



MINISTRY OF HEALTH  
SINGAPORE

# **GUIDELINES FOR THE CONDUCT OF STERILE PHARMACEUTICAL SERVICES IN HEALTHCARE INSTITUTIONS**

**Developed by  
Pharmaceutical Standards Working Committee**

**26 September 2016**

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## EXPLANATORY NOTE

**Sterile pharmaceutical activities** refer to compounding and reconstitution of sterile pharmaceutical products.

## GLOSSARY OF TERMS

Anteroom	An area providing space for hand washing, garbing, and product decontamination; it also serves as a way to further segregate the cleanroom from other, less-clean areas of the facility.
Batch	Preparing a number of non-patient specific doses, with the same characteristics and quality, with the intention to use based on future patient need.
Beyond-Use Date (BUD)	The date beyond which the product cannot be used and must be discarded. The BUD is determined from the time the CSP is compounded. (This includes the in-use time of the CSP.)
Broth transfer/ media fill test	A simulation used to qualify processes and personnel engaged in sterile compounding to ensure that the processes and personnel are able to produce CSPs without microbial contamination.
Cleanroom	An area where a primary engineering control (PEC) is located and where activities such as preparation, compounding, and staging of compounded sterile preparations (CSPs) occur. This area should provide adequate space for the PEC and may include a limited amount of shelving and/or carts for staging of compounding.
Classified area	Classified area is a space that maintains air cleanliness classification based on the International Organisation for Standardisation (ISO Class- See Appendix I). Examples include anteroom and cleanroom.
Compounded sterile preparation	A sterile preparation that is created by combining, diluting, pooling, or otherwise altering a drug product or bulk drug substance.
Hazardous Drugs	Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity in humans, organ toxicity at low dose in humans or animals, genotoxicity, or new drugs that mimic hazardous drugs in structure or toxicity. Institutions can refer to the list of antineoplastic and other hazardous drugs published by the National Institute for Occupational Safety and Health (NIOSH) to identify a hazardous drug. < <a href="http://www.cdc.gov/niosh/pubs/all_date_desc_nopubnumbers.html">http://www.cdc.gov/niosh/pubs/all_date_desc_nopubnumbers.html</a> >

Microbial testing	The microbial tests used for finished product testing are sterility and bacterial endotoxin tests.
Primary engineering control (PEC)	A ventilated device that provides an ISO Class 5 environment for sterile compounding. Examples include laminar air flow workbench (LAFW), biosafety cabinet (BSC), restricted access barrier system (RABS) and isolator.
Reconstitution	The process of dissolving or dispersing a medicinal product in, or diluting or mixing it with some other substance resulting in sterile solution or suspension as a vehicle for administration.
Settle plate	Suitable container (e.g. Petri dish) of appropriate size, containing an appropriate, sterile, culture medium which is left open for a defined period of time to collect viable particles from the surrounding air.
Starting materials	A substance, used for the preparation of a medicinal product, excluding packaging material.
Sterility testing	A documented and established laboratory procedure for detecting viable microbial contamination in a sample or preparation.
Total parenteral nutrition	Intravenous feeding that provides patients with all the fluid and the essential nutrients they require when they are unable to feed by mouth.

## ABBREVIATIONS

Abbreviation	
ACPH	Air Changes Per Hour
ACD	Automated Compounding Device
BSC	Biosafety Cabinet
BUD	Beyond-Use Date
CACI	Compounding Aseptic Containment Isolator
CSP	Compounded Sterile Preparation
CSTD	Closed System Transfer Device
FDA	Food and Drug Administration
IM	Intramuscular
ISO	International Organization for Standardization
IV	Intravenous
LAFW	Laminar Air Flow Workbench
PEC	Primary Engineering Control
PPE	Personal Protective Equipment
RABS	Restricted Access Barrier System
SC	Subcutaneous
SCA	Segregated Compounding Area
SOP	Standard Operating Procedure

## **PREFACE**

Currently, there are no existing measures to govern the compounding of sterile preparations in healthcare institutions (HCIs). In view of this, the Pharmaceutical Standards Working Committee was appointed by Director of Medical Services, Ministry of Health (MOH) in October 2014, to review existing practices.

2 The Committee comprised pharmacists from public and private hospitals, and medical doctors from private practice and it studied existing practices, identify gaps and challenges and developed the relevant guidelines for sterile pharmaceutical activities across HCIs.

3 The guidelines cover areas pertaining to the aspects of compounded sterile preparations, including personnel, facilities, transport and processes involved to produce a sterile medicinal product. HCIs conducting sterile compounding activities are encouraged to adopt the recommendations in the guidelines as good compounding practice, so as to achieve safer and better quality of sterile compounded preparations.

4 MOH also held a series of stakeholder consultations on the proposed guidelines. The Committee subsequently deliberated on the comments and feedback received from the consultation sessions, and revised the Guidelines where appropriate.

5 The Committee is pleased to be given this opportunity to contribute to the development of practice standards for sterile pharmaceutical activities in HCIs and looks forward to the implementation of this set of guidelines.

Associate Professor Benjamin Ong  
Director of Medical Services  
Ministry of Health  
26 September 2016

## CHAPTER 1: RISK ASSESSMENT

Failure to achieve and/or maintain sterility of compounded sterile preparations (CSPs) can lead to serious harm, including death. It is therefore important to evaluate the risks associated with the sterility of the CSP before starting on the activity. The trained personnel should classify CSPs into Category 1, Category 2 and Immediate-use based on the intended beyond-use date (BUD) of the finished product, so as to determine the type of facility requirements needed for the preparation. If the facility requirements cannot be met, the BUD of the product should be re-assigned accordingly. The BUD should be promptly labelled on the finished product upon completion. Aseptic technique should be strictly adhered to for all risk categories.

The table below provides a summary of the preparation requirements for each risk category of CSP and the BUD to assign respectively:

**Table 1:** Risk categorisation based on BUD and the facility requirements for non-hazardous CSPs

	Immediate-use	Category 1	Category 2
<b>BUD assignment</b>	For immediate administration upon completion of preparation	<ul style="list-style-type: none"> <li>• Less than or equal to 12 hours at room temperature (20°C—25°C)</li> <li>• Less than or equal to 24 hours if refrigerated (2°C—8°C)</li> </ul>	<ul style="list-style-type: none"> <li>• More than 12 hours at room temperature (20°C—25°C)</li> <li>• More than 24 hours if refrigerated (2°C—8°C)</li> </ul>
<b>Examples<sup>^</sup></b> <i><sup>^</sup>To consult a pharmacist or personnel trained in sterile compounding for greater clarity.</i>	Administration of intravenous (IV)/ subcutaneous (SC)/ intramuscular (IM) admixtures	<ul style="list-style-type: none"> <li>• CSPs with no stability data or with short shelf lives</li> <li>• IV antibiotics e.g. Penicillin G, Cefazolin, Piptazobactam, Vancomycin</li> </ul>	<ul style="list-style-type: none"> <li>• Compounded total parenteral nutrition</li> <li>• Compounded admixtures (with reference to published stability data)</li> <li>• Extemporaneous eyedrops (with stability data)</li> <li>• Elastomeric pumps (with stability data)</li> </ul>

	Immediate-use	Category 1	Category 2
<b>Facility requirements</b>	Nil	<ul style="list-style-type: none"> <li>• Prepared in primary engineering containment (PEC) placed in a non ISO-controlled segregated compounding area (SCA)</li> <li>• Cleanroom is not required</li> <li>• SCA to have airflow of at least 12 air changes per hour (ACPH)</li> </ul>	<ul style="list-style-type: none"> <li>• Prepared in PEC placed in an ISO Class 7 cleanroom</li> <li>• Cleanroom to have airflow of at least 30 ACPH</li> </ul>





**Table 2:** Risk categorisation based on BUD and the facility requirements for hazardous CSPs

	<b>Immediate-use</b>	<b>Category 1</b>	<b>Category 2</b>
<b>BUD assignment</b>	For immediate administration upon completion	<ul style="list-style-type: none"><li>• Less than or equal to 12 hours at room temperature (20°C—25°C)</li><li>• Less than or equal to 24 hours if refrigerated (2°C—8°C)</li></ul>	<ul style="list-style-type: none"><li>• More than 12 hours at room temperature (20°C—25°C)</li><li>• More than 24 hours if refrigerated (2°C—8°C)</li></ul>
<b>Examples<sup>^</sup></b> <i><sup>^</sup>To consult a pharmacist or personnel trained in sterile compounding for greater clarity.</i>	Pre-diluted drugs intended to be administered immediately with established stability data	Pre-diluted drugs intended to be administered within 12 hours with established stability data	Pre-diluted drugs intended to be administered after 12 hours with established stability data
<b>Facility requirements</b>	<ul style="list-style-type: none"><li>• Prepared in PEC placed in a non ISO-controlled SCA</li><li>• Cleanroom is not required</li><li>• PEC should be <i>externally vented</i>*</li><li>• SCA to have airflow of at least 12 ACPH</li></ul>		
	<p><i>*If external venting is not possible, the following should be adopted:</i></p> <ul style="list-style-type: none"><li>• Use of FDA approved <u>closed system transfer devices</u> (CSTD) during preparation;</li><li>• Increase ACPH of room; <u>and</u></li><li>• Ensure frequency of PEC maintenance of at least every 6 months</li></ul>		

## CHAPTER 2: PERSONNEL

### PRINCIPLE

*There should be sufficient and competent personnel to carry out all aseptic activities. Personnel should be aware of their responsibilities and the protocols that are put in place by their institution.*

*Personnel should receive orientation and training when new to sterile compounding. Regular continuing education and audits on skills should be made available to ensure staff skills are valid and current.*

### 2.1 Duties and Responsibilities

- 2.1.1 All personnel shall observe the policies, procedures and operational guidelines for all preparations and in packaging and labelling of medications.
- 2.1.2 The duties and responsibilities of all personnel involved in aseptic dispensing should be documented in a job description and be clearly defined.
- 2.1.3 There should be a registered healthcare professional as the person-in-charge for overseeing the quality of the prepared medicinal products, for compliance to guidelines and standard operating procedures (SOPs) set in place by the institution.
- 2.1.4 The person-in-charge should supervise the compounding and dispensing of CSPs on a daily basis and take immediate corrective action if deficient practices are observed.
- 2.1.5 Specific duties may be delegated to appropriately trained and validated competent personnel to handle CSPs (e.g. Pharmacy Technician or Nurses).



