environments (5).

laminar airflow (LAF)

A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow).

normal operating range

The range that the manufacturer selects as the acceptable values for a parameter during normal operations. This range must be within the operating range.

occupational exposure level (OEL)

Airborne concentration of substances that will not result in adverse effects to most healthy workers, exposed for 8 hours/day, 40 hours/week.

operating range

The range of validated critical parameters within which acceptable products can be manufactured.

personal protective equipment (PPE)

The necessary garments and equipment required to protect the operator in the workplace.

pressure cascade

A process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure.

qualification

The planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended.

standard operating procedure (SOP)

An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (e.g. operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

unidirectional airflow (UDAF)

A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines.

validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

4. **Risk assessment**

4.1 Not all products containing hazardous substances are equally potent and risk assessments should be carried out to determine the potential hazards to operators and to the environment. The risk assessment should also determine which phases of the product production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination.

4.2 Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators and/or the public and/or the environment, the guidelines to be followed for the design and operation of the facility should be as detailed in this document.

4.3 The toxicological data available, such as permissible occupational exposure levels (OEL) for the product, should be taken into account when conducting the risk assessment.

4.4 The risk assessment should take into account the national or international occupational health and safety requirements for OELs in the work environment.

5. **Product protection**

5.1 The requirement for producing quality products, with respect to protection from contamination and cross-contamination, clean room class of air, temperature and humidity should be as for other pharmaceutical products. These requirements are covered in other WHO GMP guidelines.

6. **Personal protection equipment and breathing air systems**

6.1 The fundamental design principle for a facility and its production equipment is to provide product containment and operator protection. Should the facility and equipment design not provide adequate product containment, operator protection should be provided. If facility and equipment design are adequate, a spillage or non-routine incident could cause a hazardous situation, in which case PPE should be available. Unless otherwise specified in the material safety data sheet, operators should be protected from exposure with an appropriate method, such as by wearing:

- flash-spun, high-density polyethylene fibre material suits or impervious washable protective suits. Integral hoods may be required depending on the respirator type used;
- flash-spun, high-density polyethylene fibre material shoes, lower leg covers or cleanable boots;
- suitable single-use, disposable gloves. Double gloves should be worn where direct active contact with the product cannot be avoided. Gloves should be taped or sealed on to the protective suit sleeves; and
- respirator eye and face protection with associated breathing air systems.

6.2 Where breathing air systems are used, these should be provided to supply safe breathing air to the operators to prevent them from inhaling air from within the facility. Personnel should be appropriately trained and assessed in the use of these systems before they can enter the area. The breathing air systems should comprise a protective face mask, which should form an integral part of a protective suit. The breathing air systems could be any of the systems described below:

- a central air supply system which connects to the operator's face mask by means of flexible hoses and quick coupling sockets, also called an airline respirator (AR). The air connection should incorporate a one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply should be treated to ensure a temperature and level of humidity that are comfortable for the operator. The air source could be a high pressure fan or an air compressor. If an air compressor is used, it should be of the oil-free type or have suitable oil removal filters fitted;
- a self-contained breathing apparatus (SCBA) or powered air purifying respirator (PAPR) that is securely attached to the operator's belt and connects to the operator's face mask. This system draws air from the room in which the operator is working and the air supply is delivered to the face mask by means of a battery-driven fan. The AR provides superior protection to the PAPR apparatus;
- for zones with lower contamination levels, a half-mask high efficiency particulate air filter (HEPA) cartridge respirator or N95-type paper filter mask may be acceptable.

6.3 The selection of the respirator type is based on the relationship between the accepted OEL and the respirator-certified protection factor (PF).

6.4 The air supplies should be filtered through a final filter, which should be a HEPA filter rated as an H13 filter according to EN 1822 (European Norm). The supply of breathing air into the face mask and/or protective suit should result in the interior of the mask and suit being at a positive pressure relative to the facility environment.

6.5 Central breathing air supply systems should have a 100% back-up system in the event of the main system failing. This could be in the form of a gas bottle system with at least 5 minutes supply. Changeover from the normal supply to the back-up supply should be automatic. The system should have a monitoring system and send alarm signals to a permanently manned location in the following situations:

- failure of main air supply;
- temperature out of specification (OOS);
- humidity OOS;
- carbon dioxide (CO₂) OOS;
- carbon monoxide (CO) OOS; and
- sulfur dioxide (SO₂) OOS.

6.6 Breathing air should be filtered by means of pre-filters, coalescing filters and final filters to have the minimum air quality specifications of ISO 8573-1 3-9-1 and EN 12021:1999.

6.7 Where air is delivered through a central system the piping should not cause any contamination to be liberated into the air stream. Stainless steel piping is preferred. The final filters should be as close as possible to the operator connection points. The operator hose connection to the air supply should be a dedicated connection specific to the breathing air system (to avoid inadvertent connection to a different gas system).

