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Ministry of Health Malaysia
Pharmaceutical Services Programme

MANUAL FOR STERILE PREPARATIONS

2ND EDITION YEAR 2021

MANUAL FOR STERILE PREPARATIONS 2ND EDITION

STERILE PHARMACEUTICAL SERVICES GUIDELINE

MINISTRY OF HEALTH MALAYSIA

MINISTRY OF HEALTH MALAYSIA

PHARMACEUTICAL SERVICES PROGRAMME

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Foreword

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Sterile pharmaceutical production is one of the core business of pharmacy service enabling accessibility to individualized compounded preparations and oftentimes extending therapeutic options to some of the most complicated patients. The advent in medical technologies and clean room engineering provide the fraternity with improved environmental air quality control which is fundamental in aseptic production.

The second edition of Manual for Sterile Preparations provides comprehensive information on various aspects of sterile pharmaceutical production in-line with the requirements of Pharmaceutical Inspection Co-operation Scheme (PIC/S) guide to Good Preparation Practice (GPP) steering towards the delivery of safe, effective and top-quality sterile preparations and at the same time warrants personnel and environmental protection against hazardous drugs exposure.

I believe this manual will be an excellent *vade mecum* to all the personnel involved in sterile pharmaceutical production and ensuring excellent pharmaceutical service to the nation. Finally, I would like to convey my gratitude to all who have participated in the development of this manual for their tireless efforts and commendable team spirit for making the publication a success.
Thank you.

Preface

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The ever-expanding pharmacy services in various fields in the hospitals especially sterile pharmaceutical production has proven its essentiality in providing care to the patients. The fundamentals of sterile pharmaceutical production revolve around the principles of Good Preparation Practice (GPP) as aligned with the current standards set by Pharmaceutical Inspection Co-operation Scheme (PIC/S) guide. The first edition of Manual for Sterile Preparations was published in 2010 and with the advancement of medical technologies as well as the continued development of modern clean room facility, it is timely for the publication of the second edition of this manual which serves as an important reference for the personnel involve in aseptic production.

Sterile pharmaceutical production involves the aseptic compounding of various sterile preparations which include cytotoxic drugs, parenteral nutrition, radiopharmaceuticals, IV admixtures, ophthalmology preparations and other sterile preparations. The second edition of Manual for Sterile Preparations provides valuable updates with expanded coverage of radiopharmaceuticals production. The structure of this manual incorporates important chapters from PIC/S guide namely personnel, premise and equipment, production, documentation, quality assurance system among others.

Maintaining sterility of compounded sterile preparations is of paramount in sterile pharmaceutical production, hence contamination control is of utmost importance. Aspects on personnel hygiene, aseptic technique, cleaning and maintenance of clean room facility to proper GPP inspection are highlighted to ensure the quality, safety and efficacy of the sterile preparations. Besides, safety of personnel and environment especially in the radiopharmaceuticals and cytotoxic drug preparations is also emphasized in the later chapter.

I sincerely hope this manual will be beneficial in providing a clear overview and better understanding on sterile pharmaceutical production in hospital setting. Just as importantly, I would like to congratulate all who have contributed hugely in the publication of the manual. Last but not least, I would like to encourage all pharmacy workforce to always collaborate and move forward congruent to the advances in medical technologies as '*Change is the only Constant*', do serve beyond boundaries!
Thank you.

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Manual for Sterile Preparations

Acronyms & Abbreviations

AHU	Air Handling Unit
ALARA	As Low As Reasonably Achievable
BP	British Pharmacopoeia
BSC	Biohazard Safety Cabinet
BUD	Beyond Use Date
CDR	Cytotoxic Drug Reconstitution
CHRA	Chemical Health Risk Assessment
CSP	Compounded Sterile Preparations
GPP	Good Preparation Practice
^{68}Ga	Gallium-68
^{68}Ge	Germanium -68
HEPA filter	High Efficiency Particulate Air filter
HSS	Hospital Support Services
ISO	International Organization for Standardization
LAFC	Laminar Air Flow Cabinet
^{177}Lu	Lutetium-177
MOH	Ministry of Health
OSHA	Occupational Safety and Health Act
PN	Parenteral Nutrition
PPE	Personal Protective Equipment
PPM	Planned Preventive Maintenance
QA	Quality Assurance
QC	Quality Control
RPO	Radiation Protection Officer
SDA	Sabouraud Dextrose Agar
SDS	Safety Data Sheets
SEV	Sterile Evacuated Vial
SOP	Standard Operating Procedure
^{99m}Tc	Technetium-99m
TSA	Tryptic Soy Agar
USP	United States Pharmacopoeia

Introduction

The compounding of pharmaceutical preparations is a fundamental part of pharmacy practice. According to Section 12 of Poison Act 1952, pharmacy personnel including pharmacists and pharmacist assistants are responsible for all the compounding of pharmaceutical preparations. Compounding activities shall strictly adhere to the standard operating procedures to produce preparations that are safe, effective and of highest quality. Moreover, compounding activities allow wider range of treatment options for prescribers to manage their patients with the best evidence-based practice tailored to individual patient needs hence enhancing treatment accessibility.

In this context, sterile pharmaceutical activities refer to the compounding and reconstitution of parenteral nutrition, cytotoxic drugs, radiopharmaceuticals, intravenous admixtures, ophthalmology preparations and other sterile preparations. Different preparations have different facility feature requirements to prevent contamination of the sterile preparations and ensuring safety of the personnel. For example, preparation of radiopharmaceuticals involves adherence to the regulations on radiation protection. Transport of radiopharmaceuticals is regulated by Atomic Energy Licensing Board and must comply with any relevant regulations from the Ministry of Transport, Malaysia. It is recognised that there are technologies, techniques, materials and procedures that are not described in this manual, which can achieve the same principles of Quality Assurance. Those methods are not prohibited and shall be validated to be at least equivalent or superior in Quality Assurance than specified in this manual.

Maintaining sterility of compounded sterile preparations (CSP) is vital as failure to do so could lead to serious harm, eventually fatality. CSP can be classified into different risk categories based on the final product beyond use date (BUD) and aseptic technique shall be strictly adhered to for all risk categories and type of facility features needed are based on the latest ISO primary engineering control requirements.

This guideline is intended to help personnel in the sterile production department of Ministry of Health (MOH) facilities to produce high quality products as well as to reduce the potential harms to both personnel and patients. The recommendations in this guideline are based on the latest published data during the development of this manual, expert opinions as well as applicable regulations and standards, which may change when new evidences emerge in the future.

Scope

The procedures outlined in this manual are intended to be used in situations where sterile products are being prepared under the supervision of a pharmacist for direct supply to patients. These procedures apply to all activities involved in preparing sterile products such as aseptic technique, documentation, quality control, cleaning, maintenance, and transportation.

This manual is not applicable to the manufacture of radiopharmaceuticals with a marketing authorisation or CSP for research or clinical trials that require specific authorisations relating to the preparation of these products.

Objectives

This guideline is intended to:

1. Provide a general overview of the operations involved in preparing sterile products
2. Provide guidance on good practices in the preparation of CSP and basic understanding of the requirements in line with current international and relevant guidelines
3. Address the importance of aseptic technique during preparation of CSP in order to eliminate or prevent the risk of contamination
4. Provide current understanding of standard procedures in maintaining the clean room and equipment

CHAPTER 1

QUALITY ASSURANCE SYSTEM

1.1 PRINCIPLES

In order to protect public health, sterile preparations shall be of high quality, safe and effective to end users. Thus, a system shall be developed to ensure that the quality of these preparations consistently complies with the defined requirements. To achieve this objective reliably, there shall be a comprehensively designed and correctly implemented quality assurance system, incorporating the principles of Good Preparation Practice (GPP). This system shall be well documented with its effectiveness monitored, and it must be up to date according to the latest knowledge or techniques.

Furthermore, in cytotoxic drug reconstitution and radiopharmaceutical production, products must be protected from contamination and cross-contamination, while the environment and the operators must also be protected against hazardous products. Data generated by the monitoring of premises and processes must be recorded and evaluated as part of the release process. Risk management approach must be used to determine the extent of qualification/ validation, while balancing GPP and Radiation Protection.

1.2 QUALITY ASSURANCE

Quality assurance ensures that:

1.2.1 The sterile preparations are planned and prepared according to the latest state of knowledge and evidence.

1.2.2 Production and control of operations are clearly specified and implemented according to the principles of GPP.

1.2.3 The CSP are only supplied if they have been correctly processed, checked and stored in accordance with the defined procedures and released by an appropriately competent person (i.e. Pharmacist In-Charge or Designated Person).

1.2.4 Adequate measures are in place to ensure CSP are released, stored and handled so that the required quality can be assured throughout their shelf life and the in-use expiry date.

1.2.5 Documentation systems are in place and maintained.

1.3 DEVIATION FROM SPECIFICATION

1.3.1 Deviations can occur during
   i. handling of starting and packaging materials and end products
   ii. maintenance and cleaning of premises and equipment

1.3.2 Any deviation from the procedures in the SOP must be investigated and approved.

1.3.3 A procedure to handle deviation from specification shall be established as follows:

NO.	PROCEDURE	DESCRIPTIONS
i.	Identification	The problems shall be clearly defined
ii.	Investigation	Shall include objective, strategy and responsibility
iii.	Analysis	a) Every possible cause is identified and the data is collected b) Data is assessed and prioritised to identify the root cause
iv.	Action Plan	a) Create a list of required tasks, which includes corrective and preventive actions b) Corrective action refers to any action to remove the deviation c) Preventive action refers to any action to avoid the deviation from repeating
v.	Implementation	Execute the action plan and document
vi.	Follow up	Verify and assess the effectiveness of action taken

1.3.4 In unexpected cases, deviation from the specified processes or methods of compounding could be justified, provided that appropriate in-house QC testing is done and finished preparation conforms to the relevant standards.

CHAPTER 2

DOCUMENTATION

2.1 PRINCIPLES

Proper documentation on paper or in electronic form constitutes an essential part of the quality assurance system. Clear, easy, and understandable written documentation prevents errors from spoken communication and permits traceability of CSP.

2.2 GENERAL REQUIREMENTS

2.2.1 All specifications, instructions and procedures shall be approved, signed and dated by the Pharmacist In-Charge or by a person appointed by the Pharmacist In-Charge.

2.2.2 All written documents shall be legible, clear, unambiguous and up to date.

2.2.3 The totality of these documents shall ensure the complete traceability of the preparation process of CSP.

2.2.4 Any alteration made to a document shall be signed and dated. The alteration shall permit the reading of the original information. The reason for alterations shall be evident. Equivalent measures shall be applied to electronic records.

2.2.5 Procedures and preparation instructions (including prescriptions/ request forms) shall be retained for a period of 2 years.[6]

2.2.6 Records shall be retained for a sufficient period. In any case, records shall be retained for at least one year after the expiry date of the relevant finished product.

2.2.7 Documents (written or electronic) related to the production of CSP must be prepared, reviewed, approved and distributed according to the written SOP.

2.2.8 Specifications must be established and documented for starting materials, labelling and packaging materials, intermediates, and finished products. This shall also include any other critical items used during production process.

2.2.9 Acceptance criteria for release and shelf life specifications shall be recorded for CSP.

2.2.10 Records of major equipment use, cleaning, sanitisation or sterilisation and maintenance shall include product name and batch number, where appropriate, in addition to the date and time and signature for the persons involved in these activities.

2.2.11 Clear written SOP describing immediate notification following failure of specifications and determination of whether a recall is necessary shall be available in regard to any radiopharmaceutical that is supplied before final testing results

are known. Any radiopharmaceutical that is supplied to other health facilities shall pass QC tests prior administration to the patient.

2.3 TYPES OF DOCUMENTATION

2.3.1 There shall be specifications for starting materials, packaging materials and finished products that are appropriately authorised and dated.

2.3.2 There shall be SOP for processing, packaging, QC and release of product. SOP shall be written in the imperative and include the following:

i. Control of documentation systems.
ii. Training of personnel (e.g., related to the realisation of hygiene measures).
iii. Entering and exiting from clean areas including the correct use of protective clothing.
iv. Cleaning and disinfection.
v. Maintenance of equipment (e.g., Biosafety Cabinet [BSC], Laminar Air Flow Cabinet [LAFC], Isolator) and facilities.
vi. Procedures for monitoring, including trending.
vii. Calibration and qualification of equipment (e.g., autoclaves, thermometers).
viii. Operation of equipment, where applicable.
ix. Receiving, sampling and releasing starting and packaging materials.
x. Counterchecking and release or rejection of finished products, including emergency release.
xi. Validation of processes.
xii. Storage and distribution.
xiii. Procedure for further actions if deviations and complaints arise.
xiv. Recall of finished products.
xv. Self-audits.

2.4 BATCH PREPARATION INSTRUCTIONS AND RECORDS

2.4.1 Batch Preparation Instructions and processing records reproduced from a suitably approved master format shall be used and approved prior to use. They shall be sufficiently detailed to allow traceability of starting materials and components to establish an audit trail for the products.

2.4.2 Processing instructions and records will vary for each unit and shall be designed to minimise the possibility of transcription errors. Processing instructions and records may be combined in one document (worksheets). Processing documentation shall comply with the general requirements.

2.4.3 The processing and packaging records shall include:

i. Qualitative and quantitative information of all materials used such as batch number of the material used or other references, enabling the traceability to further quality-related documents (e.g., product, number of analysis, number of certificate).
ii. Identification of the product (including batch number and preparation formula), the date of preparation and a specimen of the label used.
iii. Information on all operations and observations, such as documentation of cleaning, line clearance, calculations, as well as sampling.
iv. Initials or signature of the responsible operators for significant processing steps and controls.
v. Any deviations from the approved processing instruction.
vi. Name of patient or product identification number, where applicable.

2.4.4 The final processing record shall be assessed and approved by the Pharmacist In-Charge or Designated Person with date and signature.

2.5 OTHER RECORDS

2.5.1 Records for the following activities shall be maintained for a period of time that satisfies legislation or local document control policies. Such records include, but are not limited to:

i. QC tests
ii. Monitoring
iii. Maintenance
iv. Qualification and training of personnel
v. Validation
vi. Statistics
vii. Distribution
viii. Investigations and corrective actions and tracking of events to closure
ix. Description of receipt of goods, sampling, products leaflets, reference of prepared products, testing, release, rejection, calibration and performance of hygiene activities

CHAPTER 3

STANDARD OPERATING PROCEDURE: CYTOTOXIC DRUG RECONSTITUTION

Contents

CHAPTER 3

STANDARD OPERATING PROCEDURE: CYTOTOXIC DRUG RECONSTITUTION

3.1 PERSONNEL

3.1.1 Principles

There shall be sufficient and competent personnel to execute all the tasks in accordance with the current standards of practice, policies and procedures. Roles and responsibilities of each personnel shall be clearly delineated and fully understood. All personnel must be well-informed on the principles of QA, GPP, safe handling of hazardous drugs and OSHA.

3.1.2 General Requirements

i. All personnel (Pharmacist, Provisionally Registered Pharmacist (PRP), Pharmacist Assistant, Trainee and others) shall adhere to the standards of GPP and are equally accountable for the quality of all finished products. Roles and responsibilities of each personnel may vary in different healthcare establishments. These must be described clearly in the job function of respective personnel.
ii. New personnel shall be trained adequately as in Checklist of Training Topics for Personnel in Sterile Pharmaceuticals Production Unit (*Appendix 1*). Provisionally Registered Pharmacist (PRP) and trainee shall work under the supervision of trained personnel at all times.

3.1.3 Training and Continued Education

i. Training upon placement and routine continuous education/ training thereafter are necessary to improve competency at workplace.
ii. All personnel shall be trained by Pharmacist In-Charge or other qualified personnel. Training records shall be kept systematically.

3.1.4 Hygiene

i. Hand Washing

Remove make-up, jewellery and watch before gowning. Before donning sterile gown, hand washing is done by practicing the 7-step technique with appropriate disinfectant and clean water (*Appendix 2*).

ii. Personal Protective Equipment (PPE)

PPE is used to protect personnel from hazardous drug exposure, prevent or minimise spread of cytotoxic drug residues, maintain cleanliness of clean rooms and ensure sterility of finished products. Hence, PPEs are to be selected based on location of work areas and risk of exposure (depends on the activities being performed).

Sterile PPEs shall be worn when working in Grade A and B clean rooms. Single-use disposable sterile apparels are preferred to reusable ones as the latter require washing which may potentially transfer hazardous drug residues to other clothing in laundry. Cleaning and sterilisation of non-disposable apparels as well as other reusable PPEs (e.g. goggles & respirators) shall be done according to manufacturer's recommendation (if any) and standard policy.

Adequacy of protection provided by gloves, gowns and other apparels depends on their resistance to permeation by cytotoxic drugs. The American Society for Testing and Materials (ASTM) currently has two standards for testing the permeation of glove materials by chemicals;

a) ASTM standard F739 *(Standard Test Method for Resistance of Protective Clothing Materials to Permeation by Liquids or Gases Under Conditions of Continuous Contact)*, and
b) ASTM standard D6978-05 *(Standard Practice for Assessment of Resistance of Medical Gloves to Permeation by Chemotherapy Drugs)*.

