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Organization**

GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS CONTAINING HAZARDOUS SUBSTANCES

DRAFT FOR COMMENT

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[NOTE: INDEX FIELD STILL TO BE UPDATED]

1. INTRODUCTION

1.1 This guideline serves to set out good practices applicable to facilities handling pharmaceutical products (including active pharmaceutical ingredients (APIs)) that contain hazardous substances such as certain hormones. It does not replace national legislation for environmental and personnel protection.

1.2 This guideline is to be read in conjunction with other WHO good manufacturing practices (GMP) guidelines with respect to building finishes, general services installations, etc. This guideline only deals with criteria which are not covered in the other WHO GMP guidelines. Refer to the bibliography for relevant publications which serve as additional background material. This guideline's primary focus 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 where this document finds application are all zones where the handling of these products could lead to cross-contamination, exposure of personnel, or discharge to the environment. This includes research and development facilities, API manufacturing, storage and finished product manufacturing.

2. GENERAL

2.1 The main goals in the design and operation of a hazardous substance facility are threefold, as follows.

2.1.1 To ensure quality of product.

2.1.2 To protect the operators from possible harmful effects of products containing hazardous substances.

2.1.3 To protect the environment from contamination and thereby protecting the public from possible harmful effects of products containing hazardous substances.

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

These 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.

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

2.6 The effective operation of a facility requires the combination of the following aspects.

2.6.1 Appropriate facility design and layout, with the emphasis on safely containing the materials. Manufacturing processes using closed systems or barrier technology enhance operator and product protection.

2.6.2 Manufacturing process controls including adherence to standard operating procedures (SOPs).

2.6.3 Environmental control systems (ECS) or heating, ventilation and air-conditioning (HVAC).

2.6.4 Extraction systems.

2.6.5 Personal protective equipment (PPE).

- 2.6.6 Industrial hygiene.
- 2.6.7 Medical surveillance (monitoring staff exposure levels).
- 2.6.8 Administrative controls.

3. GLOSSARY

3.1 The definitions given below apply to terms used in this guideline. 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)

A substance or compound intended to be used in the manufacture of a pharmaceutical product as therapeutically active compound (ingredient).

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 (PAL, Personnel airlock and MAL, Material airlock).

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 barrier isolator is a unit supplied with HEPA filtered air that provides uncompromised continuous isolation of its interior from the external environment, including surrounding cleanroom 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.

Cleanroom

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 with the potential to cause harm.

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.

Laminar airflow (LAF)

Laminar airflow or unidirectional airflow is 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.

Operating range

Operating range is the range of validated critical parameters within which acceptable products can be manufactured.

Operator exposure level (OEL)

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

Personal protection 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

Qualification is 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)

Unidirectional airflow is 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 API manufacture to finished product distribution, would fall under the requirements of this guideline. 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 facility design and operation should be as detailed in this document.

4.3 Toxicological data available such as permissible operator exposure levels (OEL) for the relative 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 contamination and cross-contamination protection, cleanroom 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 Unless otherwise specified in the material safety data sheet, operators should be protected from exposure by the following.

6.1.1 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.

6.1.2 Wearing flash-spun, high-density polyethylene fibre material shoe/lower leg covers or cleanable boots.

6.1.3 Wearing single-use, disposable suitable gloves. Double gloves should be worn where direct active contact cannot be avoided with the product. Gloves should be taped or sealed to the protective suit sleeves.

6.1.4 Wearing 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 in order to prevent the operators from inhaling air from within the facility. Personnel should be appropriately trained and assessed in the use of these systems before entering 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.

6.2.1 There should be 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 operator comfort with respect to temperature and humidity. 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 to the system.

6.2.2 A self-contained breathing apparatus (SCBA) or powered air purifying respirator (PAPR) that is secured 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.

6.2.3 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, the 8-hour PAS and the respirator-certified protection factor (PF).