7. **Environmental protection**

7.1 Due to the hazardous nature of the products being handled in the facility, neither the product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.

7.2 The external atmosphere and the public in the vicinity of the facility should be protected from possible harm from hazardous substances.

7.3 If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.

7.4 Exhaust air filtration to ensure environmental protection is discussed in section 11.

8. **Facility layout**

8.1 The premises should be designed and constructed to prevent the ingress or egress of contaminants. In drawing up the facility design, attention should be paid to the level of containment provided by the equipment.

8.2 The link between the interior and exterior of the premises should be through airlocks (PAL and/or MAL), changing rooms, pass boxes, pass-through hatches, decontamination devices, etc. These entry and exit doors for materials and personnel should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.

8.3 The changing rooms should have an arrangement with a step-over-bench. The facilities on the exit side should incorporate showers for the operators.

8.4 The premises should be laid out and designed so as to facilitate the required pressure cascades and containment.

8.5 The premises (and equipment) should be appropriately designed and installed to facilitate cleaning and decontamination.

8.6 The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) to ensure that the designation and conditions of use of all the rooms are correctly shown.

8.7 The flow of people and products should be clearly marked on the layouts and plans.

8.8 The activities carried out in the vicinity of the site should be indicated.

8.9 Plans should describe the ventilation systems, indicating inlets and outlets, in relation to other facility air inlet and outlet points.

8.10 The facility should be a well-sealed structure with no air leakage through ceilings, cracks or service areas.

8.11 Areas of the facility where exposed product presents a risk should be maintained at a negative air pressure relative to the environment.

9. **Air-handling systems**

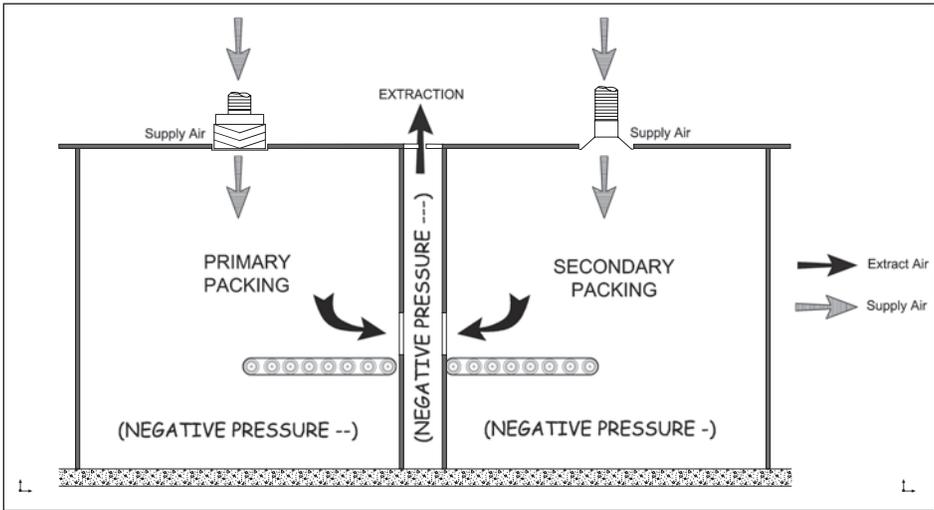
9.1 The HVAC system should be appropriately designed, installed and maintained to ensure protection of product, personnel and the environment.

9.2 The principles of airflow direction, air filtration standards, temperature, humidity and related parameters should comply with the minimum requirements as set out in Annex 2 of the fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2006 (2).

9.3 Facilities and premises dealing with hazardous substances should have the following basic air-handling characteristics:

- There should be no direct venting of air to the outside.
- Air-conditioning or ventilation should result in a negative pressure relative to the outside. Air pressure differentials should be such that there is no uncontrolled flow of air between the work area and the external environment.
- Appropriate air pressure alarm systems should be provided to warn of any pressure cascade reversal or loss of design pressure status. The appropriate design, alert and action limits should be in place. System redundancies should be in place to respond appropriately to pressure cascade failure.
- The starting and stopping of the supply and exhaust air fan should be synchronized such that the premises remain at a negative pressure during start-up and shut-down.
- The air pressure cascade within the facility, although negative relative to the environment, should comply with normal pharmaceutical pressure cascade requirements with regards to product protection, dust containment and personnel protection.
- Visual indication of the status of room pressures should be provided in each room.
- Air should be exhausted to the outside through HEPA filters and not be recirculated except to the same area, and provided that a further HEPA filtration stage is applied to the return air. Where HEPA filters are

Figure 1
Typical airflow pattern for contaminant



mentioned in these guidelines, this refers to HEPA filters with a minimum rating of H13 according to EN 1822.