ASTM standard D6978-05 allows lower permeation rate compared to F739 and testing is being conducted at human body temperature (35 $\pm$ 2 ^{0}C) using chemotherapy drugs. Health care workers who handle cytotoxic drugs shall wear gloves which have been tested by the more robust D6978 standard rather than the F739 standard which is meant for other chemicals.

ASTM standard D6978 is specific for testing gloves; there is no equivalent hazardous drug permeation test standard available for gowns and other apparels by far. As a result, some manufacturers combine sections of standards F739 and D6978 and apply the parameters to their gowns/ other apparels' permeability testing. Users must be aware of the possibilities that these products might not be as protective as advertised. It is advisable to check the details of tests conducted before making purchases.

Personnel who manage and purchase PPEs used for handling cytotoxic drug must be well informed about the specifications, performance and handling of each PPE. Requirements for commonly used PPEs are summarised as below:

a) Sterile Jumpsuit
- Made of polyethylene-coated polypropylene or other laminate materials (provides better protection against permeation by cytotoxic drugs than uncoated materials)
- Non-linting/ non-shedding
- Minimum number of seams
- Closed front
- Hooded (hood attached to jumpsuit or available separately)
- Long sleeves with tight-fitting elastic or knitted cuffs
- Well-fitting

  Jumpsuit must be changed immediately if torn or contaminated.

b) Disposable Chemotherapy Gown
- Made of polyethylene-coated polypropylene or other laminate materials (provides better protection against permeation by cytotoxic drugs than uncoated materials)
- Non-linting/ non-shedding
- No seams and closures
- Closed back (no open front)
- Long sleeves with tight-fitting elastic or knitted cuffs

  Gowns worn during compounding shall be changed as frequent as per manufacturer's recommendation. If there is no permeation information available, gowns shall be changed every 2-3 hours. All gowns must be changed immediately after a spill.

c) Head Covers (bouffant cap and etc.) and Shoe Covers
- Disposable
- Non-linting/ non-shedding
- Head covers must be snug fit and able to contain all hairs

d) Boot Covers
- Made of polyethylene-coated polypropylene or other laminate materials
- Non-linting/ non-shedding
- With shaft extended over bottom of the pant legs of jumpsuit
- Anti-skid soles

e) Chemotherapy Gloves

- Chemotherapy gloves must meet ASTM standard D6978-05 or its successor.
- Made of latex, nitrile or neoprene
- Powder-free (to prevent contamination of work areas and absorption of cytotoxic contaminants by the powder).
- With cuffs extended over wrist cuffs of jumpsuits/ gowns
  Do not wear gloves with defect(s). Double-gloving is required during compounding of cytotoxic drugs (outer layer must be sterile). Change gloves every 30 minutes or as recommended by manufacturer. It may have a shorter wear-time for handling of certain drugs with high permeability (e.g. Carmustine and Thiotepa). Change gloves immediately if damaged or obviously contaminated.

f) Respiratory Protection

Respiratory protection shall be selected based on types of activity being performed (e.g. compounding, cleaning, dispensing & etc.) and types of exposure anticipated (e.g. solid particles, liquid aerosols, oil-based aerosols, gas and vapours) as below:

- *Surgical Mask*
  Surgical mask does not provide protection against inhalation exposure of cytotoxic drugs but it can prevent possible contamination of clean room environment by personnel. It shall not be worn underneath a respirator as it may disrupt the fitting of respirator.

- *Disposable N-95 and R-95 Particulate Respirator*
  These disposable respirators protect users from inhalation of solid particles, droplets and aerosols but not gases and vapours. They are ineffective if altered or wetted or not well-fitted. The advantages of R-95 have over N-95 respirator are its abilities to filter out oil-based aerosols and smells of disinfectants and cleaning solutions.

- *Half-face Respirator with Multi-Gas Cartridge and Particulate Filter (N95 or better)*
  Half-face respirator with multi-gas cartridge and particulate filter prevents inhalation of solid particles, liquid aerosols, oil-based aerosols (depends on types of particulate filter installed), gases and vapours. Its use is strongly recommended when performing activities with high risk of inhalation exposure (e.g. compounding, cleaning of BSC & etc.). These respirators must be fit-tested prior to initial use and annually thereafter to make sure the respirator still fits. Use and care of respirator is in accordance with the manufacturer's recommendation to ensure continued protection. Users must be trained.

g) Protective Goggles
Protective goggles with side shields shall be worn by personnel working outside of a BSC or Isolator when there is risk of cytotoxic drug or waste spillage (including those who are wearing eye glasses). Eye protection is optional when working in a BSC with its glass screen set at the recommended operating level. But it is necessary when glass screen is raised for cleaning. Eye glasses alone do not protect the eyes adequately from splashes.

3.1.5 Procedures for Entry into the Clean Room

i. Before entering the Clean Room:
a) Remove accessories and make-up before entry.
b) Outdoor clothing should not be brought into changing rooms leading to Grade B and Grade C areas. Change into scrubs and clean shoes.
c) Wash hands and dry them.

ii. Inside the Changing Room:
a) Wear shoe cover and cross over.
b) Wear head cover (ensure no hair is exposed).
c) Wear respiratory protection (ensure no facial hair is exposed).
d) Wash hands with appropriate disinfectants using '7- Step Hand Washing Techniques'.
e) Dry hands with electrical hand dryer.
f) Wear a pair of sterile gloves (refer *Appendix 3* 'Gloving Techniques') for entry into Grade B and Grade C clean rooms while wear nitrile gloves for Grade D clean room.

iii. Entry into Grade D Clean Room:
a) Follow steps as explained in (i) and (ii).
b) Put on chemo gown/ isolation gown and boot covers
c) Wear a second pair of sterile gloves (gloves over sleeve cuffs of chemo gown).
d) Use full length mirror to inspect and ensure all PPEs are properly donned.
e) Enter Grade D clean room.

iv. Entry into Grade C Clean Room (Component Room):
a) Follow steps as explained in (i) and (ii).
b) Wear jumpsuit (gloves under sleeve cuffs of jumpsuit) and boot covers, minimising contact with outer layer of the garments (refer *Appendix 4* 'Aseptic Gowning Procedure').
c) Put on chemo gown/ isolation gown.
d) Wear a second pair of sterile gloves (gloves over sleeve cuffs of chemo gown).
e) Use full length mirror to inspect and ensure all PPEs are properly donned.
f) Enter Component Room.

v. Entry into Grade B Clean Room:
   a) Follow steps as explained in (i) and (ii).
   b) Enter gowning room without touching the door handle.
   c) Wear sterile jumpsuit (gloves under sleeve cuffs of jumpsuit) and boot covers, minimising contact with outer layer of the garments (refer *Appendix 4* 'Aseptic Gowning Procedure').
   d) Put on sterile chemo gown.
   e) Wear a second pair of sterile gloves (gloves over sleeve cuffs of chemo gown).
   f) Use full length mirror to inspect and ensure all PPEs are properly donned.
   g) Enter the Compounding Room.

vi. During Aseptic Compounding:
   a) Check periodically to ensure that garments are in good condition and the seams are sealed.
   b) Gloves are recommended to be changed every 30 minutes unless otherwise recommended by the manufacturer.
   c) Gloves/ chemo gown are to be changed immediately if torn/ punctured or in the event of contamination.
   d) Remove and discard outer layer of sterile gloves and chemo gown into cytotoxic waste bag/ bin in the compounding room before exit into gowning room.

vii. Exit from Clean Room:
   a) Remove PPE in gowning room (refer *Appendix 5* 'De-gowning Procedure') and discard into cytotoxic waste bag/ bin.
   b) Wash hands and exit from clean room.

3.1.6 Health Requirements

All personnel should undergo health assessment pre-placement, routinely and upon exit to evaluate their fitness to perform sterile compounding tasks and to monitor for adverse health effects of cytotoxic drug exposure. All health records should be kept for at least 30 years from the date of the last assessment.[22]

To date, there is no specific biological monitoring or health assessment technique proven to be able to adequately predict the effects of occupational exposure to cytotoxic drugs. Nevertheless, health surveillance should include assessment and documentation on current health status, medical (including reproductive) history, physical examination, laboratory testing, previous occupational exposure/ work history and symptom of complaints (if any). It is of utmost importance to remain aware of and apply any future developments for monitoring of health of personnel handling cytotoxic drugs.

All personnel must be educated on the adverse health effects associated with occupational exposure to cytotoxic drugs and wastes, the reproductive risks to men and women who are trying to conceive, pregnant or breastfeeding and precautions and safety

measures which must be practiced at workplace. Health assessment should be well planned out (as below) and closely monitored. Follow-ups and counseling should be provided for personnel with findings of concern.

Types of Health Assessment

i. Pre-placement Medical Examinations *(Appendix 8)*
   a) History taking (work history, family history and other relevant risk factors)
   b) Pregnancy status
   c) HIV, Hepatitis B and Tuberculosis screening tests
   d) Visual examination
   e) Other baseline examinations include Full Blood Count with white cell differential, biochemistry tests (Renal Profile, Liver Function Test) and physical examination (skin-related problem and neurological disorder, e.g., hand tremors)

ii. Routine Medical Examinations *(Appendix 8)*
   Routine medical examinations are recommended to be carried out annually to monitor for changes from baseline and previous health assessments. However, immediate medical attention is warranted in the event of accidental exposure due to spills, sharps or needle prick injury.

iii. Personnel Exit Review *(Appendix 9)*
   Medical examination *(Appendix 8)* should be conducted upon exit from Cytotoxic Drug Reconstitution Service. Duration of placement, reason for exit and medical examination results should be verified by Pharmacist In-Charge. The Personnel Exit Review report *(Appendix 9)* must be completed and kept with all medical examination and laboratory results for surveillance purpose.

3.1.7 Qualification and Validation

i. All permanent personnel directly involved in cytotoxic drug reconstitution shall be trained and qualified in aseptic technique and satisfy the following requirements:
   a) Fit to perform sterile compounding and other technical tasks as determined in medical examination by a physician.
   b) Undergone basic aseptic training.
   c) Adequate competency (assessed by Pharmacist In-Charge)
   d) Passed annual validation (inclusive of gloved fingertip sample and media fills).
   e) Credentialed or privileged.

ii. Every personnel involved in aseptic technique dispensing shall undergo validation test prior to working in the sterile unit.

iii. Revalidation shall be performed at least once a year. Validation of personnel is adapted from the Universal Operator Broth Transfer Validation, UK Pharmaceutical Aseptic Services Committee.

3.2 PREMISES AND EQUIPMENT

3.2.1 Principles

Premises and equipment shall be suitable for the intended activities and they shall not cause any hazard to the surroundings or compromise quality of the finished products.

3.2.2 General Requirements

i. Premises and equipment shall be appropriately maintained and upgraded, ensuring that they are suitable for the intended activities. There shall be a logical workflow and appropriate segregation of activities.
ii. In order to reduce the risk of contamination and cytotoxic drug exposure (e.g., by cross contamination or by the accumulation of dust and dirt), appropriately designed premises and equipment as well as careful and suitable working techniques shall be used. Special care shall be taken when microbiological environmental monitoring samples are taken or when equipment is cleaned and, where applicable, disinfected after repair or maintenance.
iii. Washing and cleaning activities shall not themselves be a source of contamination.
iv. Adequate measures shall be taken against the entry of insects and other animals (pest control).
v. Production, storage and quality control areas shall be accessible to authorised personnel only.
vi. Environmental conditions (temperature, humidity, light) during production, quality control and storage (including cold storage) shall be defined and monitored and, if necessary, controlled. Monitoring results shall be documented, assessed and retained. When conditions fall outside the defined limits, adequate corrective action shall be taken.
vii. All areas shall be clean, orderly and well lit.

3.2.3 Cleaning Procedure for Clean Room and Equipment

i. Responsibilities
   a) The Pharmacist In-Charge shall oversee the cleaning and disinfecting of clean room and all equipment.
   b) Cleaning and disinfecting tasks can be assigned to Pharmacy and/ or Hospital Support Service personnel, provided that they are well-trained.
   c) The Pharmacist In-Charge or a Designated Person shall provide routine training to the cleaning and disinfecting personnel.
   d) The Pharmacist In-Charge or a Designated Person shall supervise and assess all cleaning procedures done.

ii. Equipment/ Materials
   a) Dedicated sterile lint-free/ non-shedding mops (autoclavable)
   b) Dedicated multi-bucket mopping system (if required)
   c) Sterile lint-free wipes
   d) Sterile disinfectant such as sterile alcohol 70%, etc. (refer *Appendix 18*)
   e) Sterile Water for Injection (WFI)
   f) PPE
   g) Deactivation agent such as peroxide formulations, sodium hypochlorite, etc.

iii. Entry of Cleaning Materials and Equipment into Clean Room
   a) Ensure all materials and equipment are in good condition
   b) All materials entering clean room shall be disinfected with sterile alcohol 70%.
   c) Materials and equipment disinfected shall be brought into clean room through pass box, except for materials that are too bulky to be placed into the pass box.

iv. Cleaning Procedures
   Frequency of cleaning for equipment/ area is as shown in Table 3.1.

Table 3.1 Cleaning frequency for related area

Frequency	Equipment/ Area
Before and after production	CDR Safety Cabinet/ Isolator
After production or daily	Stainless steel bench and trolley in preparation room, floor, window and door knobs, pass box and clinical waste bins
Weekly	Stainless steel bench and trolley, floor, window and door knobs, pass box and clinical waste bins, walls and sinks, gowning cabinet, changing room cabinet, CDR Safety Cabinet/ Isolator
Monthly	Stainless steel bench and trolley, floor, window and door knobs, pass box and clinical waste bins, walls and sinks, gowning cabinet, changing room cabinet, ceilings, CDR Safety Cabinet/ Isolator

   a) Cleaning procedure for CDR Safety Cabinet
      - Wear PPE before entering the compounding room.
      - If CDR Safety Cabinet is turned off, switch it on and allow purging of air for as long as recommended by manufacturer (check user manual) before start cleaning.
      - Clean the back wall of the cabinet first, followed by the left and right side, the glass screen and lastly, the work bench from the cleanest area to the dirtiest area with overlapping wipes using sterile alcohol 70% as surface disinfectant to reduce any bioburden present.

- Discard all soiled wipes into the cytotoxic waste bag.
- Wait for at least 5 minutes to allow alcohol to dry before using the cabinet.
- When production completes, clean the cabinet according to the above procedure using deactivation agent, followed by sterile WFI and sterile alcohol 70%. Wipe with sterile WFI for multiple times before alcohol to remove residue of deactivation agent as much as possible.

b) Cleaning procedure for Isolator
- Wear PPE before entering the compounding room.
- If isolator is turned off, switch it on and allow purging of air for as long as recommended by manufacturer (check user manual) before start cleaning.
- Clean the external surfaces of the transfer chambers and front visor.
- Wipe all internal surfaces with sterile alcohol 70% before the start of each work session.
- Clean the inner surfaces of both transfer chambers.
- Clean the back of the isolator, followed by the left and right side, the front visor, glove sleeves and lastly, the work bench with overlapping wipes using sterile alcohol 70% as surface disinfectant to reduce any bioburden present.
- Discard all used wipes into the cytotoxic waste bin placed in the transfer chamber.
- Wait for at least 5 minutes to allow alcohol to dry before using the isolator.
- When production completes, clean the isolator according to the above procedure using deactivation agent, followed by sterile WFI and lastly, sterile alcohol 70%. Wipe with sterile WFI for multiple times before alcohol to remove residue of deactivation agent as much as possible.

c) Cleaning procedure for stainless steel work bench, trolleys, clean room chairs/ stools, cross over benches and other clean room furniture
- Wipe all equipment with low lint wipes and sterile alcohol 70%.
- Use deactivation agents, sterile water and alcohol 70% for furniture placed in compounding room.
- Ensure that all hard-to-reach areas are cleaned.

d) Cleaning procedure for window
- Clean from top to bottom with lint-free wipes and sterile alcohol 70%.
- Ensure that all hard-to-reach areas are cleaned.

e) Cleaning procedure for pass box
- Clean the inner surfaces of the pass boxes before transferring materials and equipment into the pass boxes for the first time on that day.
- Begin with the inner glass panels, top surface, followed by the left and right side, outer glass panels and lastly, the bottom surface with lint-free wipes and sterile alcohol 70%.