#### Access to Hazardous Substances

- 2.1.6 *Access to hazardous substances shall be placed under the charge of a competent person who has adequate knowledge of the properties of the hazardous substances and their risks.*

## 2.2 Training and Validation Requirements

- 2.2.1 Each compounding facility should develop a training program that describes the objectives, training and the process for evaluating the performance of individuals involved in sterile compounding.
- 2.2.2 This program should equip personnel with the appropriate knowledge and train them in the required skills necessary to perform their assigned tasks.
- 2.2.3 Records of training and validation testing received should be clearly documented as training record for each personnel.

### New Personnel

- 2.2.4 New personnel must complete training and be able to demonstrate proficiency in the theoretical principles and hands-on skills for sterile manipulations. The theoretical principles include knowledge of products, stability, sterility, microbiology, particulate contamination, pharmaceutical calculations, incompatibilities and infection control practices.
- 2.2.5 The hands-on training should cover core competencies listed in Appendix II-A.
- 2.2.6 Newly recruited personnel should also receive training in other areas that are defined in their job scopes.
- 2.2.7 All new personnel must pass initial validation tests before they are allowed to prepare CSPs in the institution. The recommended types of validation tests include the following:
  - (i) visual observation of hand hygiene and garbing procedures;
  - (ii) gloved fingertip sampling; and
  - (iii) media-fill testing.



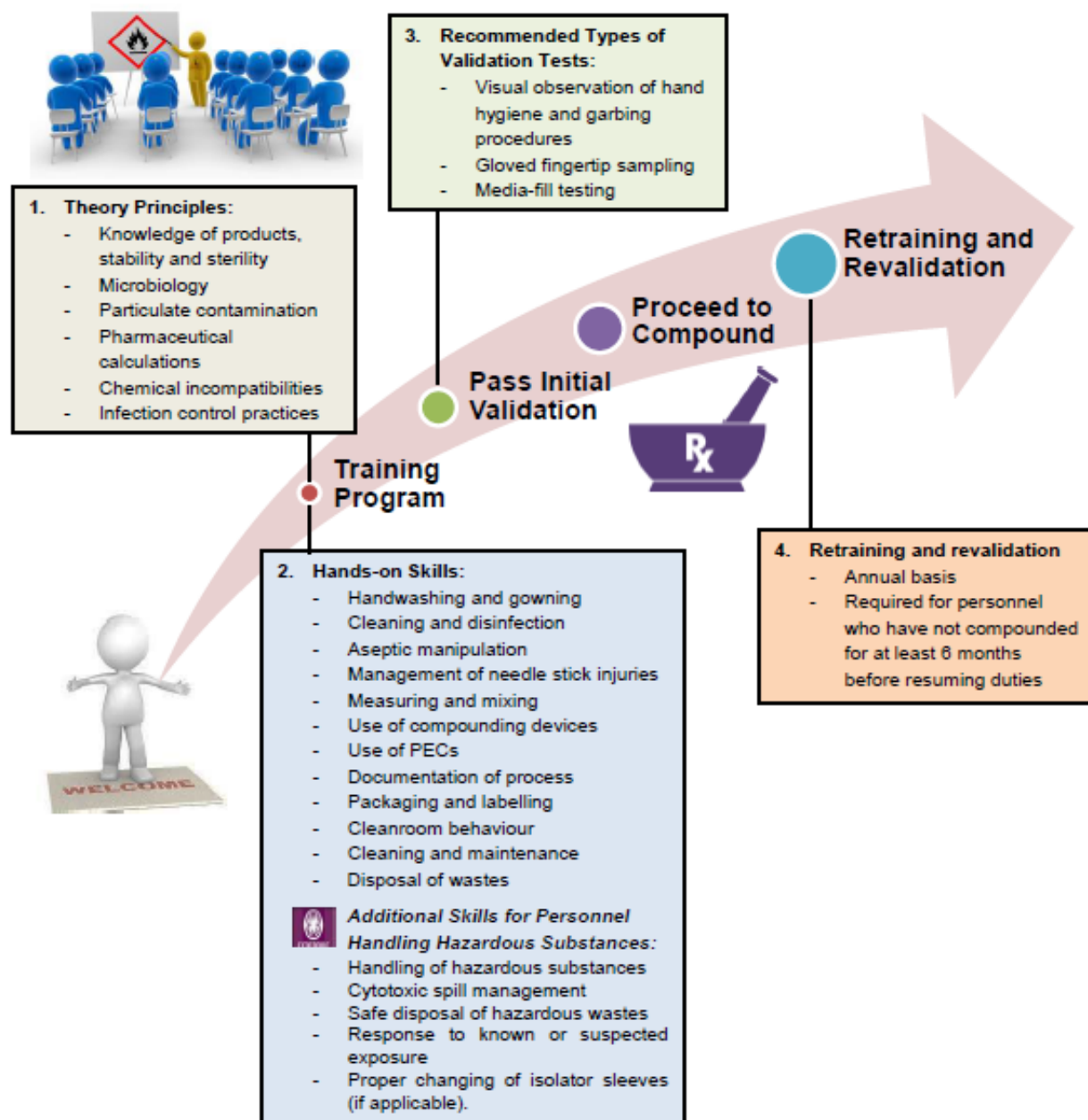
### **New Personnel Handling Hazardous CSPs**

- 2.2.8 *Personnel dealing with hazardous drugs should be familiar with the institution's list of hazardous drugs and their risks, and the SOPs for handling hazardous drugs. The additional competencies required of new personnel involved in hazardous preparations are listed in Appendix II-B.*

### Retraining and Revalidation

- 2.2.9 Compounding personnel should undergo refresher training to be revalidated in the core competencies listed in Appendix II-A at least on an annual basis.
- 2.2.10 Personnel who have not compounded CSPs in more than 6 months must be revalidated in all core competencies for sterile compounding before resuming compounding duties.v

**Diagram 1:** Training and Revalidation Requirements for Sterile Compounding



## 2.3 Workplace Safety and Health

- 2.3.1 Personnel should notify the Supervisor about infectious diseases such as upper respiratory tract infections and open lesions on the exposed surface of the body. The supervisor should also be informed if personnel is feeling unwell or is taking medications that may cause drowsiness.
- 2.3.2 The supervisor should make the decision whether the personnel is deemed suitable to carry out preparation activities without risk to himself/ herself and the sterility of the preparations.
- 2.3.3 Every institution should establish a Workplace Health Program to address aspects concerning risk assessments and incident reporting process for occupational hazards.



### Workplace Health for Personnel Handling Hazardous CSPs

- 2.3.4 *The Workplace Health Program instituted for personnel handling hazardous CSPs should include monitoring of personnel exposure to hazardous substances and routine health examination. These should comply with requirements under the Workplace Safety Health Act. An extract of the requirements can be found in Appendix II-C.*

## CHAPTER 3: PROTOCOLS AND TECHNIQUES

### PRINCIPLE

*Process requirements and common procedures should be clearly defined in institution-specific policies and guidelines. These standard operating procedures should be made available to all personnel for strict adherence so as to ensure a safe and effective working environment. All personnel should also adhere to various essential techniques and good practices during preparation to ensure the quality of compounded products.*

### 3.1 Standard Operating Procedures (SOPs)

- 3.1.1 There should be policies, SOPs and operational guidance to lay out the institutional requirements on personnel and essential procedures, as listed in Appendix III-A.
- 3.1.2 All SOPs should be assessed and verified by person-in-charge. It should be reviewed at least every 3 years.
- 3.1.3 Any deviation from SOPs would require the approval of the person-in-charge and should be duly documented.
- 3.1.4 Compounding personnel must be able to immediately recognise problems, deviations or errors from SOPs and promptly report to the person-in-charge to follow up and take corrective actions.



#### SOP for Handling Hazardous CSPs

- 3.1.5 *Material safety data sheets should be maintained on the safe use and disposal of all hazardous substances.*
- 3.1.6 *There should be SOPs on the handling and management to known or suspected exposure to hazardous substances.*

### 3.2 Infection Control

- 3.2.1 Infection control principles should be incorporated into every aspect of the sterile compounded process and included in the SOPs and training.
- 3.2.2 There should be a process to identify and escalate situations which require infection control specialists to be consulted to assist in formulating an appropriate response.

- 3.2.3 All institutions and providers should comply with infection prevention and control safeguards during compounding, such as correct aseptic techniques, using only disposable needles and the use of the same needle *only* when compounding one unit of the same drug belonging to a patient (not applicable for batch compounding).

### 3.3 Gowning and Hand Hygiene

#### Personal Hygiene

- 3.3.1 Before entering a designated compounding area (SCA and cleanroom), compounding personnel should:
- (i) remove personal outer garments (e.g., coats, jackets, scarves, headscarves sweaters);
  - (ii) remove all cosmetics because they shed particles;
  - (iii) remove all hand, wrist, and other exposed jewellery (e.g., rings, watches, bracelets) as these can harbour microorganisms or interfere with hand washing or the proper fitting of PPE;
  - (iv) keep nails clean and neatly trimmed (remove nail polish, artificial nails, and extenders);
  - (v) ensure coverage of facial hair (i.e. beards and moustaches) with a face mask/ beard cover.
- 3.3.2 PPE for cleanroom should be donned and removed in a prescribed manner as listed in Appendix III-B.
- 3.3.3 Disposable PPE should be changed each time the personnel leaves the SCA or cleanroom.
- 3.3.4 Specifications on PPE can be found in Appendix III-C.