- Where possible, single-pass air-handling systems with no recirculation should be provided.
- Exhaust air or return air should be filtered through a safe-change or bag-in-bag-out filter housing. The filter housing should contain pre-filters and HEPA filters, both of which should be removable with the safe bagging system.
- Changing rooms should be supplied with air filtered to the same standard as that for the work area they serve.
- Airlocks, pass-through hatches, etc., should have supply and extract air to provide the necessary air pressure cascade and containment. The final, or containment perimeter, airlock or pass-through hatch bordering on an external or non-GMP area should be at a positive pressure relative to the environment, to prevent the ingress of contaminants to the facility.
- If the facility provides insufficient containment, and operators' garments are contaminated with dust, the operators leaving the containment area should pass through a decontamination system, e.g. air showers or a mist shower system, to assist with removing or controlling dust particles on their garments. Operators should follow this route before de-gowning to use the ablutions or canteen facilities. All garments leaving the facility for laundering should be safely bagged. Appropriate means for protecting laundry staff and prevention of contamination of other garments from non-hazardous facilities should be in place.

9.4 If required, appropriate measures should be taken to prevent airflow from the primary packing area (through the conveyor “mouse hole”) to the secondary packing area.

Note: This could be overcome by having a pass-through chamber over the “mouse hole”, which is maintained at a negative pressure to both primary and secondary packing. This typical arrangement is illustrated in Figure 1. This principle can be applied to other situations where containment from two sides is required.

9.5 Where possible, HEPA filters in the supply air system should be terminally mounted to provide protection against back-flow cross-contamination in the event of a failure in the supply airflow.

9.6 In some cases consideration can be given to the use of biosafety cabinets, isolation systems or glove boxes as a means for containment and operator protection.

9.7 There should be a system description including schematic drawings detailing the filters and their specifications, the number of air changes per hour, pressure gradients, clean room classes and related specifications. These should be available for inspection.

9.8 There should be an indication of pressure gradients that are monitored by means of digital or analogue pressure indicators.

9.9 Consideration should be given to providing an emergency power supply, e.g. diesel generators, to ensure that safe operation of the premises and systems can be maintained at all times.

10. **Air-handling units**

10.1 The air-handling units (AHUs) supplying air to the facility should conform to AHU requirements as detailed in *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials (1)* and *Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms (2)* and the filtration should be consistent with the zone concepts and product protection required.

10.2 The decision to use return air or recirculated air should be made on the basis of a risk assessment.

10.3 Where a full fresh-air or single-pass system is used, an energy recovery wheel could be considered. In such cases, there should not be any potential for air leakage between the supply air and exhaust air as it passes through the wheel. The relative pressures between supply and exhaust air systems should be such that the exhaust-air system operates at a lower

pressure than the supply system. (Alternatives to the energy recovery wheel, such as crossover plate heat exchangers, heat pipes and water coil heat exchangers, may be used.)

10.4 Risk management principles should be applied to address the potential of cross-contamination where energy wheels are used.

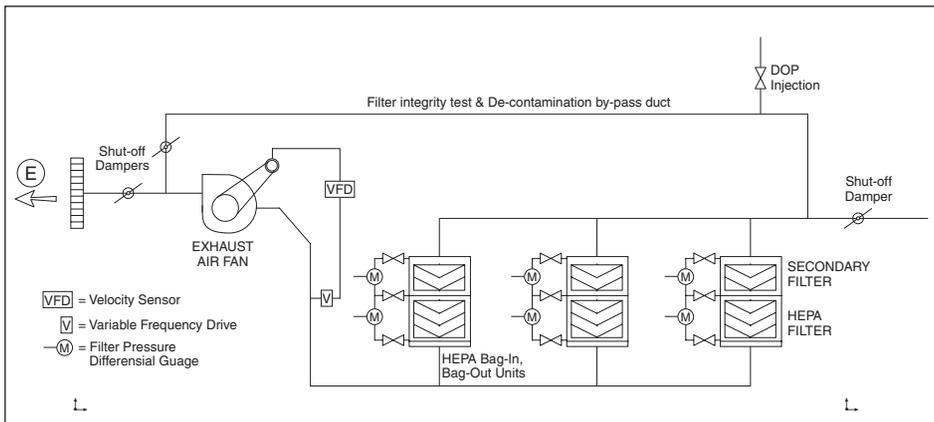
10.5 If return air is to be recirculated it should pass through a safe change filtration system before being introduced back into the supply AHU. The return air fan could form part of the AHU; however, the safe change filter should be a dedicated unit. With this arrangement the return air passes through two sets of HEPA filters in series, i.e. the return air filters in the safe change housing and the supply air HEPA filters. The supply air HEPA filters could either be located in the AHU or terminally located at the supply diffusers, depending on the clean room classification of the facility.