- Use deactivation agents, sterile WFI and alcohol 70% to clean all pass boxes when production is done.
- All items including clinical waste/ sharps bin must be disinfected before placing them into the pass box.

f) Cleaning procedure for floor
- Use appropriate disinfectant.
- Mop with overlapping strokes from the cleanest to the dirtiest area.

g) Cleaning procedure for walls
- Clean walls using lint-free wipes or extendable mop with appropriate disinfectant.
- Clean from top to bottom (ceiling to floor) or side to side from the cleanest area to the dirtiest area with overlapping strokes.
- Ensure that all hard-to-reach areas are cleaned.

h) Cleaning procedure for ceilings
- Clean ceilings using lint-free wipes or extendable mop with appropriate disinfectant from the cleanest to the dirtiest area.
- Avoid contact with HEPA filters while cleaning.
- Ensure that all hard-to-reach areas are cleaned.

v. Deactivating, Cleaning and Disinfecting

It is worthy to take note that there is no deactivation agent which is capable of neutralising all hazardous drugs and no disinfectant which is capable of eliminating all microorganism in the clean room environment. These chemicals shall be applied by wetting the sterile wipes and not by spraying (spray bottle) on surfaces to avoid spread of hazardous drug residue, with appropriate PPE for protection when cleaning or handling these chemicals. Adherence to proper cleaning procedures is the key to maintain a sterile environment and safe workplace.

a) Deactivation agents
- Check surface compatibility.
- Prepare or dilute as per manufacturer recommendations.
- Clean the surfaces multiple times with other solutions (e.g. neutraliser - if any, sterile WFI and disinfectants) after application as its residues may damage/ corrode surface materials.

b) Disinfectants
- Choice of disinfectants shall be based on the grade of clean room as well as the fauna of the clean room.
- Disinfectants used shall be sterile (in grade A and B clean rooms) and rotated at specific interval based on manufacturer's recommendation.
- Periodic use of sporicidal agents shall be considered to reduce contamination from spore forming microorganisms (eg. monthly).

- Prepare or dilute disinfectant in clean containers as per manufacturer's recommendation in the clean room.
- Label containers clearly with BUD and store as per manufacturer's recommendation.
- Partly emptied containers shall not be topped up.

vi. Storage of Cleaning Materials and Equipment
   a) Facility with utility room: all cleaning materials shall be stored in the utility room.
   b) Facility without utility room: all cleaning materials shall be stored in the component preparation room.

vii. Handling of Used Cleaning Materials
   a) All used disposable materials shall be treated as cytotoxic waste.
   b) Reusable cleaning materials shall be cleaned and sterilised based on standard protocol before the next use.

viii. Cleaning under Non-Routine Circumstances
   Thorough cleaning must be done before any production activity in the event of which the cleanliness of classified room is deemed compromised;
   a) Breakdown of Air Handling Unit (AHU)
   b) High microbial count
   c) Major and minor renovations
   d) Repair and maintenance work
   e) Deviation of room physical parameters (e.g. wet room environment and floors due to high humidity & etc.)
   f) Others
   Refer to Maintenance Procedure for Clean Room and Equipment for further details.

ix. Records and Documentation
   a) Cleaning procedures must be clearly written.
   b) All cleaning done shall be recorded. The Pharmacist In-Charge or Designated Person shall verify all documentations.
   c) All records shall be based on standard protocol (example of record - *Appendix 10* "Cleaning Log").

3.2.4 Maintenance Procedure for Clean Room and Equipment

i. Responsibilities
   a) Pharmacist In-Charge:
      - Monitor all performance testing/ recertification, maintenance and repair work.
      - Monitor all physical and microbiological parameters.
      - Analyse and verify all monitoring and testing reports.
      - Ensure performance testing are conducted by qualified/ accredited third-party agent (e.g. NEBB or NATA certified).

   b) Hospital Support Services (HSS)
      - Carry out periodic maintenance and performance testing as scheduled.
      - Appoint qualified/ accredited third-party agent (e.g. NEBB or NATA certified) for performance testing and recertification of clean room and equipment.
      - Ensure performance tests are conducted and data collected in accordance with the appropriate standards.
      - Analyse and verify all testing reports.
      - Investigate and rectify deviation from specifications in timely manner.
      - Present findings of testing report/ investigation on deviation and corrective action plan to the Pharmacist In-Charge.

ii. Equipment/ Materials
   a) All devices used for monitoring clean room and equipment parameters (pressure gauges, thermometer, hygrometer and etc.) require periodic maintenance and calibration.
   b) Equipment used for performance testing must be calibrated prior to testing done.

iii. Procedures for Clean Room Environmental Monitoring
   a) Monitoring of clean room environment and equipment performance should include:
      - Physical Monitoring
      - Microbiological Monitoring

   b) Periodic maintenance should at least include:
      - Planned Preventive Maintenance (PPM) by HSS according to facility schedule (check with hospital engineer for details)
      - Annual performance testing/ Recertification by qualified/accredited third party testing agent

   c) For physical monitoring, the parameters and minimum frequency are listed in Table 3.2.

Table 3.2 Monitoring parameter and their frequency for facility maintenance

Parameter	CDR Safety Cabinet or Isolator	Clean Room
1. Temperature		a) Before production. b) Daily if no production.
2. Humidity		a) Before production. b) Daily if no production.
3. Room Pressure Differentials		a) Before production. b) Daily if no production.
4. Pressure Differential Across HEPA Filters or Airflow Velocity	Before production.	
5. Isolator Glove Integrity	Visual checks every session.	
6. Isolator Leak test	Weekly. *depends on the brand and model of isolator (refer User Manual)	

- Room Temperature and Humidity Monitoring
  - Temperature (20±2^{0}C) and humidity (55±5%) shall be kept at the recommended ranges to prevent microbiological contamination and ensure comfort of personnel working in clean room.
  - Record the temperature and humidity readings daily in Clean Room Temperature, Humidity and Pressure Differential Record *(Appendix 11)*.
  - Check, analyse and verify the records.
  - For deviation from specification, please refer to 3.2.4 (v) and 1.3 under Chapter 1.

- Room Pressure Differentials Monitoring
  - Room pressure differentials shall be kept at the recommended ranges (refer *Appendix 12*) to maintain cleanliness of classified rooms and prevent spread of cytotoxic contaminants.
  - Record the room pressure differential readings daily in Clean Room Temperature, Humidity and Pressure Differential Record *(Appendix 11)*.
  - Check, analyse and verify the records.
  - For deviation from specification, please refer to 3.2.4 (v) and 1.3 under Chapter 1.

d) Microbiological Monitoring

- For microbiological monitoring, the monitoring parameters and frequency are listed in Table 3.3.
- Procedures for microbiological monitoring are listed in Table 3.4.

Table 3.3 Monitoring parameter and their frequency for microbiological monitoring

Parameter	CDR Safety Cabinet or Isolator	Clean Room
1. Passive air sampling	a) Every working session. b) After repair/ maintenance involving replacement of any part of the equipment (e.g. HEPA filters & etc).	a) Once a week during production. b) After renovation/ repair of room or repair/ maintenance involving replacement of any part of the AHU (e.g. HEPA filters & etc).
2. Surface sample test (Contact plate)	Once a week.	a) Once a month. b) After renovation/ repair of room or repair/ maintenance involving replacement of any part of the AHU (e.g. HEPA filters & etc).
3. Aseptic work practice assessment (Gloved fingertip sampling with contact plate)	At the end of each working session (for compounders).	
4. Active air sampling (Volumetric air-sampler) * Refer user manual of air sampler device and microbiology laboratory protocol for proper procedures	a) Every 3 months. b) After repair/ maintenance involving replacement of any part of the equipment (e.g. HEPA filters & etc).	a) Every 3 months. b) After renovation/ repair of room or repair/ maintenance involving replacement of any part of the AHU (e.g. HEPA filters & etc).

Note: All the parameters mentioned above shall be monitored during in-operation.

- In addition to the specific sampling frequencies described in this section, sampling must be performed in any of the following circumstances:
  - Certification of new facilities and equipment
  - After any modification of facilities or equipment
  - Detection of problems or worrying trends
  - Detection of changes that could impact the controlled area environments

Table 3.4 Microbial monitoring procedures

(A) Settle Plate (TSA & SDA - 90mm diameter)	(B) Contact Plate* (TSA **& SDA** - 55mm diameter)	(C) Gloved fingertip sampling with contact plate
✓ **Before the start of operation/ production, gather the required quantity of agar plates.** ✓ **Label plates with location/ sample site, date (for all plates), time of sampling starts (for settle plates), names of personnel, left & right hand (for plates used for gloved fingertip sampling).** ✓ **Disinfect before transfer the plates into pass box.**		
a) Place the settle plate at the sample site. b) Remove its lid and leave it for 4 hours or less (if production ends earlier)#. c) Put its lid back, seal with parafilm and write the end time on its label.	a) Take samples upon completion of operation/ production. b) Remove the lid of contact plate. c) Press it lightly against the surface of sample site for 2-5 seconds. d) Put its lid back, seal with parafilm. e) Clean and disinfect sampled area immediately. f) Use a new plate for each sample site.	a) Take samples after the last dose of drug compounded. b) Do not disinfect gloves before sampling. c) Remove the lid of a contact plate. d) Hold the plate at an angle that will allow four fingers of one hand to first press on the agar and create a slight impression then followed by the thumb. e) Repeat with the opposite hand on the second plate. f) Put its lid back and seal with parafilm.
✓ **Send the plates to the laboratory immediately or handle as per microbiology laboratory protocol.**		

Incubate as follows:

- TSA plates- 48hrs at 30-35°C (for bacteria)
- SDA plates-5 days at 26-30°C (for yeasts & mold)[19]

✓ **Analyse and verify all laboratory results and reports. Keep the reports systematically.**
✓ **For deviation from specification, please refer to 3.2.4 (v) and also 1.3 in Chapter 1.**

(Notes: Sampling must be done during normal operation/ production)

*Contact plate has a raised surface that allow the agar to be pressed on surfaces.

** Media used for surface- and fingertip sampling must contain added Lecithin and Polysorbate 80 (to neutralize the effects of disinfectants).

For exposure time less than 4 hours, result obtained should be extrapolated using the following equation: Count/ Time Exposed (min) X 240 = cfu/4 hr.

TSA: Tryptic Soy Agar; SDA: Sabouraud Dextrose Agar

- Identifying sample sites
  - Select critical zones and sites that are likely to capture the impact of personnel movement and work within the area. Other areas of concern to be monitored include entry points of materials/ equipment from a room with lower classification to another with higher classification, areas near doors and any other spots with air backwash turbulence. Sample sites selected shall remain constant as determined during facility qualification and well documented.

- Selecting culture media and diluents
  - The type of medium used (solid or liquid) for sampling microorganism may differ (depends on the procedure and equipment used). Alternatives to TSA and SDA can be used as long as they are suitable for the intended purpose. Soybean casein digest medium is considered equivalent to TSA and malt extract agar can be used to detect yeasts and molds in the environment.

- Swabbing method (surface swabs) can be done for irregular surfaces to supplement contact plate method for surface sampling but there is no microbial limit can be recommended. Check with microbiology laboratory for proper sampling procedure and refer to reliable references (e.g. USP 797 & etc.) for guide on interpretation of results.

- Microbiological monitoring is essential for quality assurance of finished products, evaluation of effectiveness of cleaning and disinfecting procedures and personnel adherence to aseptic work practice.

iv. PPM by Hospital Support Services (HSS) and Recertification by Third Party Testing Agent

PPM schedule should be made available to pharmacy and appointment should be made beforehand to facilitate proper arrangement for maintenance activities. PPM must include the below:

a) Changing of all primary and secondary filters as scheduled in timely manner (AHU, CDR Safety Cabinet and isolator).
b) Calibration of pressure gauges, thermometer and hygrometer.
c) Inspection of emergency push button, interlocking button and alarm button (if applicable).
d) Performance testing by third party agent on clean room and major equipment.
e) Performance testing and recertification by Third Party Testing Agent should include parameters listed in Table 3.5.

Table 3.5 Validation activities by third party agent

Parameter	CDR Safety Cabinet or Isolator	Clean Room
1. Airborne Particle Counts	a) Once a year. b) After repair/ maintenance which could potentially affect performance of the equipment (e.g. replacement of HEPA filters & etc).	a) Once a year. b) After renovation/ repair of room or repair/ maintenance which could potentially affect performance of the AHU (e.g. replacement of HEPA filters & etc).
2. HEPA Filter Integrity	a) Once a year. b) After repair/ maintenance which could potentially affect performance of the equipment (e.g. replacement of HEPA filters & etc).	a) Once a year. b) After renovation/ repair of room or repair/ maintenance which could potentially affect performance of the AHU (e.g. replacement of HEPA filters & etc).
3. Air Pressure Differential		a) Once a year. b) After renovation/ repair of room or repair/ maintenance which could potentially affect performance of the AHU (e.g. replacement of HEPA filters & etc).
4. Air Change Rate Test		a) Once a year. b) After renovation/ repair of room or repair/ maintenance which could potentially affect performance of the AHU (e.g. replacement of HEPA filters & etc).
5. Air Flow Velocities	a) Once a year. b) After repair/ maintenance which could potentially affect performance of the equipment (e.g. replacement of HEPA filters & etc).	
6. Air Flow Pattern	a) Once a year. b) After repair/ maintenance which could potentially affect performance of the equipment (e.g. replacement of HEPA filters & etc).	
7. Isolator Alarm Functional Tests	Once a year.	

Parameter	CDR Safety Cabinet or Isolator	Clean Room
8. Isolator Leak Test	a) Once a year. b) After repair/ maintenance which could potentially affect performance of the equipment (e.g. replacement of HEPA filters & etc).	
9. Isolator Pressure Hold Test	a) Once a year. b) After repair/ maintenance which could potentially affect performance of the equipment (e.g. replacement of HEPA filters & etc).	

Note: All testing shall be performed at-rest.

- Ensure all personnel from Third Party Agents adhere to proper hand washing and clean room entry procedures.
- Ensure maintenance and corrective works are complete before annual performance testing or recertification.

v. Deviation from Specifications

Deviations of physical and microbiological monitoring parameters from specifications are indicators of compromised clean/ safe environment. Immediate actions are warranted:

a) Lodge report to HSS and follow up closely.
b) Identify cause of problems and take the necessary corrective actions soonest possible.

vi. Records and Documentation

a) All reports/ records of physical and microbiological parameters monitoring, repair and maintenance work, performance testing and recertification must be verified by Pharmacist In-Charge.
b) All reports/ records of physical and microbiological parameters monitoring, repair and maintenance work, performance testing and recertification must be kept systematically or as per facility protocol (examples of records refer *Appendix 11 and Appendix 12*).

3.3 PRODUCTION

3.3.1 Principles

All production activities are aimed to produce high quality finished products, and to be performed and supervised by competent personnel.

3.3.2 General Requirements

i. All production activities shall be performed by trained personnel with strict adherence to aseptic work practices.
ii. Appropriate flow of materials, segregation and adequate line clearance procedures shall be established to ensure sterility of finished products, to prevent cross-contamination and errors (e.g. mix up of drugs & etc).
iii. Only sterile materials shall be taken into Grade A and B areas.
iv. It is recommended to use cytotoxic drug product in solution form in preference over powder form as it requires lesser manipulation and for safe handling purposes, with due consideration given to the aspects of stability and storage of the final product.

3.3.3 Pre-Production

The pharmacist shall ensure that:

i. Worksheets and labels are prepared, counterchecked and verified.
ii. Starting materials are gathered and counterchecked.
iii. All materials and equipment are disinfected with sterile alcohol 70% before transferred into pass box.
iv. CDR Safety Cabinet/ Isolator is intact and operational by checking on the display panel and isolator glove integrity.

3.3.4 During Production

i. Cleaning of CDR Safety Cabinet/ Isolator
   a) Switch on the CDR Safety Cabinet/ Isolator and leave it to purge for a minimum of 20-30 minutes or as recommended in user manual.
   (This step is not required if CDR Safety Cabinet/ Isolator is left running continuously)
   b) Clean the CDR Safety Cabinet/ Isolator (refer to 3.2.3 Cleaning Procedure for Clean Room and Equipment).

ii. Aseptic Processing

A minimum of 2 personnel is required for compounding activity at all times. Counterchecking (starting materials, drugs, volumes measured & etc) is compulsory to prevent errors. All materials, equipment and supplies must be disinfected before transferring them into the CDR Safety Cabinet/ Isolator.

a) Withdrawal of Cytotoxic Drug Solution from Ampoule

- Clearing and Preparing the Ampoule
  - Make sure that the ampoule and its contents are in good condition (i.e., intact, not expired, clear and no foreign particles).
  - If the ampoule head contains drug solution, tap the head lightly to remove it. If tapping does not work, then invert the ampoule to fill the ampoule head with drug solution. Tap to remove bubble if there is any. Swing the ampoule in inverted 'J' pattern.
  - With the ampoule in upright position, ensure that there is no solution or bubble trapped at the ampoule neck.

- Fixing Filter Straw/ Filter Needle (for Glass Ampoule)/ Needle (for Plastic Ampoule) to Syringe
  - Half unwrap the syringe, 5µm filter straw or filter needle or needle pack.
  - Fix the filter straw/ filter needle/ needle onto the syringe with special precaution not to touch the critical sites.
  - Put the assembled syringe, with filter straw/ filter needle/ needle aside to be used later.

- Breaking the Ampoule
  - Swab the neck of the ampoule with sterile alcohol 70%.
  - For glass ampoule, wrap around the neck of the ampoule with a new sterile alcohol swab/ gauze before breaking it to protect fingers from sharp edges. Alternatively, an ampoule breaker may be used.
  - Hold the head of the ampoule between the thumb and the index finger of dominant hand and the base of the ampoule between the thumb and the index of the other hand. Break it in the direction away from the body.
  - Discard the ampoule neck (with the alcohol swab/ gauze) immediately into the sharps bin.