#### Gowning Requirements for Handling Hazardous CSPs

- 3.3.5 *PPE for hazardous preparations should be made of material impermeable to hazardous drug spills (refer to Appendix III-C).*
- 3.3.6 *Personnel should change PPE immediately after a spill or splash when working with hazardous substances.*

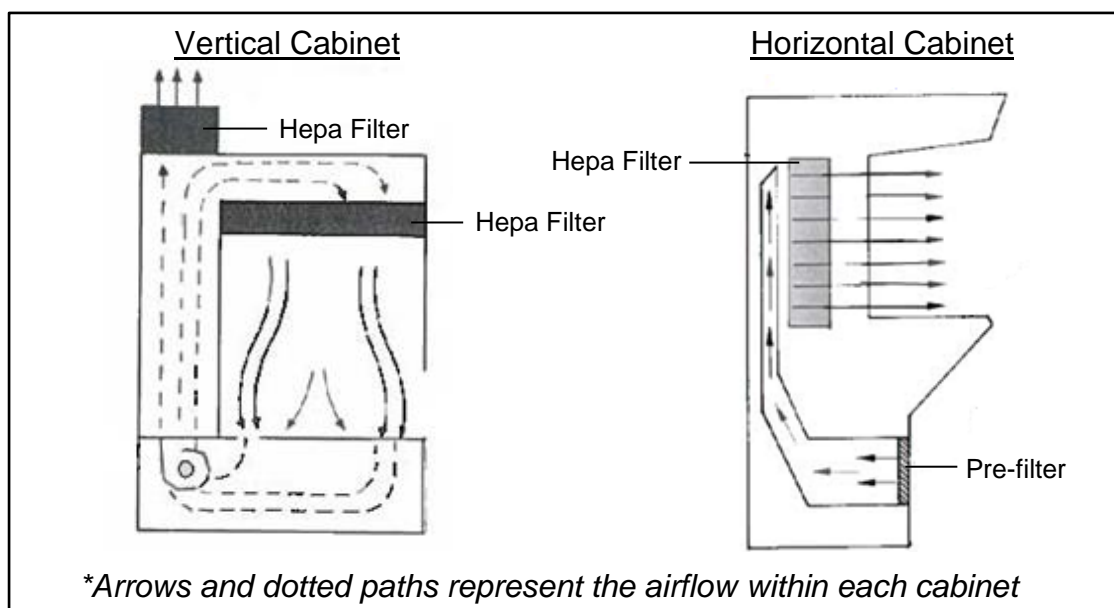
### 3.4 General Aseptic Practices

- 3.4.1 Food or drinks should not be brought into or stored in the SCA or cleanroom.
- 3.4.2 Access to the SCA or cleanroom should be restricted to qualified personnel with specific responsibilities or assigned tasks.



- 3.4.3 All supplies to be brought into the cleanroom should be wiped and surface disinfected with 70% sterile isopropyl alcohol. Objects that shed particles should not be brought into the cleanroom, e.g. pencils, cardboard cartons, paper towels or cotton items.
- 3.4.4 There should be proper disinfection of work surfaces with 70% sterile isopropyl alcohol before and after work. Regular disinfection of work surface and gloved hands during preparation should also be done.
- 3.4.5 Personnel should avoid touching critical surfaces e.g. rubber closures of container, syringe or needle tips which come in contact with the CSP and should be maintained sterile.
- 3.4.6 Upon turning on the PEC, it should be left running for a minimum of 15 minutes and disinfected before use. The air supply in the PEC should be turned on at all times during preparation.
- 3.4.7 An unobstructed airflow should be maintained between the cabinet HEPA filter and the area where aseptic manipulations are performed.

**Diagram 2:** Airflow within a Vertical and Horizontal Cabinet



Adapted from: GlobalRPh on Aseptic Technique <<http://www.globalrph.com/aseptic.htm>>

- 3.4.8 Only objects required for the preparation should be placed in the PEC. Avoid excessive movements in the PEC so as to minimise turbulence and introduction of contaminated air.
- 3.4.9 There should be a procedure in place for handling Live Vaccines. The recommended SOP is in Appendix III-D.





### Technique for Handling Hazardous CSPs

3.4.10 *Use of syringes with Luer-Lock fittings and FDA approved CSTDs are recommended when preparing hazardous CSPs.*

## 3.5 Waste Disposal

3.5.1 All waste products should be collected in suitable plastic bags and removed on a daily basis at the end of the working session.

3.5.2 Disposal of waste products should be in accordance to NEA Guidelines.

3.5.3 All sharps and needles should be disposed of in a puncture and tamper resistant container.



### Disposal of Hazardous Wastes

3.5.4 *All waste products generated from the compounding of hazardous CSPs should be treated as hazardous wastes.*

3.5.5 *There should be a sharps bin designated for sharps/ needles contaminated with hazardous substances. The sharps bin should be clearly labelled and disposed of in the same manner as for hazardous wastes.*

3.5.6 *All non-reusable PPE worn when handling hazardous drugs are considered to have been contaminated with hazardous drugs and should be disposed as hazardous wastes.*

3.5.7 *Hazardous wastes should be disposed of in bags designated for hazardous waste disposal. The bags must be securely fastened, segregated from other wastes and disposed of by a licensed waste contractor approved by NEA.*

## 3.6 Spills

3.6.1 All spills and breakages should be cleaned up immediately by personnel trained in the appropriate procedures.



### Hazardous Spills

3.6.2 *A clearly labelled hazardous spill kit should be kept in all areas where hazardous CSPs are received, prepared, administered or stored.*

3.6.3 *Spills of an unknown nature must be handled using hazardous spill procedures.*

## CHAPTER 4: FACILITIES AND EQUIPMENT

### PRINCIPLE

*Facilities and equipment should be suitable for the intended activities and prevent airborne contamination of the CSPs. There should be regular cleaning and maintenance of all facilities and equipment. Environmental monitoring must be routinely performed and documented to prove that the compounding environment is properly maintained.*

#### 4.1 Facility Requirement (*For Category 1 and 2 CSPs<sup>1</sup>*)

##### Segregated Compounding Area (SCA)

- 4.1.1 PECs used to compound category 1 CSPs may be placed in an unclassified SCA that is not ISO controlled.
- 4.1.2 The SCA should avoid conditions that could adversely affect operations of the PEC e.g. strong air current from opened doors or personnel traffic. It must not be located adjacent to construction sites, warehouses, food preparation areas or other environmental control challenges e.g. sinks, water pipes, sewer pipes.
- 4.1.3 Sinks for hand washing should be located at least 1m away from the SCA.

##### Cleanroom

- 4.1.4 All category 2 CSPs should be prepared in a PEC located within an ISO Class 7 cleanroom.
- 4.1.5 Only equipment and supplies required for the tasks to be performed should be placed in the cleanroom.
- 4.1.6 Surfaces of ceilings, walls, floors, fixtures, carts, shelving, counters and cabinets in the cleanroom should be smooth, impervious, free from cracks and crevices, non-shedding and resistant to sanitizing agents.
- 4.1.7 The cleanroom should not contain sinks or floor drains.
- 4.1.8 The cleanroom should not be used for purposes other than sterile pharmaceutical activities.

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<sup>1</sup> Urgent-use CSPs can be prepared on a sterilised counter/ bench-top but good aseptic techniques should be strictly adhered to.

## Anteroom

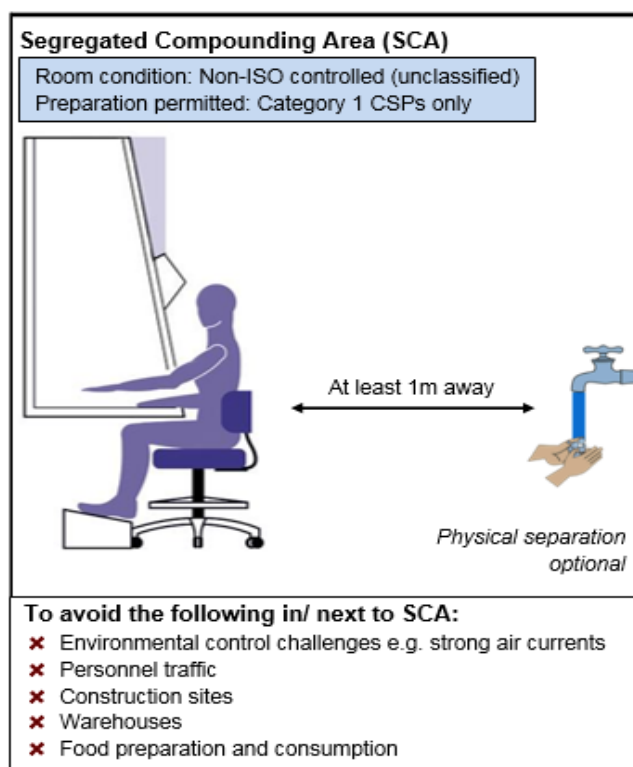
- 4.1.9 There should be an anteroom next to but separated from the cleanroom.
- 4.1.10 The anteroom should be maintained at an ISO Class 8 environment. The room can be used for gowning, hand washing and emergency rinse purposes.