6.4 The air supplies shall be filtered through a final filter, which should be a HEPA filter rated as an H13 filter according to EN 1822 (European Norm). The breathing air supply 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 event of the main system failing. This could be in the form of a gas bottle system with at least five minutes supply. Change over from the normal supply to back-up supply should be automatic. The system should have a monitoring system and send alarm signals to a permanently manned position in the following situations:

- 6.5.1 main air supply failure;
- 6.5.2 temperature out of specification (OOS);
- 6.5.3 humidity OOS;
- 6.5.4 carbon dioxide (CO₂) OOS;
- 6.5.5 carbon monoxide (CO) OOS; and
- 6.5.6 sulfur dioxide (SO₂).

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.

7. AMBIENT PROTECTION

7.1 Due to the hazardous nature of the products being handled in the facility, the product should not be allowed to escape into the atmosphere or to be discharged down drains.

7.2 The external atmosphere and public external to 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. *(Note: This aspect is not specifically related to product quality and, therefore, falls outside the scope of this guideline and should be handled as an environmental protection programme.)*

7.4 Exhaust air filtration relating to airborne environmental protection is discussed under Section 11.

8. FACILITY LAYOUT

8.1 The premises should be designed and constructed to prevent the ingress or egress of contaminants.

8.2 The link between the premises' interior and exterior should be through airlocks (PAL and/or MAL), change rooms, pass boxes, pass-through hatches, 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 change rooms should have an arrangement with step-over-bench. The ablutions on the exit side should incorporate showers for the operators.

8.4 The premises' layout and design should be such 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) so 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 penetrations.

8.11 The facility should be maintained at a negative air pressure 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 principals 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 (WHO Technical Report Series, No. 937).

9.3 Hazardous substance facilities and premises should have the following basic air-handling characteristics.

9.3.1 The absence of direct venting of air to the outside.

9.3.2 Air-conditioning/ventilation resulting 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.

9.3.3 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.

9.3.4 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.

9.3.5 The air pressure cascade within the facility, although negative pressure to environment, should comply with normal pharmaceutical pressure cascade requirements with regards to product protection, dust containment and personnel protection.

9.3.6 Visual indication of the status of room pressures should be provided in each room.

9.3.7 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 mentioned in this guideline, they refer to HEPA filters with a minimum rating of H13 according to EN 1822.

9.3.8 Where possible, single-pass air-handling systems with no recirculation should be provided.

9.3.9 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.

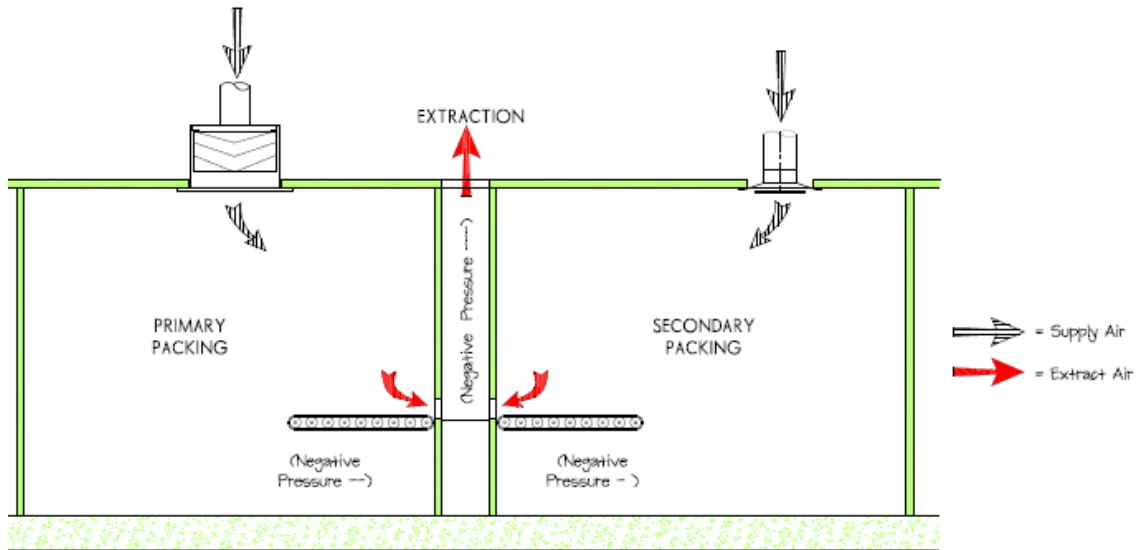
9.3.10 Changing rooms should be supplied with air filtered to the same standard as that for the work area they serve.