- Withdrawing Solution from Ampoule
  - Insert the filter straw/ needle into the ampoule cautiously, avoid contact with the ampoule neck. Position the straw/ needle in the shoulder area of the ampoule so that the bevel tip is facing downwards.
  - Hold the ampoule in one hand and syringe in the other. Pull the plunger back with the thumb and index finger to withdraw required volume of drug solution into the syringe using `non-touch' technique.
  - Remove air from the syringe and measure the volume of the content

withdrawn.

- Change the filter straw/ filter needle to a regular needle.

b) Adding Diluent to a Vial Containing Powder (not for negative pressure vial)

- Swab the rubber bung with sterile alcohol 70%.
- Hold the vial firmly on benchtop.
- Position the syringe containing diluent at 45° and place its needle on the rubber bung of the vial with the bevel facing upward and away from compounder.
- Push the needle through the rubber bung.
- Push the plunger down slowly until the entire diluent is transferred into the vial.
- Pull the plunger to its initial position. This will ensure no positive internal pressure is created within the vial (this step is not applicable for drug vials with negative internal pressure).
- Pull the needle out of the rubber bung slowly.
- Discard the syringe and needle into the sharp bin.
- Let the vial stand for a while. Roll or swirl gently to ensure powder dissolved completely. Vigorous shaking is not allowed for certain drugs.

c) Withdrawing Drug Solution from a Vial (Negative Pressure Technique and Pulse Technique)

- Swab the rubber bung of the vial with sterile alcohol 70%.
- Draw the required volume of air (equivalent to volume of drug solution needed) into the syringe by pulling the plunger.
- Hold the vial firmly on bench top.
- Position the syringe at 45° and place its needle on the rubber bung with the bevel facing upward and away from compounder.
- Push the needle through the rubber bung.
- Invert the vial with needle and syringe attached.
- Pull and push the plunger slightly and slowly to aspirate drug solution into the syringe. Repeat this `pulse technique' until the desired volume of solution is transferred into syringe.
- Do not push too much air into the vial at one time. This is to avoid creating high positive pressure in the vial, which could lead to aerosolization and leakage of its content.
- Place the vial on the bench top and pull the needle out.
- For multiple withdrawals from a single vial, do not insert the needle of subsequent syringes at the previous puncture point.
- Remove air bubbles and adjust to the desired volume with syringe still attached to the vial whenever possible. If the syringe is detached, cap its needle before removing air.

d) Transferring Drug Solution from Syringe to Infusion Bottle
- Swab the rubber bung of the infusion bottle with sterile alcohol 70%.
- Position the syringe containing drug solution at 45° and place its needle on the rubber bung with the bevel facing upward.
- Push the needle through the rubber bung.
- Push the plunger down slowly until the entire drug is transferred into the infusion bottle.
- Pull the needle out of the rubber bung slowly.
- Discard the syringe and needle into the sharp bin.
- Swab the rubber bung of the infusion bottle and seal it with parafilm.
- Inspect for presence of any foreign material in the infusion bottle. If there is presence of foreign particles, quarantine the preparation(s) and take remedial actions (Refer 3.3.5 (vi) Rejected and Returned Materials and Products).

3.3.5 Post-Production

i. Cleaning of CDR Safety Cabinet/ Isolator
a) Ensure the CDR Safety Cabinet/ Isolator is in operational mode
b) Purge CDR Safety Cabinet for at least 5 minutes (or as recommended by user manual) following the last dose of cytotoxic drug preparation compounded
c) Clean the CDR Safety Cabinet/ Isolator (refer to 3.2.3 Cleaning Procedure for Clean Room and Equipment)

ii. Labelling and Packaging
a) All finished products shall be packaged in clearly labelled (with hazard warning sign), sealed (heat sealed whenever possible), opaque and leak proof outer bags.
b) Labels shall include:
- Patient's name and other identification details
- Content (drug, dose and diluent/ fluid)
- Final volume
- Route of administration
- Date of preparation
- Expiry date and time
- Storage instructions

iii. Storage
a) Storage of intact drug vials
- Store intact drug vials under conditions recommended by manufacturer.
- Monitor stock level, expiration dates and storage conditions periodically following standard policy.

- Containers, shelves or bins used for storage must be properly labelled (with hazard warning sign).
- Containers, shelves or bins used must have barriers or other safety features which help to contain leakage and prevent breakage due to accidental falls.
- Drugs require refrigeration should be stored in a dedicated refrigerator.
- Spill kits must be readily available to personnel handling the vials.

b) Storage of partial and reconstituted drug vials
- All vials are manipulated aseptically under sterile conditions.
- All vials must be wiped with sterile alcohol and sealed with parafilm before removal from CDR Safety Cabinet/ Isolator.
- Store vials within component area and refrigerator (if required).
- Do not store partial and reconstituted vials inside CDR Safety Cabinet/ Isolator.
- The date and time of first needle-puncture or the in-use expiry date must be written/ labelled directly onto the partial or reconstituted vials. It should also be based on microbial risk level or stability data whichever is shorter.
- Stability of different brands may vary due to differences in formulation, ingredients used, manufacturing processes and packaging.
- The given in-use expiry date should be justifiable with:
  - Stability and compatibility data at the final concentration. Final concentration of any particular drug requiring reconstitution should be made the same at all times to avoid medication error and facilitate concentration limits.
  - CSP microbial contamination risk level (low/ medium/ high) as outlined in USP chapter <797> Pharmaceutical Compounding-Sterile Preparations.
  - Storage conditions
- Preservative-free products must be used within 24 hours.
- Inspect content of vials for any sign of instability before use.

c) Storage of finished products
- Points to be considered when determining expiry dates for finished products:
  - Stability of the drug at the given concentration in the given diluent/ fluid
  - CSP microbial contamination risk level (low/ medium/ high) as outlined in USP chapter <797> Pharmaceutical Compounding-Sterile Preparations
  - Storage conditions
- Storage period of finished products:
  - Should not exceed the expiration dates of the drug and any of its components
  - Should not exceed time before administration

- Should be based on microbial risk level or stability data whichever is shorter
- Clear storage instructions must be provided to end users

iv. Dispensing
   a) Wear proper PPE (gloves and mask at the least)
   b) Countercheck before dispense to ensure the following are right:
      - Right Patient
      - Right Drug
      - Right Dose
      - Right Diluent/Fluid
      - Right Final Volume
      - Right Route of Administration
      - Other auxiliary information (e.g. expiry dates, storage instructions & etc)

v. Transport of Cytotoxic Drug Preparations (Finished Products) within Hospital and between Hospitals
   a) Delivery of cytotoxic drug preparations must be made directly to the wards or daycare units within hospital by trained personnel in safe handling and spill management of cytotoxic drugs. No detours should be allowed.
   b) Containers (cold box or others) used for transporting cytotoxic drug preparations should be hard-walled, robust, made from sturdy materials.
   c) Line the containers with absorbent material in case there is leakage or spillage.
   d) Containers used should be labelled clearly and dedicated for the transport of cytotoxic drug preparations only.
   e) Use of pneumatic tubes to deliver cytotoxic drug preparations is **NOT ALLOWED** when transporting preparations within hospital.
   f) Spill kit must be readily available to personnel involved in the transport of cytotoxic drug preparations.
   g) Ensure that transit duration and condition (cold chain, risks of spillage and breakage, exposure to sunlight and others) do not affect the quality of cytotoxic drug preparations when transporting between hospitals.

vi. Rejected and Returned Materials and Products
   a) All errors, defects and complaints related to starting materials, commercial drug products and CSP shall be investigated, remediated and documented.
   b) For deviation from specifications in CSP, refer to Chapter 1. Check if other preparations are affected and cease supply until cause(s) of problem solved.
   c) Product complaints and recalls of starting materials or commercial drug products by manufacturers shall be managed in accordance with MOH policy.
   d) Rejected or recalled starting materials, commercial drug products and CSP shall be stored in a secure, segregated area while their disposition is decided.
   e) Where any doubt arises over the quality of a commercial drug product or CSP, it shall not be considered suitable for re-issue or re-use.
   f) Unused products/ preparations returned by end users from wards/ daycare

units should be disposed, unless its quality can be assured (*Appendix 13*):

- Check expiry date and inspect for any sign of instability
- Consider stability and possible microbial contamination under actual handling conditions (storage, transportation) by end users
- Determine reason(s) for medication return
- Records of re-use must be kept (identifications, assignment of new expiry date, new label, worksheet & re-dispensing)

g) Products/ preparations that have been released to a patient, or into the community, should **NEVER** be reused for other patients.

3.3.6 Disposal of Cytotoxic Waste

i. Principles

a) Materials and equipment used in the preparation and administration of cytotoxic drugs may cause injury or unwanted exposure among other personnel if not disposed properly.

b) Cytotoxic waste containers must be clearly labelled and properly sealed. Only trained personnel are allowed to handle these wastes. The personnel must take all necessary precautions to ensure personal, public and environment safety.

c) All cytotoxic waste generated from production activity, use and administration of drugs must be packaged in double bags, segregated and disposed in a manner that shall not cause personnel exposure and contamination to the environment.

d) Disposal procedures must comply with all applicable acts and regulations (refer "Guidelines on the handling of clinical wastes in Malaysia" by Department of Environment, Ministry of Natural Resources & Environment).

e) Cytotoxic waste should never be landfilled or discharged into the sewerage system.

f) Cytotoxic waste must be collected separately from pharmaceutical waste and disposed of in a hazardous waste incineration plant. Incineration at high temperature of up to 1100-1200°C (secondary chamber) is required for full destruction of cytotoxic substances.

ii. Procedure

Cytotoxic waste includes all materials that have come into contact with cytotoxic drugs during production and administration.

a) Cytotoxic waste generated in the CDR Safety Cabinet/ isolator

- All contaminated materials such as vial/ ampoule which are empty or partially used, used needles and syringes shall be discarded into the sharp bin.
- Used materials such as wrappers and infusion bottles that are potentially contaminated with cytotoxic drug residues must be discarded into the cytotoxic waste bag.
  Note: Unused drugs shall be wiped with sterile alcohol 70% before taken out from the cabinet/ isolator for storage.

b) Gowns and Gloves

- Outer layer of gloves must be discarded into a waste container (e.g. sharp bin) inside the CDR Safety Cabinet/ isolator or contained in a sealed bag for disposal outside the CDR Safety Cabinet/ isolator. Disposable gowns must be discarded into the cytotoxic waste bag before leaving the compounding room at the end of each working session.
- Personnel must never leave the compounding room with gown and outer layer gloves worn during compounding.

c) Cytotoxic Waste Bins

- Disposable (sharp or yellow bins) and non-disposable bins (clinical waste bins) shall be made available in the cytotoxic drug reconstitution units and areas/ wards where cytotoxic drugs are administered to patients.
- All cytotoxic waste bins and bags shall carry the "CYTOTOXIC WASTE" warning label.

d) Disposable Bins (sharps or yellow bins)/ Bags

- Fill all bins/ bags to the volume of not more than two-third full.
- Bins must be made of rigid and puncture resistant material.
- Full bags must be securely taped/ tied, kept inside clinical waste bins with closed lid placed at a designated area for collection by HSS personnel.
- It is the responsibility of pharmacy personnel to transfer all cytotoxic waste bags and bins from the clean rooms to the designated waste collection area.

e) Non-Disposable Bins (clinical waste bins)

- Used for holding cytotoxic waste bags temporarily before disposal.
- The bins shall not be used for other non-cytotoxic waste.
- HSS personnel shall clean the bins on regular basis or as per standard protocol.

3.4 SAFETY

3.4.1 Principles

Cytotoxic drugs are hazardous drugs. Personnel handling cytotoxic drugs must be trained in the receipt, transport, storage, handling and disposal of these drugs. All must adhere to safe handling policies and procedures in place to prevent harm to patients and others and minimise contamination at workplace.

3.4.2 General Requirements

i. Cytotoxic Drug Reconstitution services should be covered by health and safety management system of respective hospital. A workplace health and safety policy should be established to ensure the following minimum requirements are fulfilled:
   a) Installation of engineering controls (e.g. clean room with controlled physical parameters, CDR Safety Cabinets and isolators)
   b) Implementation of safe work practices that eliminate or minimise health risk associated with workplace exposure (eg. SOP, policies, training, list of cytotoxic drugs and safety data sheets [SDS])
   c) Availability of competent and trained personnel
   d) Use of appropriate PPE

ii. The health and safety manager or Pharmacist In-Charge shall ensure that all safe work systems and practices are reviewed whenever there is a significant change to the process, equipment, materials or control measures installed.

iii. Cytotoxic drugs should be stored separately from other drugs to prevent cross contamination.

iv. It is advisable to have Chemical Hazard Risk Assessment (CHRA) done by the Occupational Safety and Health unit of respective hospital. This assessment would enable more precise decisions to be made on the control measures, training, exposure monitoring and health surveillance activities required for better protection of workers.

3.4.3 Cytotoxic Spill Management

i. Materials
   a) Content of Spill Kit (*Appendix 14*)
   b) Flow Chart on the Management of Cytotoxic Spill (*Appendix 15*)
   c) Spillage Reporting Form (*Appendix 16*)

ii. Procedure
   a) Within the cabinet
      - Ensure that the cabinet remains operating
      - For liquid spill, contain spill using absorbent pads or gauze and dispose them into the sharps bin*
      - For powder spill, use gauze or pads (wetted with water) and dispose them into the sharps bin*
      - Any broken glass fragments shall be disposed into sharps bin*
      - Wipe the entire area using sterile gauze or lint-free wipe wetted with deactivation agent for several times
      - Wipe with sterile WFI for several times
      - Swab with sterile alcohol 70%
      - Discard all contaminated items into the sharps bin
        Note: If spill occurred on preparation mat, skip step (*). Wrap up mat together with spilled contents and discard into the sharps bin.

   b) Outside the cabinet, in the clean room once spill occur,
      - Halt all ventilations in the area by pushing the emergency button
      - Open a spill kit available in the unit:
      - Contain the spill with absorbent pads/ gauze
        - Absorb liquid spill with absorbent pads/ gauze
        - Absorb powder spill with gauze/pads wetted with water
      - Any broken glass fragments shall be scooped using brush and dustpan and disposed in sharps bin. Discard used brush and dustpan in cytotoxic waste bag
      - Wipe the entire area using lint-free wipes wetted with deactivation agent for several times
      - Wipe with sterile WFI for several times until clean followed by sterile alcohol 70%
      - Discard contaminated items (e.g., lint-free wipes, first layer of glove) into the cytotoxic waste bag
      - Tie the cytotoxic waste bag and put into a second bag
      - Release emergency button
      - De-gown and dispose garment according to procedure
      - Wash hands thoroughly with soap and water
      - Report spillage to Pharmacist In-Charge (*Appendix 16: Spillage Reporting Form*) and replenish spill kit

c) Outside the clean room once spill occur,
Open a spill kit available in the unit

- Place a caution sign at the incident area
- Wear respiratory protection first and other PPE provided in the spill kit
- Contain the spill with absorbent pads/ gauze
  - Absorb liquid spill with absorbent pads/ gauze
  - Absorb powder spill with gauze/ pads wetted with water
- Any broken glass fragments shall be scooped using brush and dustpan and disposed into sharps bin. Discard used brush and dustpan into cytotoxic waste bag
- Wipe the entire area using gauze or wipes wetted with deactivation agent for several times
- Wipe with water for several times until clean
- Discard contaminated items (e.g., gauze, first layer of glove) into the cytotoxic waste bag
- Tie the cytotoxic waste bag and put it into a second bag
- Put respiratory protection, gown, footwear and glove into the cytotoxic waste bag
- Tie the cytotoxic bag and put into a non-disposable cytotoxic waste bin (clinical waste bin)
- Wash hands thoroughly with soap and water
- Report spillage to Pharmacist In-Charge (*Appendix 16: Spillage Reporting Form*) and replenish spill kit

d) Personnel Exposure

In the event of personnel contamination by cytotoxic drugs, ask for help whenever possible and the following procedure should be followed:

- All overtly contaminated protective clothing should be removed and disposed into the cytotoxic waste bag
- All contaminated clothing should be removed and discarded into the cytotoxic waste bin. Clothing with minimal amount of contamination could be laundered separately in accordance with standard policy/ procedure (if any)
- Use shower if necessary. If emergency shower is not available, cleanse affected skin area with soap and rinse with running water for at least 15 minutes
- For needle prick injury, rinse the area with running water (allow wound to bleed freely to flush out any drug). Do not squeeze the injured finger. Wash the area thoroughly with soap and water and for at least 15 minutes
- Flush affected eyes gently with clean water or normal saline or other isotonic eyewashes for 15 minutes. If eyewash station and eyewash bottle are not available, use a large syringe or a small receptacle with a pouring spout. Do not rub affected eyes
- Seek medical advice immediately

- Report and record incident in accordance with standard regulation/ policy. Follow up and manage each case as per recommendations from Occupational Safety & Health Unit

3.5 QUALITY CONTROL

3.5.1 Principles

Quality control ensures that all requirements related to quality are met. Quality control and release activities shall be independent of preparation activities.

3.5.2 General Requirements

Testing of finished products is not required for extemporaneously prepared products. However, it should be made compulsory for permanent personnel in aseptic unit to pass annual validation (inclusive of gloved fingertip sampling and media fills) at the least.