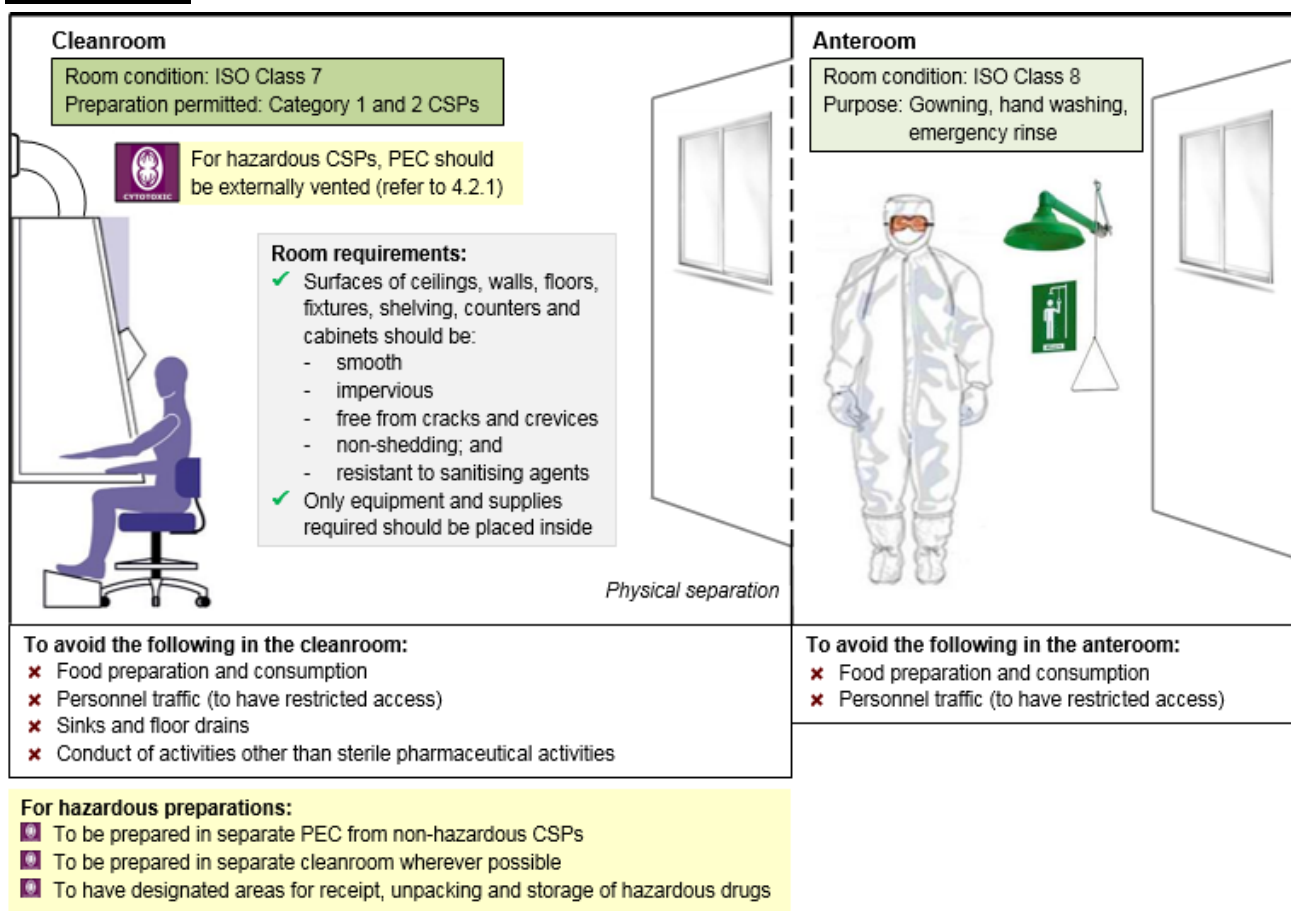
### **Additional Facility Requirements for Hazardous CSPs**

- 4.1.11 PECs and background environment for handling hazardous CSPs should be externally vented, wherever possible. If this is not possible, alternative precautions should be adopted, including the use of CSTDs during preparations, increasing the ACPH of the room, and doing half-yearly checks on the integrity of HEPA filters (see Table 2 of Chapter 1).
- 4.1.12 Upon turning on the PEC, it should be left running for a minimum of 15 minutes before and after use and disinfected before work commencement. The air supply in the PEC should be turned on at all times during preparation. The PEC should be decontaminated and cleaned thoroughly after work is completed.
- 4.1.13 The environment should be maintained at a negative pressure differential in relation to its surroundings.
- 4.1.14 Hazardous CSPs should be prepared in separate PECs and wherever possible, in a separate room from non-hazardous CSPs preparation area, unless the non-hazardous CSP is for a patient who is also using hazardous drugs.
- 4.1.15 There should be designated areas for the receipt, unpacking and storage of hazardous drugs.
- 4.1.16 A sink for emergency access to water should be made available for removal of hazardous substances from eyes and skin in the event of an accidental exposure.

**Diagram 3a: Segregated Compounding Area**



**Diagram 3b: Cleanroom/ Anteroom**



## 4.2 Cleaning Requirements

- 4.2.1 Cleaning and sanitisation of facilities and equipment within the cleanroom and anteroom should be duly performed with an appropriate disinfectant at its recommended frequency (refer to Table 1 of Appendix IV-A).
- 4.2.2 The selection and use of disinfectants should be guided by the germicidal activity, inactivation by organic matter, residue and shelf-life. Sporocidal agents should be used at least weekly for cleaning. Choice of cleaning and disinfection products should be approved by the organisation's appropriate authority (e.g. the Infection Control Committee).
- 4.2.3 If there is evidence of resistant strains, a different type of disinfectant should be used.
- 4.2.4 Cleaning activity should be carried out during a time when no aseptic preparation taking place.
- 4.2.5 There should be designated cleaning tools for cleanroom as well as anteroom. Tools (e.g. rags, sponges and mops) used to clean the cleanroom should be non-shedding. There should also be a separate set of cleaning tools for areas involved in the preparation of hazardous products.



### Cleaning of Facilities for Hazardous Preparations

- 4.2.6 *Areas where hazardous CSPs are handled should be routinely deactivated/ decontaminated (see methods of cleaning Table 2 of Appendix IV-A).*

## 4.3 Environmental Quality Control

- 4.3.1 Sterile pharmaceutical facilities should be established initially using environmental air and surface sampling to establish a baseline level of environmental quality. Surface sampling provides a snapshot of the effectiveness of disinfection procedures (including technique and cleaning products) and must be part of the overall quality assurance plan.
- 4.3.2 Thereafter, a monitoring system should be established to maintain and ensure constant environmental conditions within the facility— both in the PEC and the cleanroom. Aspects to be monitored are listed in Appendix IV-B.
- 4.3.3 In-house environmental monitoring should include both physical and microbial monitoring (refer to Table 1 in Appendix IV-B). There should be an annual physical inspection of the walls, floors, ceiling, doors and glass panels of the work area/ rooms.

- 4.3.4 Institutions should engage external vendors to conduct monitoring through certification tests of its facilities at frequencies listed in Table 2 of Appendix IV-B.
- 4.3.5 Facilities must be recertified if there are changes to the area such as redesign, construction, replacement or relocation of PEC, or alteration in the configuration of the room that could affect airflow and air quality.
- 4.3.6 All in-house monitoring and certification tests done by external vendors should be duly documented and the records kept for at least 3 years.
- 4.3.7 Prompt corrective action in response to any adverse data should be taken (refer to Table 3 and 4 of Appendix IV-B for the action levels for air sampling and surface sampling respectively).
- 4.3.8 Evaluation should be done following corrective actions to confirm that the actions taken have been effective in maintaining the environmental quality.

#### **4.4 Equipment**

- 4.4.1 Equipment, apparatus and devices used to compound CSPs should be maintained in good operating conditions and fit for immediate use at all times.
- 4.4.2 Manufacturer recommendations should be followed for equipment calibration, maintenance, monitoring for proper function, and controlled procedures for use of the equipment. Written procedures shall specify a time interval for CSP-related equipment maintenance activities.
- 4.4.3 Refrigerator, freezer temperatures should be checked daily and recorded.
- 4.4.4 Equipment problems should be promptly addressed.
- 4.4.5 Availability of a back-up emergency power supply during power failure is recommended to ensure that temperatures remain constant in all freezers and refrigerators.

## CHAPTER 5: QUALITY CONTROL IN PRODUCTION

### PRINCIPLE

*There should be proper documentation on all operations during the preparation, (including information on the starting materials), intermediate products and all calculations and readings of intermediate steps. Finished products should be labelled and verified promptly according to good dispensing practices. All finished products should be stored and transported according to protocols stipulated.*

### 5.1 Starting Materials and Intermediate Products

- 5.1.1 All starting supplies, including any intermediate product, should be clearly labelled with the date of first opening and expiry, and stored according to manufacturer requirements.
- 5.1.2 Expiry date of all materials should be checked before use.
- 5.1.3 A visual inspection of starting materials should be performed to ensure that the ingredient appears to be what it is represented to be; and the batch examined for evidence of deterioration and other aspects of unacceptable quality.
- 5.1.4 Any ingredient found to be of unacceptable quality should be promptly rejected with clear labels, and segregated to prevent their use before appropriate disposal.
- 5.1.5 Qualitative and quantitative information of all materials used should be documented (e.g. batch number for reference).
- 5.1.6 Information on all operations during the preparation should also be documented and verified against the medication order (e.g. weighing, yields of intermediate steps, dilution, dosage calculations and sequence of addition).

### 5.2 Good Dispensing Practices

- 5.2.1 Finished products should be labelled immediately upon completion with the following details:
  - (i) Details of CSP including name and strength of drug, final volume prepared, date of preparation and/or beyond-use date.



- (ii) Details of patient to be administered including name and identification number of patient as well as ward and bed number (if applicable).
  - (iii) Details of instructions for administration, including route of administration, infusion period and other cautionary labels e.g. 'refrigerate' or 'protect from light'.
- 5.2.2 Details of finished products should be verified by another trained personnel against the medication order.
- 5.2.3 A visual inspection should be done on the finished product to identify any apparent physical defect, visible particulates or discoloration. Pre-release inspection should also include a visual inspection of container-closure integrity (e.g. leakage or cracks in containers).
- 5.2.4 Light sensitive CSPs must be placed in a light proof bag.