10.6 The starting and stopping of the supply and exhaust air fans, and associated system ventilation fans, should be synchronized such that the premises retain their design pressure and flow relationships during start-up and shut-down. Processing should stop when the fans are not running. This fan interlock sequence should also apply if any fan should fail, to ensure that there is no airflow reversal in the system.

11. Safe change filter housings

11.1 Safe change or bag-in-bag-out filter housings should be suitably designed to provide operator protection and to prevent dust from the filters entering the atmosphere when filters are changed.

Figure 2
Safe change filter bypass arrangement



11.2 The final filters on the safe change unit should be HEPA filters with at least an H13 classification according to EN 1822 filter standards. For dusty return, air pre-filtration may also be required to prolong the life of the HEPA filters. The pre-filtration filters should also be removable through the bag-in-bag-out method.

11.3 For exhaust systems where the discharge contaminant is considered particularly hazardous, two banks of HEPA filters in series should be considered to provide additional protection should the first filter fail.

11.4 All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading and remaining lifespan of the filters. Connection to these gauges should be copper or stainless steel and not plastic tubing, which could perish causing a contamination hazard. The tube connections on the filter casing should be provided with stopcocks, for safe removal or calibration of gauges.

11.5 Monitoring of filters should be done at regular intervals to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.

11.6 Computer-based data monitoring systems may be installed to monitor filter condition.

11.7 Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.

11.8 Installed filter leakage tests should be performed in accordance with ISO 14644-3. Injection ports (upstream) and access ports (downstream) should, therefore, be provided for this purpose.

11.9 The exhaust air fan on a safe change filter system should be located after the filters so that the filter housing is maintained at a negative pressure. This poses a difficulty when carrying out filter integrity tests, and for this reason a bypass damper system should be provided, as illustrated in Figure 2, so that air can be circulated through the HEPA filters, while the scanning ports are open. Alternatively an independent booster fan system can be used, with appropriate shut-off dampers.

11.10 The bypass arrangement as shown in Figure 2 also permits decontamination of the filters by means of circulation of a sanitizing agent.

11.11 All exhaust systems from the facility, including dust extraction systems, vacuum system exhaust, fluid bed drier exhaust and coating pan exhaust, should be passed through safe change filter housings before being exhausted to the atmosphere.

11.12 All exhaust points outside the building should be located as far as possible from air entry points, and exit points should be at a high level to minimize the possibility of re-entrainment of exhaust air. Dominant and seasonal wind directions should be taken into account when positioning exhaust and supply points.

11.13 Where excessively dust-laden air is handled, a dust collector or bag house should be considered, with the dust collector being located in an enclosed room maintained at a negative pressure. Access control, maintenance staff, personal protection equipment (PPE) and breathing air systems should then be provided to protect the operators during removal of dust from the collector bins.

11.14 Portable vacuum cleaners and portable dust collectors should be fitted with H13 HEPA filters. These types of units should be emptied and cleaned in a room which is under negative pressure relative to the environment. Personnel should be provided with suitable PPE.

11.15 Records of the safe disposal of all contaminated filters and dust should be kept.

12. Personnel decontamination systems

12.1 If required, a means of preventing contaminants from leaving the facility on the garments of personnel should be provided. This could be in the form of an air shower; mist shower, water shower or appropriate device.

12.2 An air shower comprises an airlock where high velocity air is supplied through air nozzles (e.g. from the sides of the airlock) in order to dislodge dust particles. Air extraction grilles (e.g. at low level) should draw the air away and return it to the filtration system. Some air showers may also incorporate a vertical unidirectional airflow section at the exit end, to flush contaminants away.

Note: When air showers are used these should be correctly designed to effectively extract dust.

Air filtration of the supply air and return or exhaust air should comply with the same filtration standards as used in the manufacturing facility. Normally the fan should be activated by opening the door as the operator enters the shower, with a timing device on the exit door interlock to allow sufficient time for the decontamination process to be effective.

12.3 Flushing devices similar to air or mist showers for personnel could be used at material exits to assist with removing contaminants.

12.4 Wet mist or fog decontamination systems for operators can be employed for deactivating contaminants on the operator's garments, or

causing contaminants to adhere to the garments so that they are not easily liberated.

12.5 Personnel should change into clean garments after having taken a shower.

13. **Effluent treatment**

13.1 Liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.

13.2 All effluent should be disposed of in a safe manner, and the means of disposal should be documented. Where external contractors are used for effluent disposal they should have certification authorizing them to handle and treat hazardous products.

14. **Maintenance**

14.1 The efficient and safe operation of a facility handling hazardous materials is reliant on regular maintenance being carried out, to ensure that all parameters remain within specified tolerances. See *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials (1)* or WHO Technical Report Series, No. 937, Annex 2, section 8.3 (2) for further details on maintenance.

15. **Qualification and validation**

15.1 System qualification and validation should be carried out as described in other WHO guidelines.

References

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