3.5.3 Product Release

i. All personnel shall adhere strictly to the standards of GPP and are equally accountable for the quality of all finished products. Finished products should be released or dispensed by Releasing Officer accordingly (refer 3.3.5 (iv) Dispensing).
ii. End-users should verify all finished products that they received. Proper record/ documentation of product release and receipt are required.

CHAPTER 4

STANDARD OPERATING PROCEDURE: PARENTERAL NUTRITION

Contents

CHAPTER 4

STANDARD OPERATING PROCEDURE: PARENTERAL NUTRITION

4.1 PERSONNEL

4.1.1 Principles

There shall be sufficient and competent personnel to execute all the tasks. Personnel's responsibilities shall be documented and clearly understood. All personnel must be well-informed on the principles of QA, GPP, and OSHA.

4.1.2 General Requirements

i. Every personnel involved (Pharmacist, Provisionally Registered Pharmacist (PRP), Pharmacist Assistant, others) is to be responsible for the quality of all finished products and adhere to GPP. Responsibilities of each personnel will depend on the duties and the requirement of the activities in the organization. The responsibilities shall be put into the job function or description clearly.
ii. New personnel shall be trained in all necessary areas as in Checklist of Training Topics for Personnel in Sterile Pharmaceuticals Production Unit (*Appendix 1*). Training of new personnel shall be documented. Provisionally Registered Pharmacist (PRP) and trainee shall be trained and supervised by trained personnel at all times.

4.1.3 Training and Continued Education

i. Upon job recruitment and on a continuous basis, personnel are required to receive vital training in all areas, which are crucial for the fulfilment of their duties.
ii. New personnel shall be adequately trained (on a continuous basis) by pharmacist and assessed for competency. All training shall be documented.

4.1.4 Hygiene

i. Hand Washing
Remove make-up, jewellery and watch before gowning. Before donning sterile gown, hand washing is done by practicing the 7-step technique with appropriate disinfectant and clean water (*Appendix 2*).

ii. Personal Protective Equipment
Sterile garments shall be worn at all times when preparing parenteral nutrition (PN).

a) Sterile Jumpsuit
- Non-linting/ non-shedding
- Minimum number of seams
- Closed front
- Hooded (hood attached to jumpsuit or available separately)
- Long sleeves with tight-fitting elastic or knitted cuffs
- Well-fitting

  Jumpsuit must be changed immediately if torn or contaminated.

b) Head Covers (bouffant cap and etc.) and Shoe Covers
- Disposable
- Non-linting/ non-shedding
- Head covers must be snug fit and able to contain all hairs

c) Boot Covers
- Made of low permeability fabric
- Non-linting/ non-shedding
- With shaft extended over bottom of the pant legs of jumpsuit
- Anti-skid soles

d) Sterile Gloves
- Non-linting
- Long enough to cover wrist cuffs of the garment and powder free

e) Surgical Mask
- Surgical mask shall be worn all the time to prevent droplets contamination
- Beards shall be covered accordingly

iii. Gowning Procedure

STEPS	PROCEDURES
1	Wear shoe cover and cross over.
2	Put on a head cover, making sure that all hair is contained.
3	Put on a face mask and make sure that no facial hair is exposed.
4	Wash hands according to the '7-Step Hand Washing Technique'.
5	Dry hands with electrical hand dryer.
6	Wear the hood on top of head cover (if the hood is a separate piece).
7	Wear sterile jumpsuit; make sure that the jumpsuit does not touch the ground.
8	Zip all the way to the top.
9	Take a set of booties and place it over your feet.
10	Wear gloves according to the gloving procedure.
11	Use the full-length mirror in the gowning room to ensure that all clean room apparel is worn correctly and properly fitted.

iv. Gloving Procedure

STEPS	PROCEDURES
1	Put on the right glove.
2	Do not uncover the folded sleeve.
3	Put on the left glove by inserting fingers of the right hand under the folded sleeve.
4	Uncover the folded sleeve of the left glove with the fingers without touching the arm.
5	Fold back the folded sleeve on the right glove in the same way (*Appendix 3*).

4.1.5 Procedures for Entry into the Clean Room

i. Before entering the Clean Room:
   a) Remove accessories and make-up before entry.
   b) Outdoor clothing should not be brought into changing rooms leading to Grade B and Grade C areas. Change into scrubs and clean shoes.
   c) Wash hands and dry them.

ii. Inside the Changing Room:
   a) Wear shoe cover and cross over.
   b) Wear head cover and mask.
   c) Wash hands with appropriate disinfectants using '7- Step Hand Washing

Techniques'

d) Dry hands with electrical hand dryer.
e) Enter the gowning room without touching the door handle.

iii. Entry into Grade C or Grade D Clean Room (except Changing Room):
a) Follow steps as explained in (i) and (ii).
b) Wear non-sterile garment.
c) Put on sterile non-powdered gloves (for Component Room only).

iv. Entry into Grade B Clean Room:
a) Follow steps as explained in (i) and (ii).
b) Enter gowning room without touching the door handle.
c) Wear sterile garments (hood, jumpsuit and boots), minimising contact with outer layer of the garments.
d) For 3-piece garments, wear the hood first, followed by the jumpsuit. Booties are worn last and fastened over the pants.
e) For disposable garments, put the jumpsuit on (avoid touching the floor), followed by the hood. Booties are worn last.
f) Wear non-powder sterile glove according to gloving techniques with ends fastened over the sleeve cuffs.

v. During Aseptic Compounding:
a) Check periodically to ensure that garments are in good condition and the seams are sealed.
b) Gloves shall be regularly disinfected during compounding operations.

vi. Exit from Clean Room:
a) Remove PPE in gowning room and discard into clinical waste bag.
b) Wash hands and exit from clean room.

4.1.6 Health Requirements

i. Health assessment shall be carried out at least once a year to prevent possible product contamination to occur.
ii. Personnel involve with the aseptic activities shall notify the Pharmacist In-Charge if there is risk or admitted of infectious disease.
iii. Types of Health Assessment
a) Pre-placement (baseline)
- Social History (potential risk factors, occupational history)
- HIV test, Hepatitis B, Tuberculosis
- Full Blood Profile, Liver Function Test and Renal Profile
- Vision examination
- Physical observation (skin-related problem and neurological disorder, e.g., hand tremors)

b) Routine Medical Examinations (*Appendix 8*)
Routine medical examinations are recommended to be carried out annually to monitor for changes from baseline and previous health assessments.

4.1.7 Qualification and Validation

i. All permanent personnel directly involved in the preparation of PN solutions shall be trained and qualified in aseptic technique and satisfy the following requirements:
   a) Fit to perform sterile compounding and other technical tasks as determined in medical examination by a physician.
   b) Undergone basic aseptic training.
   c) Adequate competency (assessed by Pharmacist In-Charge)
   d) Passed annual validation (inclusive of gloved fingertip sample and media fills).
   e) Credentialed or privileged.

ii. Every personnel involved in aseptic technique dispensing shall undergo validation test prior to working in the sterile unit.

iii. Revalidation shall be performed at least once a year. Validation of personnel is adapted from the Universal Operator Broth Transfer Validation, UK Pharmaceutical Aseptic Services Committee.

4.2 PREMISES AND EQUIPMENT

4.2.1 Principles

Premises and equipment shall be suitable for the intended activities and they shall not present any hazard to the quality of the product.

4.2.2 General Requirements

i. Premises and equipment shall be appropriately maintained and upgraded, ensuring that they are suitable for the intended activities and to minimise the risk of errors. There shall be appropriate workflow and segregation of activities.
ii. In order to reduce the risk of contamination (e.g., by cross contamination or by the accumulation of dust and dirt), appropriately designed premises and equipment as well as careful and suitable working techniques shall be used. Special care shall be taken when samples are taken or when equipment is cleaned, and where applicable, disinfect after repair or maintenance.

iii. Adequate measures shall be taken against the entry of insects and other animals (pest control).
iv. Washing and cleaning activities shall not themselves be a source of contamination.
v. Production, storage and quality control areas shall be accessible to authorised personnel only.
vi. Environmental conditions (temperature, humidity, light, sound, and pressure differential) during production, quality control and storage (including cold storage) shall be defined and monitored, and if necessary, controlled.
vii. Monitoring results shall be documented, assessed and retained. When conditions fall outside the defined limits, adequate corrective action shall be taken.
viii. All areas shall be clean, orderly and well lit.

4.2.3 Cleaning Procedure for Clean Room and Equipment

i. Responsibilities
   a) The Pharmacist In-Charge shall oversee the cleaning and disinfecting of clean room and all equipment.
   b) Cleaning and disinfecting tasks can be assigned to Pharmacy and/ or Hospital Support Service personnel, provided that they are well-trained.
   c) The Pharmacist In-Charge or a Designated Person shall provide routine training to the cleaning and disinfecting personnel.
   d) The Pharmacist In-Charge or a Designated Person shall supervise and assess all cleaning procedures done.

ii. Equipment/ Materials
   a) Dedicated sterile low shedding mops (autoclavable)
   b) Dedicated multi-bucket mopping system (if required)
   c) Sterile low lint wipes
   d) Sterile disinfectant such as sterile alcohol 70%, etc. (refer *Appendix 18*)
   e) Sterile Water for Injection (WFI)
   f) PPE

iii. Entry of Cleaning Materials and Equipment into Clean Room
   a) Ensure that all materials and equipment are in good condition.
   b) All materials entering clean room shall be disinfected with sterile alcohol 70%.
   c) Materials and equipment disinfected shall be brought into clean room through pass box, except for materials that are too bulky to be placed into the pass box.

iv. Cleaning Procedures
   Frequency of cleaning for equipment/ area is as shown in Table 4.1.

Table 4.1 Cleaning frequency for related area

Frequency	Equipment/Area
Before and after production	Laminar Air Flow Cabinet (LAFC).
After production or daily	Stainless steel bench and trolley in preparation room, floor, window and door knobs, pass box and clinical waste bins, stainless steel bench and trolley.
Weekly	Floor, window and door knobs, pass box and clinical waste bins, stainless steel bench and trolley, walls and sinks, gowning cabinet, changing room cabinet, LAFC.
Monthly	Floor, window and door knobs, pass box and clinical waste bins, stainless steel bench and trolley, Ceilings, walls and sinks, gowning cabinet, changing room cabinet, LAFC.

a) Cleaning procedure for Laminar Air Flow Cabinet (LAFC)
- Wear PPE before entering the preparation room.
- The cabinet shall be cleaned at the start and at the end of each work session.
- The top surface of the cabinet shall be cleaned first, followed by the left and right side and lastly, the working bench.
- The top surface, left and right side and working bench of the cabinet are wiped from the least contaminated area to the most contaminated area with overlapping strokes using sterile alcohol 70% as surface disinfectant to reduce any bioburden present.
- Avoid contact with High Efficiency Particulate Air (HEPA) filters while cleaning.
- All soiled wipes shall be thrown into the clinical waste bag.
- After the completion of aseptic preparation, clean the cabinet according to the above procedure using sterile WFI followed by sterile alcohol 70%.

b) Cleaning procedure for stainless steel bench, trolley in preparation room, door knobs and clinical waste bins
- Wipe all equipment with low lint wipes and sterile alcohol 70%.
- Ensure that all hard-to-reach areas are cleaned.

c) Cleaning procedure for window
- Clean from top to bottom with low lint wipes and sterile alcohol 70%.
- Ensure that all hard-to-reach areas are cleaned.

d) Cleaning procedure for pass box
- Clean the inner surface of the pass box before transferring materials and equipment into the pass box for the first time on that day.
- Begin with the top surface, followed by the left and right side, glass panels and lastly, the bottom surface with low lint wipes and sterile alcohol 70%.

e) Cleaning procedure for floor
- Wipe (mop) the floor using appropriate disinfectant.
- Use overlapping strokes from the cleanest area to the dirtiest.

f) Cleaning procedure for walls
- Clean walls using low lint wipes or extendable mop with appropriate disinfectant (sterile alcohol 70%).
- Clean from top to bottom (ceiling to floor) or side to side from the least contaminated area to the most contaminated area using overlapping strokes.
- Ensure that all-hard-to reach areas are cleaned.

g) Cleaning procedure for ceilings
- Clean ceilings using low lint wipes or extendable mop with appropriate disinfectant (sterile alcohol 70%) from the cleanest area to the dirtiest.
- Avoid contact with HEPA filters while cleaning.
- Ensure that all hard-to-reach areas are cleaned.

v. Use of Disinfectants
a) Choice of disinfectants shall be based on the grade of clean room as well as the fauna of the clean room.
b) Disinfectants used shall be sterile (in grade A and B clean rooms) and rotated at specific interval based on manufacturer's recommendation.
c) Periodic use of sporicidal agents shall be considered to reduce contamination from spore forming microorganisms (eg. monthly).
d) Prepare or dilute disinfectant in clean containers as per manufacturer's recommendation in the clean room.
e) Label containers clearly with BUD and store as per manufacturer's recommendation.
f) Partly emptied containers shall not be topped up.

vi. Storage of Cleaning Materials
a) Facility with utility room: all cleaning materials shall be stored in the utility room.
b) Facility without utility room: all cleaning materials shall be stored in the component preparation room.

vii. Management of Used Cleaning Materials
a) All waste shall be disposed daily after each production.
b) Reusable cleaning materials shall be rinsed and sterilised before the next use.

viii. Cleaning Procedure under Non-Routine Circumstances
Thorough cleaning must be done before any production activity in the event of which the cleanliness of classified room is deemed compromised;

a) Breakdown of Air Handling Unit (AHU)
b) High microbial count
c) Major and minor renovations
d) Repair and maintenance work
e) Deviation of room physical parameters (e.g. wet room environment and floors due to high humidity & etc.)
f) Others

Refer to Maintenance Procedure for Clean Room and Equipment for further details.

ix. Documentation
a) All cleaning done shall be recorded.
b) The Pharmacist In-Charge or Designated Person shall verify all the documentation.
c) All records shall be maintained according to Hospital Documentation Procedure.
d) Cleaning Log (*Appendix 10*).

4.2.4 Maintenance Procedure for Clean Room and Equipment

i. Responsibilities
a) Pharmacist In-Charge
- Monitor all performance testing/ recertification, maintenance and repair work.
- Monitor all physical and microbiological parameters.
- Analyse and verify all monitoring and testing reports.
- Ensure performance testing are conducted by qualified/ accredited third-party agent (e.g. NEBB or NATA certified).

b) Hospital Support Services (HSS)
- Carry out periodic maintenance and performance testing as scheduled.
- Appoint qualified/ accredited third-party agent (e.g. NEBB or NATA certified) for performance testing and recertification of clean room and equipment.
- Ensure performance tests are conducted and data collected in accordance with the appropriate standards.
- Analyse and verify all testing reports.
- Investigate and rectify deviation from specifications in timely manner.
- Present findings of testing report/ investigation on deviation and corrective action plan to the Pharmacist In-Charge.

ii. Equipment/ Materials
a) All devices used for monitoring clean room and equipment parameters (pressure gauges, thermometer, hygrometer and etc.) require periodic

maintenance and calibration.

b) Equipment used for performance testing must be calibrated prior to testing done.

iii. Procedure for monitoring

a) Generally, the monitoring activities could be divided into:
   - Physical Monitoring
   - Microbiological Monitoring

b) Planned Preventive Maintenance (PPM) could be divided into:
   - Planned Preventive Maintenance (PPM) by HSS according to facility schedule (check with hospital engineer for details)
   - Annual performance testing/ Recertification by qualified/accredited third party testing agent

c) Physical Monitoring – the monitoring parameter and frequency are as listed in Table 4.2.

Table 4.2 Monitoring parameter and their frequency for facility maintenance

Parameter	LAFC	Clean Room
1. Temperature		a) Before preparation. b) Every day if no preparation.
2. Humidity		a) Before preparation. b) Every day if no preparation.
3. Air Pressure Differential		a) Before preparation. b) Every day if no preparation.
4. Pressure Differential Across HEPA Filter or Airflow Velocity	Before preparation.	

- Temperature and Humidity Monitoring
  - Record the temperature and humidity reading in the Clean Room Temperature, Humidity and Pressure Differential Record (*Appendix 11*).
  - Check, analyse and verify the records.
  - For deviation from specification, please refer to 4.2.4 (v) and also 1.3 under Chapter 1.

- Air Pressure Differential Monitoring
  - Record the air pressure differential reading in the Clean Room Temperature, Humidity and Pressure Differential Record (*Appendix 11*).

- Check, analyse and verify the records.
- For deviation from specification, please refer to 4.2.4 (v) and also 1.3 under Chapter 1.

d) Microbiological Monitoring

- Microbiological monitoring parameter and frequency are as listed in Table 4.3.
- Procedures for microbial monitoring are listed in Table 4.4.

Table 4.3 Monitoring parameter and their frequency for microbiological monitoring

Parameter	LAFC	Clean Room
1. Settle plate (90mm diameter)	a) Every working session. b) After major breakdown or after major maintenance.	a) Once a week during preparation. b) After major breakdown or after major maintenance.
2. Surface sample test (Contact plate-55 mm diameter/Swab test)	Once a week.	a) Once a month. b) After major breakdown or after major maintenance.
3. Personnel monitoring - gloved finger dabs	At the end of each working session.	
4. Active air samples	a) Every 3 months. b) After major breakdown or major maintenance.	a) Every 3 months b) After major breakdown or after major maintenance.