#### **Hazardous Finished Product**

- 5.2.5 *All finished hazardous CSPs should be placed in sealed bags and clearly labelled as "Hazardous" before being dispensed.*

### **5.3 Storage of Finished Products**

- 5.3.1 CSPs should be refrigerated at 2-8°C when the preparation is not immediately dispensed or administered, unless the chemical and physical stability of the CSPs are adversely affected by the refrigerated temperature.
- 5.3.2 Storage areas should be verified daily to ensure that such spaces are not subject to prolonged temperature fluctuations.
- 5.3.3 If a CSP has been exposed to temperatures that exceed storage temperature limits, the CSP should be evaluated to determine if the CSP is still suitable for use.
- 5.3.4 All CSPs should only be stored for as long as the intended BUD according to its content and preparation method. Routine stock-take should be in place to ensure the timely disposal of expired CSPs.

### **5.4 End Product Testing (Applicable only to Category 2 CSPs)**

- 5.4.1 End product sterility testing and bacterial endotoxins testing should be performed, wherever possible, for open-system transfer preparations (e.g. batch CSPs) or preparations compounded using non-sterile ingredients (e.g. concentrated morphine solutions prepared using powdered ingredients).
- 5.4.2 BUD periods for category 2 CSPs can be further assigned based on sterilisation condition, sterility testing and addition of preservatives (refer to Appendix V-A).



## 5.5 Transport of Finished Product

- 5.5.1 For finished products to be transported out of pharmacy, the type of packaging used, handling method, storage and transport processes should be appropriate so as to maintain the physical integrity, sterility, and stability of the products.
- 5.5.2 The instructions on storage of the CSP should be clearly labelled on the outer packaging.
- 5.5.3 The transport processes of finished products and delivery performance of personnel should be periodically reviewed for effectiveness.



### Transport of Hazardous CSPs

- 5.5.4 *Appropriate safeguards such as sealed plastic bags and leak-proof containers with cautionary labels should be used for transporting hazardous CSPs.*
- 5.5.5 *There should be adequate training for delivery personnel responsible for the handling, transport and storage of CSPs released out of the pharmacy. Training should include spills management and handling of hazardous substances.*

## 5.6 In-use Times of CSPs

- 5.6.1 The in-use times of CSPs after it has been opened or needle-punctured should not exceed the BUD assigned.

## CHAPTER 6: WORK CONTRACTED OUT

### PRINCIPLE

*There should be technical service level agreements for all services that are contracted out to another department or organisation. The agreement should specify details of the work to be done, the specifications it should meet and responsibilities of each party. The agreement should be authorised and signed by both parties.*

### 6.1 Service Requirements and Specifications

- 6.1.1 Service level agreements should be made available for all services concerning sterile pharmaceutical activities that are contracted out to another department or organisation (e.g. handling of wastes, environmental monitoring or preparation of certain CSPs not performed in the institution).
- 6.1.2 The service level agreement should specify the details of the work to be done, the specification it should meet and the responsibilities of each party.
- 6.1.3 The agreement should be authorised and signed by the contract acceptor and by the person-in-charge of the sterile activities or any other authorised personnel within the institution.
- 6.1.4 The person-in-charge should routinely review the reports generated by the external vendors contracted to ensure that the service/ product is in compliance with the required specification and of acceptable quality.
- 6.1.5 Audits on the external vendor contracted are also recommended to check that work is performed in accordance with the agreement. Quality checks could be in the form of documentation of certification, service delivery report and tracking of rejection rate, turnaround times and integrity of products upon delivery.

### 6.2 Business Continuity Planning

- 6.2.1 Each institution should have a contingency plan stating responsibilities and procedures to follow in the event of interruption of operation e.g. fire evacuation plan, emergency power supply for cold supply chains.
- 6.2.2 Ministry of Health (MOH) should be informed of any cessation of operation in accordance with the Private Hospitals and Medical Clinics (PHMC) Regulation 9.

- 6.2.3 If the institution decides to discontinue sterile pharmaceutical operations temporarily, there shall be a process to distribute the remaining inventory, under the oversight of a competent staff.
- 6.2.4 There should be a procedure in place to inform recipients of finished CSPs in the event that the institution ceases the production of sterile CSPs.
- 6.2.5 Operations should be discontinued in a manner that minimises disruption of care to patients.
- 6.2.6 If the institution decides to resume operations, the following should be in compliance:
- (i) review of the procedures to meet the current practice;
  - (ii) inspection of inventory and supplies for expiry dates;
  - (iii) validation of equipment maintenance;
  - (iv) stability of existing inventory; and
  - (v) re-validation of staff competency.
- 6.2.7 If operations is disrupted or discontinued for a period exceeding six months, there should be revalidation and documentation of the training and competency of all staff to perform the duties assigned upon resumption of activities.

## CHAPTER 7: COMPLAINTS AND PRODUCT RECALLS

### PRINCIPLE

*In order to be able to promptly and effectively recall finished products which have severe deficiencies, a suitable procedure should be developed. There should be an established process for product recalls which should be duly documented. There should also be a quality assurance program to provide a mechanism for monitoring, evaluating, correcting and improving activities and processes.*

### 7.1 Product Recalls

- 7.1.1 There should be an available adverse events reporting system for patient feedback and complaints so as to activate product recalls if necessary.
- 7.1.2 All errors, defects, complaints and other signs of quality problems should be reviewed carefully according to a written procedure.
- 7.1.3 When product deficiencies are detected, product recall should be initiated immediately according to established protocol and the case should be reported to the relevant authorities.
- 7.1.4 Recalled products for further investigation should be clearly labelled and stored separately from other finished products or supplies.
- 7.1.5 The process of the recall, including recovered quantities of the product, investigation result and remedial actions taken, should be clearly documented.

### 7.2 Quality Assurance Program

- 7.2.1 There should be an ongoing, systematic program for quality assessment and improvement that provides a mechanism for monitoring, evaluating compliance and effectiveness of processes, correcting, and improving all activities associated with CSPs. This includes personnel training and assessment and environmental monitoring.
- 7.2.2 There should be a review of system-wide documentation on medication errors involving CSPs to analyse and aggregate data, identify trends, and develop methods for improving quality in CSPs.

- 7.2.3 Errors, defects, complaints and other signs indicating quality issues should be investigated. Appropriate measures should be put in place to ensure that effective remedial action is taken.
- 7.2.4 Risk assessment and evaluation of activities should be routinely conducted to review and improve existing SOPs if necessary, for quality assurance.
- 7.2.5 All adverse events or serious reportable events should be reported to the relevant authorities.

## APPENDIX I: ISO CLASSIFICATION

ISO Classification of particulate matter in controlled environments

ISO Class	Particle Count*/m <sup>3</sup>	Federal Standard 209E	
		English	Metric
3	35.2	1	M1.5
4	352	10	M2.5
5	3,520	100	M3.5
6	35,200	1,000	M4.5
7	352,000	10,000	M5.5
8	3,520,000	100,000	M6.5

*\*Limits for number of particles  $\geq 0.5\mu\text{m}$  measured under typical operating conditions.*

## APPENDIX II-A: TRAINING REQUIREMENT FOR ALL NEW PERSONNEL

All new personnel should be proficient in the following core competencies:

- (i) Handwashing and gowning procedure;
- (ii) Cleaning and disinfection;
- (iii) Aseptic manipulation;
- (iv) Management of needle stick injuries
- (v) Measuring and mixing;
- (vi) Proper use of compounding devices;
- (vii) Proper use of PECs;
- (viii) Documentation of the compounding process (e.g. master formulation);
- (ix) Packaging and labelling of sterile preparations;
- (x) Proper cleanroom behaviour e.g. moving materials in and out; and
- (xi) Cleaning and maintenance of devices and equipment.



## **APPENDIX II-B: TRAINING REQUIREMENT FOR HANDLERS OF HAZARDOUS CSPs**

*In addition to Appendix II-A, all new personnel preparing hazardous CSPs should be proficient in the following:*

- (i) Handling of hazardous substances;*
- (ii) Cytotoxic spill management;*
- (iii) Safe disposal of hazardous wastes*
- (iv) Response to known or suspected exposure*
- (v) Proper changing of isolator sleeves (if applicable); and*
- (vi) Dosage calculations, drug /diluent compatibility.*



## **APPENDIX II-C: WORKPLACE SAFETY AND HEALTH ACT REQUIREMENTS (As of last amended version on 14 April 2014)**

### **General Interpretations**

2) For the purposes of this Act —

(b) any reference to the health of a person shall, where that person is pregnant, include a reference to the health of any unborn child which that person is carrying.

### **Duties of employers**

12.—(1) It shall be the duty of every employer to take, so far as is reasonably practicable, such measures as are necessary to ensure the safety and health of his employees at work.

(2) It shall be the duty of every employer to take, so far as is reasonably practicable, such measures as are necessary to ensure the safety and health of persons (not being his employees) who may be affected by any undertaking carried on by him in the workplace.

(3) For the purposes of subsection (1), the measures necessary to ensure the safety and health of persons at work include —

- (a) providing and maintaining for those persons a work environment which is safe, without risk to health, and adequate as regards facilities and arrangements for their welfare at work;
- (b) ensuring that adequate safety measures are taken in respect of any machinery, equipment, plant, article or process used by those persons;
- (c) ensuring that those persons are not exposed to hazards arising out of the arrangement, disposal, manipulation, organisation, processing, storage, transport, working or use of things —
  - (i) in their workplace; or

- (ii) near their workplace and under the control of the employer;
  - (d) developing and implementing procedures for dealing with emergencies that may arise while those persons are at work; and
  - (e) ensuring that those persons at work have adequate instruction, information, training and supervision as is necessary for them to perform their work.
- (4) Every employer shall, where required by the regulations, give to persons (not being his employees) the prescribed information about such aspects of the way in which he conducts his undertaking as might affect their safety or health while those persons are at his workplace.