9.3.11 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, air lock or pass-through hatch bordering on an external or non-GMP area should be at a positive pressure to prevent the ingress of contaminants into the facility.

9.3.12 Operators leaving the containment area should pass through a decontamination system, e.g. air showers or mist dust control system, to assist with removing or controlling dust particles on operator 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 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.)*

Figure 1. Typical airflow pattern for contaminant



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

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, cleanroom 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 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 Annex 2 of the fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2006 (WHO Technical Report Series, No. 937), 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 determined by a risk assessment study.

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 cleanroom classification of the facility.

10.6 All ventilation, AHU and exhaust fans should be started and stopped in the correct sequence to ensure that a negative pressure is maintained during power-up and power-down.

10.7 For an emergency shut-down (e.g. total power failure) an automatic shut-off damper should be located in the supply air stream to ensure the rate of decline of the supply air quantity, relative to the exhaust air quantity, ensures that the facility is maintained at a negative pressure.

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.

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 able to be removed 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 life span 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 in order 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

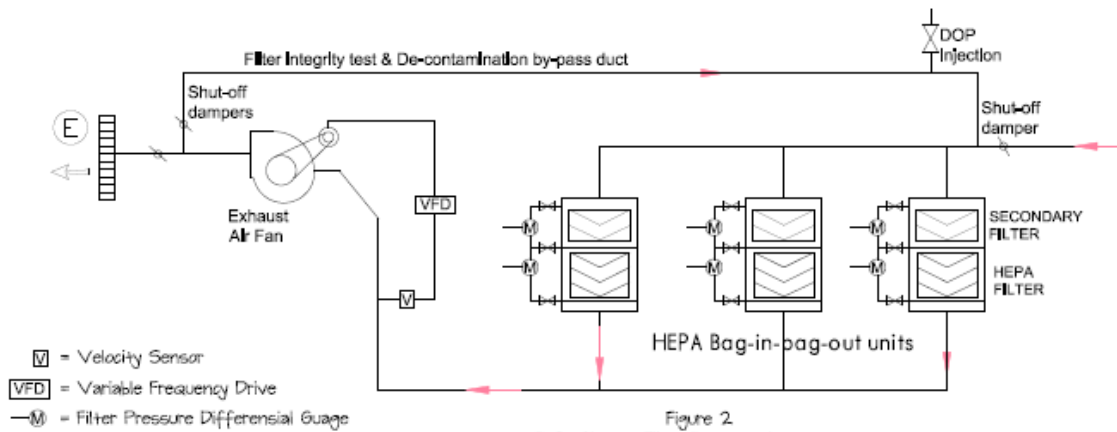
11.7 Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.

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 detailed 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 in Figure 2 also permits decontamination of the filters by means of circulation of a sanitizing agent.

Figure 2. Safe change filter bypass arrangement



11.11 All exhaust systems from the facility, including dust extract systems, vacuum system exhaust, fluid bed drier exhaust, coating pan exhaust, etc., 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 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 dust removal 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 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 A means of preventing contaminants from leaving the facility on personnel garments 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 extract 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 additionally flush contaminants away.

Air filtration on the supply air and return/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 showers for personnel could be used at material exits to assist with removing contaminants.

12.4 Wet mist/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 A normal water shower can be used with personnel changing into clean garments after the shower.

13. EFFLUENT TREATMENT

13.1 Liquid and solid waste effluent should be handled in a manner so as not to present a product, personnel or environmental contamination risk.

13.2 All effluent should be disposed 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. Refer to Annex 2 of the fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2006 (WHO Technical Report Series, No. 937, section 8.3 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.

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