Note: All the parameters mentioned above shall be monitored during in-operation.

- In addition to the specific sampling frequencies described in this section, sampling must be performed in any of the following circumstances:
  - Certification of new facilities and equipment
  - After any modification of facilities or equipment
  - Detection of problems or worrying trends
  - Detection of changes that could impact the controlled area environments

Table 4.4 Microbial monitoring procedures

(A) Settle Plate (TSA & SDA - 90mm diameter)	(B) Contact Plate* (TSA **& SDA** - 55mm diameter)	(C) Gloved fingertip sampling with contact plate
✓ **Before the start of operation/ production, gather the required quantity of agar plates.** ✓ **Label plates with location/ sample site, date (for all plates), time of sampling starts (for settle plates), names of personnel, left & right hand (for plates used for gloved fingertip sampling).** ✓ **Disinfect before transfer the plates into pass box.**		
a) Place the settle plate at the sample site. b) Remove its lid and leave it for 4 hours or less (if production ends earlier)#. c) Put its lid back, seal with parafilm and write the end time on its label.	a) Take samples upon completion of operation/ production. b) Remove the lid of contact plate. c) Press it lightly against the surface of sample site for 2-5 seconds. d) Put its lid back, seal with parafilm. e) Clean and disinfect sampled area immediately. f) Use a new plate for each sample site.	a) Take samples after the last dose of drug compounded. b) Do not disinfect gloves before sampling. c) Remove the lid of a contact plate. d) Hold the plate at an angle that will allow four fingers of one hand to first press on the agar and create a slight impression then followed by the thumb. e) Repeat with the opposite hand on the second plate. f) Put its lid back and seal with parafilm.
✓ **Send the plates to the laboratory immediately or handle as per microbiology laboratory protocol.**		

Incubate as follows:

- TSA plates- 48hrs at 30-35°C (for bacteria)
- SDA plates-5 days at 26-30°C (for yeasts & mold)[19]

✓ **Analyse and verify all laboratory results and reports. Keep the reports systematically.**
✓ **For deviation from specification, please refer to 4.2.4 (v) and also 1.3 in Chapter 1.**

(Notes: Sampling must be done during normal operation/ production)

*Contact plate has a raised surface that allow the agar to be pressed on surfaces.

** Media used for surface- and fingertip sampling must contain added Lecithin and Polysorbate 80 (to neutralize the effects of disinfectants).

For exposure time less than 4 hours, result obtained should be extrapolated using the following equation: Count/ Time Exposed (min) X 240 = cfu/4 hr.

TSA: Tryptic Soy Agar; SDA: Sabouraud Dextrose Agar

- Identifying sample sites
  - Select critical zones and sites that are likely to capture the impact of personnel movement and work within the area. Other areas of concern to be monitored include entry points of materials/ equipment from a room with lower classification to another with higher classification, areas near doors and any other spots with air backwash turbulence. Sample sites selected shall remain constant as determined during facility qualification and well documented.

- Selecting culture media and diluents
  - The type of medium used (solid or liquid) for sampling microorganism may differ (depends on the procedure and equipment used). Alternatives to TSA and SDA can be used as long as they are suitable for the intended purpose. Soybean casein digest medium is considered equivalent to TSA and malt extract agar can be used to detect yeasts and molds in the environment.

- Swabbing method (surface swabs) can be done for irregular surfaces to supplement contact plate method for surface sampling but there is no microbial limit can be recommended. Check with microbiology laboratory for proper sampling procedure and refer to reliable references (e.g. USP 797 & etc.) for guide on interpretation of results.

- Microbiological monitoring is essential for quality assurance of finished products, evaluation of effectiveness of cleaning and disinfecting procedures and personnel adherence to aseptic work practice.

iv. PPM by Hospital Support Services (HSS) and Recertification by Third Party Testing Agent

PPM schedule should be made available to pharmacy and appointment should be made beforehand to facilitate proper arrangement for maintenance activities. PPM must include the below:

a) Changing of all primary and secondary filters as scheduled in timely manner (AHU, LAFC).
b) Calibration of pressure gauges, thermometer and hygrometer.
c) Inspection of emergency push button, interlocking button and alarm button (if applicable).
d) Performance testing by third party agent on clean room and major equipment.
e) Performance testing and recertification by Third Party Testing Agent should include parameters listed in Table 4.5.

Table 4.5 Validation activities by third party agent

Parameter	LAFC	Clean Room
1. Airborne Particle Counts	a) Once a year. b) After major breakdown/ After major maintenance.	a) Once a year. b) After major breakdown/ After major maintenance.
2. HEPA Filter Integrity Tests	a) Once a year. b) After major breakdown/ After major maintenance.	a) Once a year. b) After major breakdown/ After major maintenance.
3. Air Pressure Differential Test		a) Once a year. b) After major breakdown/ After major maintenance.
4. Air Change Rate Test		a) Once a year. b) After major breakdown/ After major maintenance.
5. Air Flow Velocities (Grade A)	a) Once a year. b) After major breakdown/ After major maintenance.	
6. Air Flow Pattern Test (Grade A)	a) Once a year. b) After major breakdown/ After major maintenance.	

Note: All the parameters mentioned above shall be monitored during at-rest.

- Ensure all personnel from Third Party Agents adhere to proper hand washing and clean room entry procedures.
- Ensure maintenance and corrective works are complete before annual performance testing or recertification.

v. Deviation from Specifications

Deviations of physical and microbiological monitoring parameters from specifications are indicators of compromised clean/ safe environment. Immediate actions are warranted:

a) Lodge report to HSS and follow up closely.
b) Identify cause of problems and take the necessary corrective actions soonest possible.

vi. Records and Documentation

a) All reports/ records of physical and microbiological parameters monitoring, repair and maintenance work, performance testing and recertification must be verified by Pharmacist In-Charge.
b) All reports/ records of physical and microbiological parameters monitoring, repair and maintenance work, performance testing and recertification must be kept systematically or as per facility protocol (examples of records refer *Appendix 11 and Appendix 12*).

4.3 PRODUCTION

4.3.1 Principles

All production activities are aimed to produce high quality finished products, and to be performed and supervised by competent personnel.

4.3.2 General Requirements

i. All production activities shall be performed by trained personnel with strict adherence to aseptic work practices.
ii. Appropriate flow of materials, segregation and adequate line clearance procedures shall be established to ensure sterility of finished products, to prevent cross-contamination and errors (e.g. mix up of drugs & etc.).
iii. Only sterile materials shall be taken into Grade A and B areas.

4.3.3 Pre-Production

The pharmacist shall ensure that:

i. Worksheets and labels are done, counterchecked and verified.
ii. Starting materials are gathered and counterchecked.
iii. Worksheets and labels are brought in plastic covers.
iv. Starting materials and worksheets are sprayed and swabbed with sterile alcohol 70% when put into pass box or air lock.
v. LAFC is intact and operational by checking on the display panel.

4.3.4 During Production

i. Cleaning of LAFC
   a) Shall be left running for a minimum of 20-30 minutes or as recommended by user manual.
   b) Shall be cleaned prior to commencement of production, using sterile alcohol 70% with caution to prevent spraying directly into the HEPA filter.

ii. Aseptic Processing
   a) Minimum of 2 personnel shall be involved in production at all times. These personnel are responsible to countercheck on each other in terms of accuracy of measurement.

   b) Items are arranged accordingly, such as:
      • Place the items (ampoule/ vial) in a linear arrangement with minimum

spacing of 2.5cm to allow filtered air to pass through.

- Arrange small objects in a linear arrangement with minimum spacing of 1cm or in zigzag arrangement to allow filtered air to pass through.

c) Withdrawal of Solution from Ampoule

- Clearing and Preparing the Ampoule
  - Make sure that the ampoule and contents of the ampoule are in good condition, i.e., intact, not expired, clear and no foreign particles.
  - If the ampoule head contains drug solution, tap the head to ensure that it is empty. If tapping does not work, then invert the ampoule upside down. Make sure that the ampoule head is filled with the drug solution and no air bubbles is present (a little tap might be able to remove the bubbles). Swing the ampoule in inverted `J' pattern.
  - With the ampoule in upright position, ensure that no more solution or bubble is trapped at the ampoule neck.

- Fixing Needle to Syringe
  - Half unwrap the syringe pack and the needle pack.
  - Hold both the needle and the syringe.
  - Fix the syringe to needle with special precaution not to touch the critical sites.
  - Put the syringe and needle aside to be used later.

- Breaking the Ampoule
  - Swab the neck of the ampoule with sterile alcohol 70%.
  - For glass ampoule, wrap around the neck of the ampoule with a new sterile alcohol swab/ gauze before breaking it to protect fingers from sharp edges. Alternatively, an ampoule breaker may be used.
  - Hold the head of the ampoule between the thumb and the index finger of dominant hand and the base of the ampoule between the thumb and the index of the other hand. Break it in the direction away from the body.
  - Discard the ampoule neck (with the alcohol swab/ gauze) immediately into the sharps bin.

- Withdrawing Solution from Ampoule
  - Insert the filter straw/ needle into the ampoule cautiously, avoid contact with the ampoule neck. Position the straw/ needle in the shoulder area of the ampoule so that the bevel tip is facing downwards.
  - Hold the ampoule in one hand and syringe in the other. Pull the plunger back with the thumb and index finger to withdraw required volume of drug solution into the syringe using `non-touch' technique.
  - Remove air from the syringe and measure the volume of the content withdrawn.
  - Change the filter straw/ filter needle to a regular needle.

d) Adding Diluent to a Vial Containing Powder

- Swab the rubber bung with sterile alcohol 70%.
- Hold the vial firmly on benchtop.
- Position the syringe containing diluent at 45° and place its needle on the rubber bung of the vial with the bevel facing upward and away from compounder.
- Push the needle through the rubber bung.
- Push the plunger down slowly until the entire diluent is transferred into the vial.
- Pull the plunger to its initial position. This will ensure no positive internal pressure is created within the vial.
- Pull the needle out of the rubber bung slowly.
- Discard the syringe and needle into the sharp bin.
- Let the vial stand for a while. Roll or swirl gently to ensure powder dissolved completely. Vigorous shaking is not allowed for certain drugs.

e) Withdrawing Drug Solution from a Vial

- Swab the rubber bung with alcohol 70%.
- Pull in the required volume of air into the syringe.
- Place the vial upright in a vertical position and hold firmly.
- Position the syringe at 45° and place the needle (attached to the syringe) on the rubber bung with the bevel pointing upward.
- Push the needle down and at the same time, pierce the needle through the rubber bung.
- Invert the whole set with the vial on top of the syringe.
- Pull the plunger slightly downwards and then, push upwards slowly to withdraw drug solution into the syringe. Repeat this technique (pulse technique) until the entire solution is transferred into the syringe.
- Place the vial on the working cabinet bench top and pull out the needle from the vial.
- Remove air bubbles and adjust to the required volume.

f) Procedure for Compounding of Pediatric PN

- Prepare PN bags one by one.
- Affix a transfer set to the infusion port if necessary. Close all the clamps of the transfer set.
- Open the clamp and infuse amino acid, dextrose and water for injection into the bag through the transfer set (based on worksheet).
- Fix the injection port with 0.2 µm filter.
- Infuse electrolytes through the injection port in the order of stability, e.g., Sodium Chloride, Sodium Glycerophosphate, Magnesium Sulphate, Potassium Chloride, Calcium Gluconate and trace elements.
- Infuse other necessary additives into the bag.

- Agitate the bag from time to time.
- Flush the filter. Make sure that the filter is intact throughout the process.
- If preparing all-in-one bag, infuse lipid emulsion as the last component.
- If preparing two-in-one bag, prepare the lipid separately.
- When all components have been filled into the bag, remove the filter and close the opening.
- Remove as much air as possible from the bag by pushing out the air through its opening. Close it back with the stopper and seal its opening with the sealer clip.
- Check the bag visually. Take sample if required.
- Label the bag.

g) Procedure for Compounding of Adult PN

- Remove caps of amino acid, dextrose and water for injection vials and swab the rubber bungs with alcohol.
- Run all the components from the vials according to the required quantity to a PN bag via transfer set.
- Attach 0.2 µm filter into the injection port of the PN bag.
- Withdraw required volume/amount of micronutrients and inject into PN bag via the filter connected.
- Mix the solution until homogeneous and check for foreign particles.
- If there is no presence of foreign particle, infuse required amount of lipid emulsion into the PN bag via transfer set.
- Inject required amount of multivitamin into the PN bag.
- Mix the solution until homogeneous.
- Discard air bubbles and clamp the infusion port. Sample if required
- Label the bag.

h) Preparation of Lipid Emulsion for Pediatric

- Withdraw lipid emulsion into a syringe according to the amount stated on the worksheet.
- Withdraw multivitamin using a 5.0µm filter.
- With a needle, add multivitamin into the lipid syringe.
- Mix the mixture until homogenous. Discard air from the lipid syringe. Cover and tighten the stopper.
- Label the syringe.

i) Procedure for Addition into Ready-Mix Bag

- Mix amino acid and glucose chamber of the Ready-Mix PN.
- Swab the injection port of the Ready-Mix PN.
- Attach a 0.2 µm filter with a new needle into the injection port of the PN bag for addition of additives.
- Detach the needle with the filters from the injection port.

- Mix the solution until homogeneous and check for foreign particles.
- Mix the final lipid chamber of the Ready-Mix PN until homogeneous.
- Swab the injection port with sterile alcohol.
- Wrap the injection port.

4.3.5 Post-Production

i. Cleaning
   a) Remove all broken ampoules, needles and syringes from working bench and floor, and dispose them into a sharps bin.
   b) Spread water for injection liberally on the bench and wipe with wipers until dry.
   c) Start swabbing the LAFC as detailed in the cleaning procedure.

ii. Packaging and Labelling of PN Preparation
   a) The packaging material used for PN preparation shall allow antimicrobial treatment and sufficient protection against external influences and possible contamination.
   b) All compounded PN shall be protected with a lightproof external wrapper.
   c) Labels shall include:
      - Product name
      - Patient details (if any)
      - Final volume (include osmolarity)
      - Content and amount
      - Batch number (if required)
      - Date of preparation
      - Expiry date

iii. Storage
   a) All PN preparations shall be stored in the refrigerator (2-8°C).
      - Storage period of PN preparations:
        - Should not exceed the expiration dates of the PN preparations and any of its components
        - Should not exceed time before administration
        - Should be based on microbial risk level or stability data whichever is shorter
      - Clear storage instructions must be provided to end users
   b) Facilities for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary) shall be made available.
   c) Records of these conditions shall be maintained, as they are critical for the maintenance of material characteristics.
   d) Unless there is an alternative system to prevent the unintentional or

unauthorised use of quarantined, rejected, returned or recalled materials, separate storage areas shall be assigned for their temporary storage until further actions are decided.

iv. Dispensing
   a) Countercheck to ensure that all labels are completed with patient's particulars and appropriate filter is supplied.
   b) To ensure that PN bags are transported in a manner that does not adversely affecting their quality, PN bags shall be:
      - Placed in a container of suitable packaging material to protect product during transportation (cold-chain required for long distance travel).
      - Taken directly to their destination without delay or detour.

v. Rejected and Returned Materials and Products
   a) All errors, defects and complaints related to starting materials, commercial PN products and CSP shall be investigated, remediated and documented.
   b) For deviation from specifications in CSP, refer to Chapter 1. Check if other preparations are affected and cease supply until cause(s) of problem solved.
   c) Product complaints and recalls of starting materials or commercial PN products by manufacturers shall be managed in accordance with MOH policy.
   d) Rejected or recalled starting materials, commercial drug products and CSP shall be stored in a secure, segregated area while their disposition is decided.
   e) Where any doubt arises over the quality of a commercial drug product or CSP, it shall not be considered suitable for re-issue or re-use.
   f) Unused products/ preparations returned by end users from wards should be disposed, unless its quality can be assured:
      - Check expiry date and inspect for any sign of instability
      - Consider stability and possible microbial contamination under actual handling conditions (storage, transportation) by end users
      - Determine reason(s) for medication return
      - Records of re-use must be kept (identifications, assignment of new expiry date, new label, worksheet & re-dispensing)
   g) Products/ preparations that have been released to a patient, or into the community, should **NEVER** be reused for other patients.

4.3.6 Disposal of PN Waste

i. Materials that have been used in the preparation and administration of PN drugs may present a source of injury to personnel not involved in the preparation and administration if the disposal is not properly handled.
ii. Containers used for disposal of PN waste shall be properly labelled, sealed, covered and handled by trained personnel only. Such personnel shall take necessary precaution to ensure personal, public and environmental protection.

iii. Materials
   a) General waste disposable - dispose into plastic bag
   b) Clinical waste (bottle/vial) - dispose into yellow bag
   c) Sharp objects (e.g. needle, syringe, ampoule) - dispose into sharps bin

4.4 QUALITY CONTROL

4.4.1 Principles

Quality control ensures that all requirements related to quality are met. Quality control and release activities shall be independent of preparation activities.