### **Duties of persons at work**

15.—(1) It shall be the duty of every person at work —

- (a) to use in such manner so as to provide the protection intended, any suitable appliance, protective clothing, convenience, equipment or other means or thing provided (whether for his use alone or for use by him in common with others) for securing his safety, health and welfare while at work; and
  - (b) to co-operate with his employer or principal and any other person to such extent as will enable his employer, principal or the other person, as the case may be, to comply with the provisions of this Act.
- (2) No person at work shall wilfully or recklessly interfere with or misuse any appliance, protective clothing, convenience, equipment or other means or thing provided (whether for his use alone or for use by him in common with others) pursuant to any requirement under this Act for securing the safety, health or welfare of persons (including himself) at work.
- (3) Any person at work who, without reasonable cause, wilfully or recklessly does any act which endangers the safety or health of himself or others shall be guilty of an offence.

<Full Act can be assessed through the AGC website- [link](#).>

### **Workplace Safety and Health (General Provisions) Regulations (Extract)**

#### **PART IV— SPECIAL PROVISIONS RELATING TO HEALTH, SAFETY AND WELFARE**

##### **Toxic dust, fumes or other contaminants**

39.—(1) Where any process or work carried on in any workplace is likely to produce or give off any toxic dust, fumes, gas, vapour, mist, fibre or other contaminants, all reasonably practicable measures shall be taken to —

- (a) prevent their accumulation in the workplace; and
  - (b) protect persons at work in the workplace against exposure to the toxic dust, fumes, gas, vapour, mist, fibre or other contaminants through inhalation, ingestion or skin contact.
- (2) The measures to be taken under paragraph (1) shall, where appropriate, include one or more of the following:

- (a) carrying out the process or work in isolated areas where persons not connected with the process or work are prohibited from being present;
  - (b) carrying out the process or work in closed vessels or systems to prevent persons at work in the workplace from coming into contact with the toxic dust, fumes, gas, vapour, mist, fibre or other contaminants;
  - (c) providing adequate ventilation to dilute the fumes, gas, vapour, mist, fibre or other contaminants;
  - (d) providing local exhaust ventilation to remove the toxic dust, fumes, gas, vapour, mist, fibre or other contaminants at their sources of emission; and
  - (e) carrying out the process or work wet.
- (3) The local exhaust ventilation system referred to in paragraph (2)(d) shall be so designed, constructed, operated and maintained that the toxic dust, fumes, gas, vapour, mist, fibre or other contaminants are safely and effectively removed at the source of generation and are not dispersed or scattered in the surrounding air.
- (4) Accumulation of toxic dust, fibre or waste on the floors, walls, work benches or other surfaces in any workplace shall be removed by washing, vacuum cleaning or other suitable means in a manner that will not make the toxic dust, fibre or waste airborne.
- (5) No stationary internal combustion engine shall be used unless provision is made for conducting the exhaust gases from the engine into the open air.
- (6) The atmosphere of any place of work in which toxic substances are manufactured, handled, used or given off shall be tested by a competent person at sufficient intervals to ensure that toxic dust, fumes, gases, vapours, mists or fibres are not present in quantities liable to injure the health of persons at work.
- (7) Notwithstanding paragraph (6), the Commissioner may, by order in writing, require the occupier of a workplace to engage a competent person —
- (f) to monitor, test or assess the environment of any workplace for potential health hazards; and
  - (g) to take air samples in the breathing zone of the persons who are exposed to toxic dust, fumes, gases, vapours, mists, fibres or other contaminants by using appropriate personal sampling equipment.
- (8) A record of the result of every test carried out under paragraphs (6) and (7) shall be kept available for inspection by an inspector for at least 5 years from the date of the test or such other period as the Commissioner may specify in writing.
- (9) Paragraphs (1), (2), (6) and (7) shall not apply to any workplace where —
- (a) it is impracticable to comply with such requirements; and
  - (b) suitable air-supplied breathing apparatus is used by every person at the workplace.
- (10) The air-supplied breathing apparatus used under paragraph (9) shall be supplied with air —
- (a) of a temperature and humidity comfortable for breathing; and
  - (b) which has been suitably treated to remove particles of any material, oil mist, vapour, odour, carbon monoxide and carbon dioxide.
- (11) It shall be the duty of the occupier of a workplace to comply with paragraphs (1) to (6), (8) and (10).



(12) It shall be the duty of a competent person to exercise all due diligence in conducting any test under this regulation.

#### Permissible exposure levels of toxic substances

40.—(1) It shall be the duty of the occupier of a workplace to take all reasonably practicable measures to ensure that no person at work in the workplace is exposed to the toxic substances specified in the First Schedule in excess of the permissible exposure levels specified in that Schedule.

(2) Where the PEL (Short Term) of a toxic substance is not specified in the First Schedule, the PEL (Short Term) of the substance shall be deemed to be exceeded if the time weighted average concentration of the substance measured over a 15-minute period during any working day exceeds 5 times the PEL (Long Term) of that substance as specified in that Schedule.

(3) Where there is exposure to more than one toxic substance at the same time and the substances have similar harmful effects, the permissible exposure level shall be deemed to have been exceeded if the sum of the ratios between the time weighted average concentration and the permissible exposure level of each substance exceeds one.

#### Hazardous substances

41.—(1) All hazardous substances in a workplace shall be placed under the control of a competent person who has adequate knowledge of the properties of the hazardous substances and their dangers.

(2) Adequate warning notices in languages understood by all persons at work in a workplace specifying the nature of the danger of the hazardous substances shall be placed —

(a) at all entrances to any workroom; and

(b) at appropriate locations, where the hazardous substances are used or present.

(3) Persons at work in a workplace who are liable to be exposed to hazardous substances shall be warned of the hazards involved and the precautionary measures to be taken.

(4) All hazardous substances in a workplace shall be kept, stored, used, handled or disposed of in such a manner as not to pose a risk to the health and safety of any person at work in the workplace.

(5) It shall be the duty of the occupier of a workplace to comply with paragraphs (1) to (4).

(6) Any person at work in a workplace who wilfully or recklessly does any act that may result in any other person being exposed to hazardous substances shall be guilty of an offence and shall be liable on conviction to a fine not exceeding \$20,000 or to imprisonment for a term not exceeding 2 years or to both.

#### Warning labels

42. It shall be the duty of the occupier of a workplace in which there is any container of hazardous substances to ensure that, so far as is reasonably practicable, every such container is affixed with one or more warning labels that conform with —

- (a) any Singapore Standard relating to the classification and labelling of hazardous substances; or
- (b) such other standards, codes of practice or guidance relating to the classification and labelling of hazardous substances as is issued or approved by the Council.

#### Safety data sheet

43.—(1) Where any hazardous substance is used, handled or stored in a workplace, it shall be the duty of the occupier of the workplace to —

- (a) obtain a safety data sheet of the substance;
- (b) assess the information in the safety data sheet and take precautionary measures to ensure the safe use of the substance; and
- (c) make available the safety data sheet to all persons at work in the workplace who are liable to be exposed to the substance.

(2) Where any hazardous substance is sold to any person for use in a workplace, it shall be the duty of the seller or any agent of the seller who caused or procured the sale to provide the buyer with a safety data sheet for the substance that —

- (a) gives accurate and adequate information on the substance; and
- (b) conforms with any Singapore Standard relating to safety data sheets or such other standards, codes of practice or guidance as is issued or approved by the Council.

(3) Any seller or agent of any seller who fails to provide a safety data sheet under paragraph (2) or any person who provides inaccurate, inadequate or misleading information in a safety data sheet shall be guilty of an offence and shall be liable on conviction to a fine not exceeding \$10,000.

#### Exclusion from regulations 41, 42 and 43

44.—(1) Regulations 41, 42 and 43 shall not apply in respect of the use, handling or storage in a workplace, or the sale for use in a workplace, of any hazardous substance that is in a consumer package and that is intended for retail sale.

<Full Regulations can be assessed through the AGC website- [link](#).>

### **Workplace Safety and Health (Medical Examinations) Regulations 2011 (Extract)**

#### Application

3. These Regulations shall apply to all workplaces in which persons are employed in any hazardous occupation, being any occupation involving —

- (a) the use or handling of or exposure to the liquid, fumes, dust, mist, gas or vapour of arsenic, cadmium, lead, manganese or mercury or any of their compounds;
- (b) the use or handling of or exposure to the fumes or vapour of benzene, perchloroethylene, trichloroethylene, organophosphates or vinyl chloride monomer;
- (c) the use or handling of or exposure to tar, pitch, bitumen or creosote;

- (d) the use or handling of or exposure to the dust of asbestos, raw cotton or silica;
- (e) exposure to excessive noise; or
- (f) any work in a compressed air environment.

Persons to be medically certified fit for employment

4.—(1) It shall be the duty of the responsible person of a person who is to be employed in any hazardous occupation described in regulation 3(a) to (e) to ensure that the person shall undergo a pre placement medical examination by a designated workplace doctor and be certified fit to work in such occupation, not later than 3 months after the date he commences his employment in such occupation.

(2) It shall be the duty of the responsible person of a person who is to be employed in the hazardous occupation described in regulation 3(f) to ensure that the person shall be medically examined by a designated workplace doctor and certified fit to work in such occupation within 30 days before the date he is to commence his employment in such occupation.

(3) The medical examination referred to in paragraph (1) or (2) shall —

- (a) consist of the examinations and investigations specified in the Schedule and such other examinations or investigations as the Commissioner may require from time to time in any particular case; and
- (b) include —
  - (i) a clinical examination of the person for symptoms and signs of any diseases that may result from exposure to the hazards of the occupation in which the person is employed; and
  - (ii) an assessment as to whether the person who is to be employed in a hazardous occupation is fit to work in that occupation.

Periodic medical examinations

5.—(1) It shall be the duty of the responsible person of a person employed in any hazardous occupation to ensure that the person shall be periodically examined by a designated workplace doctor.

(2) The periodic medical examinations referred to in paragraph (1) shall —

- (a) consist of the examinations and investigations specified in the Schedule;
- (b) include —
  - (i) a clinical examination of the person for symptoms and signs of any diseases that may result from exposure to the hazards of the occupation in which the person is employed; and
  - (ii) an assessment as to whether the person who is employed in a hazardous occupation is fit to continue working in that occupation; and
- (c) take place at the intervals specified in the Schedule.

(3) Notwithstanding paragraph (2), the Commissioner may, in cases where he considers expedient, require any person to be examined at intervals other than or in addition to those specified in the Schedule.

#### Other medical examinations

6.—(1) The Commissioner may require any person or category of persons employed in any hazardous occupation to undergo a medical examination other than or in addition to the medical examinations referred to in regulations 4 and 5.

(2) Where a person employed in any hazardous occupation is required to undergo any audiometric examinations under these Regulations, it shall be the duty of the responsible person of that person to ensure that the audiometric examinations shall be carried out by persons who have undergone a course of training in audiometric screening acceptable to the Commissioner (as specified by the Commissioner at the Ministry of Manpower website).

(3) Any responsible person who contravenes paragraph (2) shall be guilty of an offence and shall be liable on conviction to a fine not exceeding \$1,000 and, in the case of a second or subsequent conviction, to a fine not exceeding \$2,000.

#### Registers of employees in hazardous occupations

8.—(1) It shall be the duty of the responsible person of a person or persons employed in any hazardous occupation in a workplace to keep registers of such persons.

(2) The responsible person shall ensure that the registers referred to in paragraph (1) are —

- (a) kept in such form and manner as may be required by the Commissioner;
- (b) updated at all times such as to show at any time, the particulars of all persons who are currently employed in any hazardous occupation in the workplace and all the persons who had or have been employed in the hazardous occupation in the workplace in the last 5 years; and
- (c) be produced for inspection upon request by an inspector.

(3) Any person who contravenes paragraph (1) or (2) shall be guilty of an offence and shall be liable on conviction to a fine not exceeding \$5,000 and, in the case of a second or subsequent conviction, to a fine not exceeding \$10,000.

<Full Regulations can be assessed through the AGC website- [link](#).>

## Workplace Safety and Health (Incident Reporting) Regulations (*Summary*)

What to report	Who should report	Reporting timeline
A workplace accident which resulted in the death of an employee	<ul style="list-style-type: none"> <li>the employer of the deceased worker</li> </ul>	<ul style="list-style-type: none"> <li>notify immediately; and</li> <li>submit the report within 10 days of the accident</li> </ul>
An occupational disease	<ul style="list-style-type: none"> <li>the employer of the person with the disease and</li> <li>the doctor who diagnosed the disease</li> </ul>	<ul style="list-style-type: none"> <li>submit the report within 10 days of receipt of the written diagnosis (employer)</li> <li>submit the report within 10 days of the diagnosis (doctor)</li> </ul>
A workplace accident which resulted in the injury of an employee and who is given more than 3 consecutive days of medical leave or hospitalized for at least 24 hours	<ul style="list-style-type: none"> <li>the employer of the injured person</li> </ul>	<ul style="list-style-type: none"> <li>submit the report within 10 days of the accident</li> </ul>
A workplace accident which involved a self-employed person or member of public and resulted in his or her death for being taken to hospital for treatment of injury	<ul style="list-style-type: none"> <li>the occupier of the workplace</li> </ul>	<ul style="list-style-type: none"> <li>notify immediately; and</li> <li>submit the report within 10 days of the accident</li> </ul>
A dangerous occurrence	<ul style="list-style-type: none"> <li>the occupier of the workplace</li> </ul>	<ul style="list-style-type: none"> <li>notify immediately; and</li> <li>submit the report within 10 days of the accident</li> </ul>

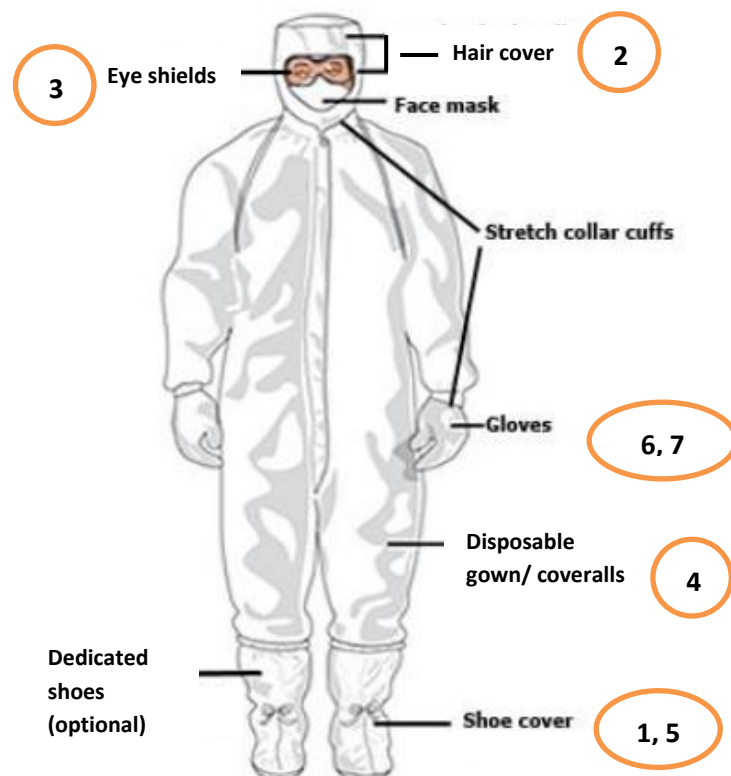
<Full Regulations can be assessed through the AGC website- [link](#).>

## **APPENDIX III-A: PROCEDURES REQUIRING WRITTEN POLICIES**

There should be policies, SOPs or operational guidance on the following:

- (i) Duties and responsibilities of personnel and person-in-charge
- (ii) Training and validation programme for personnel
- (iii) Gowning procedure and aseptic technique
- (iv) Cleaning and disinfecting
- (v) Handling of sharps and needles
- (vi) Use of PPE based on activity
- (vii) Waste disposal
- (viii) Incident reporting for personnel
- (ix) Sterile preparations performed in the institution
- (x) Master formulation record of batch CSPs
- (xi) Labelling, packaging, storage, validation and transport of finished products
- (xii) End product sterility testing (not for Total Parenteral Nutrition and Cytotoxic preparations) and quality checks
- (xiii) Adverse events reporting and recall of finished products
- (xiv) Operation, cleaning and maintenance of facilities and equipment
- (xv) Quality assurance programme; and
- (xvi) Work contracted out to other organisations.

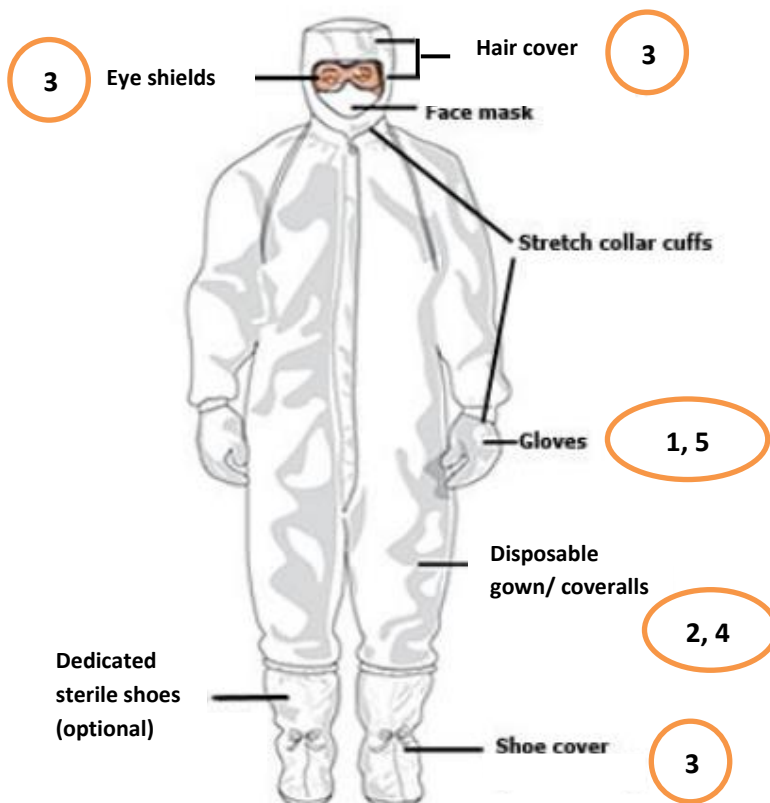
## APPENDIX III-B: GOWNING PROCEDURE FOR WORKING IN CLEANROOM



PPE should be **donned** in the following order:

1. Dedicated shoes or shoe covers
2. Hair cover
3. Face mask (beard cover and eye shields if required)
4. Non-shedding gown with a closed front, long sleeves and elastic or knit closed cuffs (Coveralls are only required for cleanroom procedures)
5. If handling hazardous drugs, a second pair of shoe covers should be donned.
6. Perform hand hygiene with antiseptic wash
7. Powder-free gloves

*If handling hazardous drugs, second pair of gloves must be worn, with the outer pair extending over the cuff of the gown.*



**After preparation of hazardous products**

PPE should be **removed** in the following order:

1. Remove **outer** gloves and place in a cytotoxic waste bag
2. Remove disposable gown/ coveralls
3. Remove hair cover, mask, (beard cover and eye shield if applicable) and shoe covers
4. Place PPE for disposal in a cytotoxic waste bag (for non-reusable PPE)
5. Remove **inner** gloves and place them in

**After preparation of non-hazardous products**

PPE can be removed in the same order as above. Dispose of PPE in black general waste


Diagram adapted from Cole-Parmer Singapore — Cleanroom Garments  
<<http://www.coleparmer.com/TechLibraryArticle/63>>