4.4.2 General Requirements

i. Testing equipment shall be suitable for its intended use.
ii. All operations shall be performed in accordance with the defined procedures and recorded. Test records shall be retained for at least one year after the expiry date of the starting materials or of the finished product, whichever is the longest.

4.4.3 Sampling

i. Samples taken for analysis shall be representative of the material being tested.
ii. Samples shall be taken from the final container of the preparation prior to sealing of infusion port.

4.4.4 Testing of Finished Products

i. The risk assessment to define the testing of finished products shall especially consider product properties, the use of the product as well as risks associated with its preparation.
ii. No quality control testing is necessary for extemporaneously prepared products.
iii. Microbiological analysis is not necessary on each batch. Alternatively, a regular programme of microbiological analysis of the preparations produced over a certain period of time or a regular programme of media fills (i.e. process validation using broth) may be acceptable.

4.4.5 Product Release

i. All personnel shall adhere strictly to the standards of GPP and are equally accountable for the quality of all finished products. Finished products should be released or dispensed by Releasing Officer accordingly (refer 4.3.5 (iv) Dispensing).
ii. End-users should verify all finished products that they received. Proper record/ documentation of product release and receipt are required.

CHAPTER 5

STANDARD OPERATING PROCEDURE: IV ADMIXTURES, OPTHALMIC AND OTHER STERILE PREPARATIONS

Contents

CHAPTER 5

STANDARD OPERATING PROCEDURE: IV ADMIXTURES, OPHTHALMIC AND OTHER STERILE PREPARATIONS

5.1 PERSONNEL

5.1.1 Principles

There shall be sufficient and competent personnel to execute all the tasks. Personnel's responsibilities shall be documented and clearly understood. All personnel must be well-informed on the principles QA, GPP, and OSHA.

5.1.2 General Requirements

i. Every personnel involved (Pharmacist, Provisionally Registered Pharmacist (PRP), Pharmacist Assistant, others) is to be responsible for the quality of all CSP and adhere to GPP. Responsibilities of each personnel will depend on the duties and the requirement of the activities in the organization. The responsibilities shall be put into the job function or description clearly.
ii. New personnel shall be trained in all necessary areas as in Checklist of Training Topics for Personnel in Sterile Pharmaceuticals Production Unit (*Appendix 1*). Training of new personnel shall be documented. Provisional Registered Pharmacist (PRP) and trainee shall be trained and supervised by trained personnel at all times.

5.1.3 Training and Continued Education

i. Upon job recruitment and on a continuous basis, personnel are required to receive vital training in all areas, which are crucial for the fulfilment of their duties.
ii. New personnel shall be adequately trained by pharmacist (on a continuous basis) and assessed for competency. All training shall be documented.

5.1.4 Hygiene

i. Hand Washing
Remove make-up, jewelleries and watch before gowning. Before donning sterile gown, hand washing is done by practicing the 7-step technique with appropriate disinfectant and clean water (*Appendix 2*).

ii. Personal Protective Equipment
Sterile garments are worn at all times when preparing IV admixtures, ophthalmic and other CSP.

a) Sterile Jumpsuit
- Non-linting/ non-shedding
- Minimum number of seams
- Closed front
- Hooded (hood attached to jumpsuit or available separately)
- Long sleeves with tight-fitting elastic or knitted cuffs
- Well-fitting

Jumpsuit must be changed immediately if torn or contaminated.

b) Head Cover (bouffant cap and etc.) and Shoe covers
- Disposable
- Non-linting/ non-shedding
- Head covers must be snug fit and able to contain all hairs

c) Boot Covers
- Made of low permeability fabric
- Non-linting/ non-shedding
- With shaft extended over bottom of the pant legs of jumpsuit
- Anti-skid soles

d) Sterile Gloves
- Non-linting
- Long enough to cover wrist cuffs of the garment and powder free

e) Surgical Mask
- Surgical mask shall be worn all the time to prevent droplets contamination
- Beards shall be covered accordingly

iii. Gowning Procedure

STEPS	PROCEDURES
1	Wear shoe cover and cross over.
2	Put on a head cover, making sure that all hair is contained.
3	Put on a face mask and make sure that no facial hair is exposed.
4	Wash hands according to the '7-Step Hand Washing Technique'.
5	Dry hands with electrical hand dryer.
6	Wear the hood on top of head cover (if the hood is a separate piece).
7	Wear sterile jumpsuit; make sure that the jumpsuit does not touch the ground.
8	Zip all the way to the top.
9	Take a set of booties and place it over your feet.
10	Wear gloves according to the gloving procedure.
11	Use the full-length mirror in the gowning room to ensure that all clean room apparel is worn correctly and properly fitted.

iv. Gloving Procedure

STEPS	PROCEDURES
1	Put on the right glove.
2	Do not uncover the folded sleeve.
3	Put on the left glove by inserting fingers of the right hand under the folded sleeve.
4	Uncover the folded sleeve of the left glove with the fingers without touching the arm.
5	Fold back the folded sleeve on the right glove in the same way (*Appendix 3*).

5.1.5 Procedures for Entry into the Clean Room

i. Before entering the Clean Room:
   a) Remove accessories and make-up before entry.
   b) Outdoor clothing should not be brought into changing rooms leading to Grade B and Grade C areas. Change into scrubs and clean shoes.
   c) Wash hands and dry them.

ii. Inside the Changing Room:
   a) Wear shoe cover and cross over.
   b) Wear head cover and mask.
   c) Wash hands with appropriate disinfectants using '7- Step Hand Washing Technique'.
   d) Dry hands with electrical hand dryer.
   e) Enter the gowning room without touching the door handle.

iii. Entry into Grade C or Grade D Clean Room (except Changing Room):
   a) Follow steps as explained in (i) and (ii).
   b) Wear non-sterile garment.
   c) Put on sterile non-powdered gloves (for Component Room only).

iv. Entry into Grade B Clean Room:
   a) Follow steps as explained in (i) and (ii).
   b) Enter gowning room without touching the door handle.
   c) Wear sterile garments (hood, jumpsuit and boots), minimising contact with outer layer of the garments.
   d) For 3-piece garments, wear the hood first, followed by the jumpsuit. Booties are worn last and fastened over the pants. For disposable garments, put the jumpsuit on (avoid touching the floor), followed by the hood. Booties are worn last.
   e) Wear non-powder sterile glove according to gloving techniques with ends fastened over the sleeve cuffs.

v. During Aseptic Compounding:
   a) Check periodically to ensure that garments are in good condition and the seams are sealed.
   b) Gloves shall be regularly disinfected during compounding operations.

vi. Exit from Clean Room:
   a) Remove PPE in gowning room and discard into clinical waste bag.
   b) Wash hands and exit from clean room.

5.1.6 Health Requirements

i. Health assessment shall be carried out at least once a year to prevent possible product contamination to occur.
ii. Personnel involve with the aseptic activities shall notify the Pharmacist In-Charge if there is risk or admitted of infectious disease.
iii. Type of health assessment are as follow:
   a) Pre-placement (baseline)
      - Social History (potential risk factors, occupational history)
      - HIV test, Hepatitis B, Tuberculosis

- Full Blood Profile, Liver Function Test and Renal Profile
- Vision examination
- Physical observation (skin-related problem and neurological disorder, e.g., hand tremors)

b) Routine Medical Examinations (*Appendix 8*)
Routine medical examinations are recommended to be carried out annually to monitor for changes from baseline and previous health assessments.

5.1.7 Qualification and Validation

i. All permanent personnel directly involved in the compounding of IV Admixtures, ophthalmic and other sterile preparations shall be trained and qualified in aseptic technique and satisfy the following requirements:
   a) Fit to perform sterile compounding and other technical tasks as determined in medical examination by a physician.
   b) Undergone basic aseptic training.
   c) Adequate competency (assessed by Pharmacist In-Charge)
   d) Passed annual validation (inclusive of gloved fingertip sample and media fills).
   e) Credentialed or privileged.

ii. Every personnel involved in aseptic technique dispensing shall undergo validation test prior to working in the sterile unit

iii. Revalidation shall be performed at least once a year. Validation of personnel is adapted from the Universal Operator Broth Transfer Validation, UK Pharmaceutical Aseptic Services Committee.

5.2 PREMISES AND EQUIPMENT

5.2.1 Principles

Premises and equipment shall be suitable for the intended activities and they shall not present any hazard to the quality of the product.

5.2.2 General Requirements

i. Premises and equipment shall be appropriately maintained and upgraded, ensuring that they are suitable for the intended activities and to minimise the risk of errors. There shall be appropriate workflow and segregation of activities.
ii. In order to reduce the risk of contamination (e.g., by cross contamination or by the accumulation of dust and dirt), appropriately designed premises and equipment

as well as careful and suitable working techniques shall be used. Special care shall be taken when samples are taken or when equipment is cleaned and, where applicable, disinfected after repair or maintenance.

iii. Adequate measures shall be taken against the entry of insects and other animals (pest control).

iv. Washing and cleaning activities shall not themselves be a source of contamination.

v. Production, storage and quality control areas shall be accessible to authorised personnel only.

vi. Environmental conditions (temperature, humidity, light, sound, and pressure differential) during production, quality control and storage (including cold storage) shall be defined and monitored, if necessary, controlled.

vii. Monitoring results shall be documented, assessed and retained. When conditions fall outside the defined limits, adequate corrective action shall be promptly addressed.

viii. All areas shall be clean, orderly and well lit.

5.2.3 Cleaning Procedure for Clean Room and Equipment

i. Responsibilities
   a) The Pharmacist In-Charge shall oversee the cleaning and disinfecting of clean room and all equipment.
   b) Cleaning and disinfecting tasks can be assigned to Pharmacy and/ or Hospital Support Service personnel, provided that they are well-trained.
   c) The Pharmacist In-Charge or a Designated Person shall provide routine training to the cleaning and disinfecting personnel.
   d) The Pharmacist In-Charge or a Designated Person shall supervise and assess all cleaning procedures done.

ii. Equipment/ Materials
   a) Dedicated sterile low shedding mops (autoclavable)
   b) Dedicated multi-bucket mopping system (if required)
   c) Sterile low lint wipes
   d) Sterile disinfectant such as sterile alcohol 70%, etc. (refer *Appendix 18*)
   e) Sterile Water for Injection (WFI)
   f) PPE

iii. Entry of Cleaning Materials and Equipment into Clean Room
   a) Ensure that all materials and equipment are in good condition.
   b) All materials entering clean room shall be disinfected with sterile alcohol 70%.
   c) Materials and equipment disinfected shall be brought into clean room through pass box, except for materials that are too bulky to be placed into the pass box.

iv. Cleaning Procedures
   Frequency of cleaning for equipment/ area is as shown in Table 5.1.

Table 5.1 Cleaning frequency for related area

Frequency	Equipment/Area
Before and after production	Biohazard safety cabinet (BSC)/ Isolator.
After production or daily	Stainless steel bench and trolley in preparation room, floor, window and door knobs, pass box and clinical waste bins, stainless steel bench and trolley.
Weekly	Floor, window and door knobs, pass box and clinical waste bins, stainless steel bench and trolley, walls and sinks, gowning cabinet, changing room cabinet, BSC/ Isolator.
Monthly	Floor, window and door knobs, pass box and clinical waste bins, stainless steel bench and trolley, ceilings, walls and sinks, gowning cabinet, changing room cabinet, BSC/ Isolator.

a) Cleaning procedure for Biohazard Safety Cabinet (BSC)

- Wear PPE before entering the preparation room.
- The cabinet shall be cleaned at the start and at the end of each work session.
- The back of the cabinet shall be cleaned first, followed by the left and right side, the safety glass panel and lastly, the working bench.
- The left, back and right side, the safety glass panel and working bench of the cabinet are wiped from the least contaminated area to the most contaminated area with overlapping strokes using sterile alcohol 70% as surface disinfectant to reduce any bioburden present.
- All soiled wipes shall be thrown into the clinical waste bag.
- After the completion of aseptic preparation, clean the cabinet according to the above procedure using sterile WFI followed by sterile alcohol 70%.

b) Cleaning procedure for Isolator

- Wear PPE before entering the preparation room.
- The isolator shall be cleaned at the start and the end of each work session.
- Clean the external surfaces of the transfer chambers and front visor.
- Wipe all internal surfaces with sterile alcohol 70% before the start of each work session.
- Clean the inner surfaces of both transfer chambers.
- Clean the back of the isolator, followed by the left and right side, the front visor, glove sleeves and lastly, the work bench with overlapping wipes using sterile alcohol 70% as surface disinfectant to reduce any bioburden present.
- Discard all used wipes into the waste bin placed in the transfer chamber.
- After the completion of sterile preparation, clean the isolator according to the above procedure using sterile WFI followed by sterile alcohol 70%.

c) Cleaning procedure for stainless steel bench, trolley in preparation room, door knobs and clinical waste bins
- Wipe all equipment with low lint wipes and sterile alcohol 70%.
- Ensure that all hard-to-reach areas are covered during cleaning.

d) Cleaning procedure for window
- Clean from top to bottom with low lint wipes and sterile alcohol 70%.
- Ensure that all hard-to-reach areas are cleaned.

e) Cleaning procedure for pass box
- Clean the inner surface of the pass box before transferring materials and equipment into the pass box for the first time on that day.
- Begin with the top surface, followed by the left and right side, glass panels and lastly, the bottom surface with low lint wipes and sterile alcohol 70%.

f) Cleaning procedure for floor
- Wipe (mop) the floor using appropriate disinfectant.
- Use overlapping strokes from the cleanest area to the dirtiest.

g) Cleaning procedure for walls
- Clean walls using low lint wipes or extendable mop with appropriate disinfectant (sterile alcohol 70%).
- Clean from top to bottom (ceiling to floor) or side to side from the least contaminated area to the most contaminated area using overlapping strokes.
- Ensure that all hard-to-reach areas are cleaned.

h) Cleaning procedure for ceilings
- Clean ceilings using low lint wipes or extendable mop with appropriate disinfectant (sterile alcohol 70%) from the cleanest area to the dirtiest.
- Avoid contact with HEPA filters while cleaning.
- Ensure that all hard-to-reach areas are cleaned.

v. Use of Disinfectants

a) Choice of disinfectants shall be based on the grade of clean room as well as the fauna of the clean room.

b) Disinfectants used shall be sterile (in grade A and B clean rooms) and rotated at specific interval based on manufacturer's recommendation.

c) Periodic use of sporicidal agents shall be considered to reduce contamination from spore forming microorganisms (eg. monthly).

d) Prepare or dilute disinfectant in clean containers as per manufacturer's recommendation in the clean room.

e) Label containers clearly with BUD and store as per manufacturer's recommendation.
f) Partly emptied containers shall not be topped up.

vi. Storage of Cleaning Materials
a) Facility with utility room: all cleaning materials shall be stored in the utility room.
b) Facility without utility room: all cleaning materials shall be stored in the component preparation room.

vii. Management of Used Cleaning Materials
a) All waste shall be disposed daily after each production.
b) Reusable cleaning materials shall be rinsed and sterilised before the next use.

viii. Cleaning Procedure under Non-Routine Circumstances
Thorough cleaning must be done before any production activity in the event of which the cleanliness of classified room is deemed compromised;
a) Breakdown of Air Handling Unit (AHU)
b) High microbial count
c) Major and minor renovations
d) Repair and maintenance work
e) Deviation of room physical parameters (e.g. wet room environment and floors due to high humidity & etc.)
f) Others
Refer to Maintenance Procedure for Clean Room and Equipment for further details.

ix. Documentation
a) All cleaning done shall be recorded.
b) The Designated Person shall verify all the documentation.
c) All records shall be maintained according to Hospital Documentation Procedure.
d) Cleaning Log (*Appendix 10*).

5.2.4 Maintenance Procedure for Clean Room and Equipment

i. Responsibilities
a) Pharmacist In-Charge:
- Monitor all performance testing/ recertification, maintenance and repair work.
- Monitor all physical and microbiological parameters.
- Analyse and verify all monitoring and testing reports.
- Ensure performance testing are conducted by qualified/ accredited third-party agent (e.g. NEBB or NATA certified).

b) Hospital Support Services (HSS)
- Carry out periodic maintenance and performance testing as scheduled.
- Appoint qualified/ accredited third-party agent (e.g. NEBB or NATA certified) for performance testing and recertification of clean room and equipment.
- Ensure performance tests are conducted and data collected in accordance with the appropriate standards.
- Analyse and verify all testing reports.
- Investigate and rectify deviation from specifications in timely manner.
- Present findings of testing report/ investigation on deviation and corrective action plan to the Pharmacist In-Charge.

ii. Equipment/ Materials
a) All devices used for monitoring clean room and equipment parameters (pressure gauges, thermometer, hygrometer and etc.) require periodic maintenance and calibration.
b) Equipment used for performance testing must be calibrated prior to testing done.

iii. Procedure for Monitoring
a) Generally, the monitoring activities could be divided into:
- Physical Monitoring
- Microbiological Monitoring

b) Planned Preventive Maintenance (PPM) could be divided into:
- Planned Preventive Maintenance (PPM) by HSS according to facility schedule (check with hospital engineer for details)
- Annual performance testing/ Recertification by qualified/accredited third party testing agent

c) Physical monitoring parameter and frequency are listed in Table 5.2.