### Hand Washing Procedure:

1. Wash hands and forearms up to the elbows with soap and water for at least 30 seconds
2. Dry hands and forearms to the elbows completely with low-lint disposable towels or wipes
3. Apply alcohol-based handrub
4. Allow hands to dry thoroughly before proceeding with the next activity e.g. don sterile gloves

### APPENDIX III-C: SPECIFICATIONS ON PPE

CSP Category	PEC Type	Recommended PPE				
		Non-cotton, low-lint, disposable gown or coveralls	Low lint, disposable covers for shoes and hair	Sterile gloves and sleeves	Goggles/ eye protection	N95 Respirator
Category 1	Any	√	√	√	X	X
Category 2	LAFW	√	√	√	X	X
Category 2	RABS (CAI or CACI) or isolator	√	√	√	√	X

	PEC Type	Recommended PPE				
		Non-cotton, low-lint, disposable gown or coveralls	Low lint, disposable covers for shoes and hair	Sterile nitrile gloves and sleeves	Goggles/ eye protection	N95 Respirator
<b>Hazardous CSPs</b>	Class II or III BSC or CACI  *LAFW and CAI should not be used for compounding antineoplastics.	<b>Impermeable</b> disposable gowns- to be made of <b>lamine</b> material (absorbent materials should not be used); <b>no front opening</b> (to close in the back); seamless with elastic/ knitted <b>closed cuffs</b>	<b>Impermeable</b> disposable covers for shoes and hair	√	√	√



## **APPENDIX III-D: SAMPLE SOP FOR HANDLING LIVE VACCINES**

### **(A) Gowning and Hand Hygiene**

1. Gown according to Appendix III-B. In addition, the operator should put on 2 pairs of gloves.

### **(B) Loading of the Laminar Air Flow Cabinet**

2. Place necessary materials for the preparation into the cabinet to prevent the need for the operator to remove and re-insert his/her hands into the cabinet.

### **(C) Reconstitution and Preparation**

3. Do not open the cleanroom door or hatch during preparation. This avoids compromising safety due to disruption to the air flow.
4. SOPs should be followed as for cytotoxic preparations to minimise the operator's risk of exposure.
5. Avoid excessive movements while performing aseptic manipulations within the LAFW.
6. Place a chemo spill mat or an absorbent pad with spill-proof backing on the work surface. This reduces the hazards of surface contamination caused by droplets or minor spills.
7. All work should be carried out within the recommended working zones of the cabinet.
8. Avoid resting arms, elbows on the air return plenum.
9. If gloves become contaminated, remove the first layer in the cabinet and put on a new pair in the changing room.
10. At the end of preparation, remove the first layer of gloves in the cabinet and dispose as infectious waste.
11. After removal of the first layer of gloves, the operator should wait one minute before withdrawing his arms and hands from the cabinet. This time allows for any aerosols to be carried into the filter and any particles to settle and prevents the piston-like motion of the arm leaving the cabinet from pulling aerosol-containing air out from within the cabinet.
12. The cabinet should be cleaned according to the SOP and any unused consumables should be discarded. Allow the cabinet to continue to run for 30 minutes before using it for subsequent preparations or before turning it off.
13. Immediately stop any manipulations if the laminar air flow cabinet stops working (e.g. power failure). All open materials should be discarded and new consumables should be used when preparation resumes.

(D) Disposal of Waste Materials and Hazardous drugs

14. All the materials (used or unused) inside the hood including the outer gloves should be placed into a ziploc bag. The ziploc bag should be sealed within the cabinet.
15. The ziploc bag should then be removed and disposed in a biohazard container.

(E) Degowning and Cleaning

16. After preparation, the inner gloves should be discarded.
17. Discard disposable gown into cytotoxic waste bag.
18. Hands should be washed before leaving the changing room.
19. A new set of gown and gloves should be used if the operator were to re-enter the cleanroom.
20. Wash all the trays used during preparation with hot water (e.g. 80-85°) after use.
21. Wipe all the folders with a bold water towel soaked with 70% isopropyl alcohol. This reduces the risk of cross contaminations.

(F) Cleaning up Spillages and Breakages

22. Keep the cabinet turned on. The cabinet should not be turned off when there is a spill.
23. When a small amount of liquid is spilled without splashing, the spillage should be covered promptly with a bold water towel and 70% isopropyl alcohol should be poured gently on the towel, working from the outside inwards. The towel should be kept damp by pouring fresh 70% isopropyl alcohol when necessary.
24. After 30 minutes, the bold water towel should be removed with forceps and discarded into a ziploc bag in the cabinet.
25. A fresh bold water towel soaked in 70% isopropyl alcohol should be used to swab the area and then discarded into the same ziploc bag.
26. Another bold water towel soaked in 70% isopropyl alcohol should be used to cover the area for another 30 mins, then discarded into the ziploc bag which is to be sealed and discarded as biohazard waste.
27. At the end of the decontamination, the cabinet should be cleaned according to the SOP.
28. Leave the cabinet to run for another 10 minutes before using it again.

- 29.If breakage occurs outside the laminar airflow cabinet but within the cleanroom area, the operator should leave the room immediately and re-enter only after 30 minutes to clean up the spill.
- 30.Always use forceps to handle broken vials or other materials. Never handle directly by hand.
- 31.Spillage on the floor can also be cleaned by using sodium hypochlorite 10,000 ppm.

## APPENDIX IV-A: CLEANING SCHEDULE AND METHODS

**Table 1:** Cleaning of facilities and equipment and its recommended frequency

Facility	Frequency
Critical work areas and devices used	Before and after use
Isolators	Before start of and at the end of session
Background environment (e.g. counters, work benches and floors in cleanroom or SCA)	Daily
Ceilings, walls and storage shelving	Monthly

**Table 2:** Summary on the methods of cleaning

Cleaning Step	Purpose	Agents
Deactivation	Render compound inert or inactive	As listed in the Hazardous Drug labelling or if no specific information available, sodium hypochlorite or other suitable oxidizer
Decontamination	Remove inactivated residue	Sterile alcohol, sterile water, peroxide, or sodium hypochlorite
Cleaning	Remove organic and inorganic material	Germicidal detergent and sterile water
Disinfection	Destroy microorganisms	Sterile 70% isopropyl alcohol or other disinfectant appropriate for use

## APPENDIX IV-B: ENVIRONMENTAL MONITORING

The following aspects should be monitored to ensure constant environmental conditions within the compounding facility:

- (i) Differential pressure across HEPA filters of the PEC
- (ii) Differential pressure between rooms (at least 5 Pascal)
- (iii) Non-viable and viable airborne particle count
- (iv) Air velocity and room air changes (at least 12 ACPH in SCA and 30 ACPH in cleanroom)
- (v) Relative humidity (guidance value of 60% or below)
- (vi) Room temperature (guidance value of 20°C – 25°C)
- (vii) Integrity of HEPA filters
- (viii) Lighting intensity (recommended levels of 300 to 750 Lux<sup>2</sup>)
- (ix) Noise level (ambient noise level should not exceed 65dB)

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<sup>2</sup> MOM Guidelines on Office Ergonomics

**Table 1:** Recommended types and frequencies of environmental monitoring

Type of monitoring	Recommended Frequency	
	Critical working environment (PEC)	Background environment (cleanroom)
Differential pressure	Daily before start of work	Daily before start of work
Particle count monitoring	Every 6 months	Every 6 months
Settle plates	Weekly	Weekly
Glove finger dabs	Weekly	NA
Surface samples (swabs or contact plates)	Weekly	Monthly
Active air samples	Every 3 months	Every 3 months

**Table 2:** Types and frequencies of certification tests carried out by qualified operator

Type of monitoring	Frequency	
	Critical working environment (BSC/LAFW)	Background environment
Differential pressure	Every 6 months	Every 6 months
Airborne particle count	Every 6 months	Every 6 months
Airflow velocity	Every 6 months	Every 6 months
Room air changes	NA	Every 6 months
Relative humidity	NA	Every 6 months
Room temperature	NA	Every 6 months
HEPA filter integrity	Once a year	Once a year
Light intensity	Once a year	Once a year
Noise level	Once a year (Optional)	Every 6 months

**Table 3:** Action Levels for Viable Airborne Particle Air Sampling

ISO Class	Air Sampling Action Levels (CFU/m <sup>3</sup> )*
5	≥1
7	≥10
8	≥100

*\*All action levels must be based on sampling in the vicinity of exposed materials/articles during compounding operations.*

**Table 4:** Action Levels for Surface Sampling

ISO Class	Work surfaces sampled using contact plates (CFU/plate)	Work surfaces sampled using swabs (CFU/ 25 cm <sup>3</sup> or per sample)	Non-work surfaces sampled using contact plates (CFU/plate)	Non-work surfaces sampled using swabs (CFU/ 25 cm <sup>3</sup> or per sample)
5	≥3	≥3	NA	NA
7	≥5	≥5	≥10	≥10
8	≥25	≥25	≥50	≥50

*\*Work surfaces refer to the critical work areas in the PEC. Non-work surfaces refer to background environment.*

**APPENDIX V-A: DETAILED BUD GUIDANCE FOR CATEGORY 2 CSPS**  
**(Revised USP797)**

	Preparation Characteristics			Storage Conditions			
	Method of achieving sterility	Sterility Testing performed	Preservative added	Controlled room temperature (20°C – 25°C)	Refrigerator (2°C – 8°C)	Freezer (-25°C – -10°C)	
BUD	Aseptically prepared	No	No	From non-sterile starting materials:			
				4 days	7 days	45 days	
				From sterile starting materials:			
				6 days	9 days	45 days	
		Yes	28 days	42 days	45 days		
			Yes	No	28 days	42 days	45 days
				Yes	42 days	42 days	45 days
				Terminally sterilised	No	No	14 days
	Yes	28 days	42 days			45 days	
	Yes	No	28 days		42 days	45 days	
		Yes	42 days		42 days	45 days	

**Note: The stability (chemical) of the product should be considered when assigning the BUD.**

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