Table 5.2 Monitoring parameter and their frequency for facility maintenance

Parameter	BSC/ Isolator	Clean Room
1. Temperature		a) Before preparation. b) Every day if no preparation.
2. Humidity		a) Before preparation. b) Every day if no preparation.
3. Air Pressure Differential		a) Before preparation. b) Every day if no preparation.
4. Pressure Differential Across HEPA Filter or Airflow Velocity	Before preparation.	
5. Isolator Glove Integrity	Once a week (if any).	
6. Isolator Leak test	Weekly. *depends on the brand and model of isolator (refer User Manual)	

- Temperature and Humidity Monitoring
  - Record the temperature and humidity reading in the Clean Room Temperature, Humidity and Pressure Differential Record (*Appendix 11*).
  - Check, analyse and verify the records.
  - For deviation from specification, please refer to 5.2.4 (v) and also 1.3 under Chapter 1.

- Air Pressure Differential Monitoring
  - Record the air pressure differential reading in the Clean Room Temperature, Humidity and Pressure Differential Record (*Appendix 11*).
  - Check, analyse and verify the records.
  - For deviation from specification, please refer to 5.2.4 (v) and also 1.3 under Chapter 1.

d) Microbiological Monitoring

- Microbiological monitoring parameter and frequency are as listed in Table 5.3.
- Procedures for microbial monitoring are as in Table 5.4.

Table 5.3 Monitoring parameter and their frequency for microbiological monitoring

Parameter	BSC/ Isolator	Clean Room
1. Settle plate (90mm diameter)	a) Every working session. b) After major breakdown or after major maintenance.	a) Once a week during preparation. b) After major breakdown or after major maintenance.
2. Surface sample test (Contact plate-55 mm diameter/Swab test)	Once a week.	a) Once a month. b) After major breakdown or after major maintenance.
3. Personnel monitoring - gloved finger dabs	At the end of each working session.	
4. Active air samples	a) Every 3 months. b) After major breakdown or major maintenance.	a) Every 3 months. b) After major breakdown or after major maintenance.

Note: All the parameters mentioned above shall be monitored during in-operation.

- In addition to the specific sampling frequencies described in this section, sampling must be performed in any of the following circumstances:
  - Certification of new facilities and equipment
  - After any modification of facilities or equipment
  - Detection of problems or worrying trends
  - Detection of changes that could impact the controlled area environments

Table 5.4 Microbial monitoring procedures

(A) Settle Plate (TSA & SDA - 90mm diameter)	(B) Contact Plate* (TSA **& SDA** - 55mm diameter)	(C) Gloved fingertip sampling with contact plate
✓ **Before the start of operation/ production, gather the required quantity of agar plates.** ✓ **Label plates with location/ sample site, date (for all plates), time of sampling starts (for settle plates), names of personnel, left & right hand (for plates used for gloved fingertip sampling).** ✓ **Disinfect before transfer the plates into pass box.**		
a) Place the settle plate at the sample site. b) Remove its lid and leave it for 4 hours or less (if production ends earlier)#. c) Put its lid back, seal with parafilm and write the end time on its label.	a) Take samples upon completion of operation/ production. b) Remove the lid of contact plate. c) Press it lightly against the surface of sample site for 2-5 seconds. d) Put its lid back, seal with parafilm. e) Clean and disinfect sampled area immediately. f) Use a new plate for each sample site.	a) Take samples after the last dose of drug compounded. b) Do not disinfect gloves before sampling. c) Remove the lid of a contact plate. d) Hold the plate at an angle that will allow four fingers of one hand to first press on the agar and create a slight impression then followed by the thumb. e) Repeat with the opposite hand on the second plate. f) Put its lid back and seal with parafilm.
✓ **Send the plates to the laboratory immediately or handle as per microbiology laboratory protocol.**		

Incubate as follows:

- TSA plates- 48hrs at 30-35°C (for bacteria)
- SDA plates-5 days at 26-30°C (for yeasts & mold)[19]

✓ **Analyse and verify all laboratory results and reports. Keep the reports systematically.**
✓ **For deviation from specification, please refer to 5.2.4 (v) and also 1.3 in Chapter 1.**

(Notes: Sampling must be done during normal operation/ production)

*Contact plate has a raised surface that allow the agar to be pressed on surfaces.

** Media used for surface- and fingertip sampling must contain added Lecithin and Polysorbate 80 (to neutralize the effects of disinfectants).

For exposure time less than 4 hours, result obtained should be extrapolated using the following equation: Count/ Time Exposed (min) X 240 = cfu/4 hr.

TSA: Tryptic Soy Agar; SDA: Sabouraud Dextrose Agar

- Identifying sample sites
  - Select critical zones and sites that are likely to capture the impact of personnel movement and work within the area. Other areas of concern to be monitored include entry points of materials/ equipment from a room with lower classification to another with higher classification, areas near doors and any other spots with air backwash turbulence. Sample sites selected shall remain constant as determined during facility qualification and well documented.

- Selecting culture media and diluents
  - The type of medium used (solid or liquid) for sampling microorganism may differ (depends on the procedure and equipment used). Alternatives to TSA and SDA can be used as long as they are suitable for the intended purpose. Soybean casein digest medium is considered equivalent to TSA and malt extract agar can be used to detect yeasts and molds in the environment.

- Swabbing method (surface swabs) can be done for irregular surfaces to supplement contact plate method for surface sampling but there is no microbial limit can be recommended. Check with microbiology laboratory for proper sampling procedure and refer to reliable references (e.g. USP 797 & etc.) for guide on interpretation of results.

- Microbiological monitoring is essential for quality assurance of finished products, evaluation of effectiveness of cleaning and disinfecting procedures and personnel adherence to aseptic work practice.

iv. PPM by Hospital Support Services (HSS) and Recertification by Third Party Testing Agent

PPM schedule should be made available to pharmacy and appointment should be made beforehand to facilitate proper arrangement for maintenance activities. PPM must include the below:

a) Changing of all primary and secondary filters as scheduled in timely manner (AHU, BSC and isolator).
b) Calibration of pressure gauges, thermometer and hygrometer.
c) Inspection of emergency push button, interlocking button and alarm button (if applicable).
d) Performance testing by third party agent on clean room and major equipment.
e) Performance testing and recertification by Third Party Testing Agent should include parameters listed in Table 5.5.

Table 5.5 Validation activities by third party agent

Parameter	BSC/ Isolator	Clean Room
1. Airborne Particle Counts	a) Once a year. b) After major breakdown/ After major maintenance.	a) Once a year. b) After major breakdown/ After major maintenance.
2. HEPA Filter Integrity Tests	a) Once a year. b) After major breakdown/ After major maintenance.	a) Once a year. b) After major breakdown/ After major maintenance.
3. Air Pressure Differential Test		a) Once a year. b) After major breakdown/ After major maintenance.
4. Air Change Rate Test		a) Once a year. b) After major breakdown/ After major maintenance.
5. Air Flow Velocities (Grade A)	a) Once a year. b) After major breakdown/ After major maintenance.	
6. Air Flow Pattern Test (Grade A)	a) Once a year. b) After major breakdown/ After major maintenance.	
7. Isolator Alarm Functional Tests	Once a year.	
8. Isolator Leak Test	a) Once a year. b) After major breakdown/ After major maintenance.	
9. Isolator Pressure Hold Test	a) Once a year. b) After major breakdown/ After major maintenance.	

Note: All the parameters mentioned above shall be monitored during at-rest.

- Ensure all personnel from Third Party Agents adhere to proper hand washing and clean room entry procedures.
- Ensure maintenance and corrective works are complete before annual performance testing or recertification.

v. Deviation from Specifications

Deviations of physical and microbiological monitoring parameters from specifications are indicators of compromised clean/ safe environment. Immediate actions are warranted:

a) Lodge report to HSS and follow up closely.
b) Identify cause of problems and take the necessary corrective actions soonest possible.

vi. Records and Documentation
   a) All reports/ records of physical and microbiological parameters monitoring, repair and maintenance work, performance testing and recertification must be verified by Pharmacist In-Charge.
   b) All reports/ records of physical and microbiological parameters monitoring, repair and maintenance work, performance testing and recertification must be kept systematically or as per facility protocol (examples of records refer *Appendix 11* and *Appendix 12*).

5.3 PRODUCTION

5.3.1 Principles

All production activities are aimed to produce high quality finished products, and to be performed and supervised by competent personnel.

5.3.2 General Requirements

i. All production activities shall be performed by trained personnel with strict adherence to aseptic work practices.
ii. Appropriate flow of materials, segregation and adequate line clearance procedures shall be established to ensure sterility of finished products, to prevent cross-contamination and errors (e.g. mix up of drugs & etc.).
iii. Only sterile materials shall be taken into Grade A and B areas.

5.3.3 Pre-Production

Before entering the clean room, pharmacist shall ensure that:
i. Worksheets and labels are done, counterchecked and verified.
ii. Starting materials are gathered and counterchecked.
iii. Worksheets and labels are brought in plastic covers.
iv. Starting materials and worksheets are sprayed and swabbed with alcohol 70% when put into pass box or air lock.
v. BSC/ Isolator is intact and operational by checking on the display panel and isolator glove integrity.

5.3.4 During Production

i. Cleaning of BSC/ Isolator
   a) The BSC/ Isolator shall be left running for a minimum of 20-30 minutes or as recommended by the user manual.
   b) BSC/ Isolator shall be cleaned prior to commencement of production, using sterile alcohol with caution to prevent spraying directly into the HEPA filter.

ii. Aseptic Processing
   a) A minimum of 2 personnel shall be involved in production at all times. These personnel shall countercheck each other in terms of accuracy of measurement.

   b) Aseptic processing of IV Admixture, ophthalmic and other sterile preparations shall be based on valid formulation. The key elements of the aseptic processing should be practiced the whole time to ensure the quality of the final products.

   c) For antibiotic preparations, a BSC is recommended to be used and for other preparations, a horizontal LAFC is sufficient.

   d) For preparations using horizontal LAFC, items are arranged accordingly, such as:
      - Place the items (ampoule/vial) in a linear arrangement with a minimum spacing of 2.5cm to allow filtered air to pass through.
      - Arrange small objects in a linear arrangement with a minimum spacing of 1cm or in zigzag arrangement to allow filtered air to pass through.

   e) Withdrawal of Solution from Ampoule
      - Clearing and Preparing the Ampoule
        - Make sure that the ampoule and contents of the ampoule are in good condition, i.e., intact, not expired, clear and no foreign particles.
        - If the ampoule head contains drug solution, tap the head to ensure that it is empty. If tapping does not work, then invert the ampoule upside down. Make sure that the ampoule head is filled with the drug solution and no air bubbles is present (a little tap might be able to remove the bubbles). Swing the ampoule in inverted 'J' pattern.
        - With the ampoule in upright position, ensure that no more solution or bubble is trapped at the ampoule neck.

      - Fixing Needle to Syringe
        - Half unwrap the syringe pack and the needle pack.
        - Hold both the needle and the syringe.
        - Fix the syringe to needle with special precaution not to touch the critical sites.
        - Put the syringe and needle aside to be used later.

- Breaking the Ampoule
  - Swab the neck of the ampoule with sterile alcohol 70%.
  - For glass ampoule, wrap around the neck of the ampoule with a new sterile alcohol swab/ gauze before breaking it to protect fingers from sharp edges. Alternatively, an ampoule breaker may be used.
  - Hold the head of the ampoule between the thumb and the index finger of dominant hand and the base of the ampoule between the thumb and the index of the other hand. Break it in the direction away from the body.
  - Discard the ampoule neck (with the alcohol swab/ gauze) immediately into the sharps bin.

- Withdrawing Solution from Ampoule
  - Insert the filter straw/ needle into the ampoule cautiously, avoid contact with the ampoule neck. Position the straw/ needle in the shoulder area of the ampoule so that the bevel tip is facing downwards.
  - Hold the ampoule in one hand and syringe in the other. Pull the plunger back with the thumb and index finger to withdraw required volume of drug solution into the syringe using `non-touch' technique.
  - Remove air from the syringe and measure the volume of the content withdrawn.
  - Change the filter straw/ filter needle to a regular needle.

f) Adding Diluent to a Vial Containing Powder
- Swab the rubber bung with sterile alcohol 70%.
- Hold the vial firmly on benchtop.
- Position the syringe containing diluent at 45° and place its needle on the rubber bung of the vial with the bevel facing upward and away from compounder.
- Push the needle through the rubber bung.
- Push the plunger down slowly until the entire diluent is transferred into the vial.
- Pull the plunger to its initial position. This will ensure no positive internal pressure is created within the vial.
- Pull the needle out of the rubber bung slowly.
- Discard the syringe and needle into the sharp bin.
- Let the vial stand for a while. Roll or swirl gently to ensure powder dissolved completely. Vigorous shaking is not allowed for certain drugs.

g) Withdrawing Drug Solution from a Vial
- Swab the rubber bung with alcohol 70%.
- Pull in the required volume of air into the syringe.
- Place the vial upright in a vertical position and hold firmly.
- Position the syringe at 45° and place the needle (attached to the syringe)

on the rubber bung with the bevel pointing upward.

- Push the needle down and at the same time, pierce the needle through the rubber bung.
- Invert the whole set with the vial on top of the syringe.
- Pull the plunger slightly downwards and then, push upwards slowly to withdraw drug solution into the syringe. Repeat this technique (pulse technique) until the entire solution is transferred into the syringe.
- Place the vial on the working cabinet bench top and pull out the needle from the vial.
- Remove air bubbles and adjust to the required volume.

5.3.5 Post-Production

i. Cleaning
   a) Remove all broken ampoules, needles and syringes from working bench and floor, and dispose them into a sharp bin.
   b) Spread water for injection liberally on the bench and wipe with wipers until dry.
   c) Start swabbing the BSC/ Isolator as detailed in the cleaning procedure.

ii. Packaging and Labeling of IV Admixture, Ophthalmic and Other Sterile Preparations
   a) The packaging material used for IV admixture, Ophthalmic and Other Sterile Preparations shall allow an antimicrobial treatment and sufficient protection against external influences and possible contamination.
   b) Labels shall include:
      - Product name
      - Patient details (if any)
      - Final volume
      - Content and amount
      - Batch number (compulsory for batch preparations)
      - Date of preparation
      - Expiry date

iii. Storage
   a) All IV admixtures, Ophthalmic and Other Sterile Preparations shall be stored according to individual preparation storage temperature requirement.
      - Storage period of IV admixtures, Ophthalmic and Other Sterile Preparations:
        - Should not exceed the expiration dates of the compounded products and any of its components
        - Should not exceed time before administration
        - Should be based on microbial risk level or stability data whichever is

shorter

- Clear storage instructions must be provided to end users

b) Facilities for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary) shall be made available.

c) Records of these conditions shall be maintained if they are critical for the maintenance of material characteristics.

d) Unless there is an alternative system to prevent the unintentional or unauthorised use of quarantined, rejected, returned or recalled materials, separate storage areas shall be assigned for their temporary storage until further actions are decided.

iv. Dispensing

a) Countercheck to ensure that all labels are complete with the patient's particulars

b) To ensure that IV admixtures, Ophthalmic and Other Sterile preparations are transported in a manner that does not adversely affect their quality, IV admixtures, Ophthalmic and Other Sterile preparations shall be:

- Placed in a container of suitable packaging material to protect product during transportation (cold-chain required for long distance travel).
- Taken directly to their destination without delay or detour.

v. Rejected and Returned Materials and Products

a) All errors, defects and complaints related to starting materials, commercial drug products and CSP shall be investigated, remediated and documented.

b) For deviation from specifications in CSP, refer to Chapter 1. Check if other preparations are affected and cease supply until cause(s) of problem solved.

c) Product complaints and recalls of starting materials or commercial drug products by manufacturers shall be managed in accordance with MOH policy.

d) Rejected or recalled starting materials, commercial drug products and CSP shall be stored in a secure, segregated area while their disposition is decided.

e) Where any doubt arises over the quality of a commercial drug product or CSP, it shall not be considered suitable for re-issue or re-use.

f) Unused products/ preparations returned by end users from wards should be disposed, unless its quality can be assured:

- Check expiry date and inspect for any sign of instability
- Consider stability and possible microbial contamination under actual handling conditions (storage, transportation) by end users
- Determine reason(s) for medication return
- Records of re-use must be kept (identifications, assignment of new expiry date, new label, worksheet & re-dispensing)

g) Products/ preparations that have been released to a patient, or into the community, should **NEVER** be reused for other patients.

5.3.6 Disposal of IV Admixtures, Ophthalmic and Other Sterile Preparations Waste

i. Materials that have been used in the preparation and administration of IV admixture, Ophthalmic and Other Sterile preparations may present a source of injury to personnel not involved in the preparation and administration if the disposal is not properly handled.
ii. Containers used for disposal of IV admixture, Ophthalmic and Other Sterile preparations waste shall be properly labelled, sealed, covered and handled by trained personnel only. Such personnel shall take necessary precaution to ensure personal, public and environmental protection.
iii. Materials
    a) General disposable - dispose into plastic bag.
    b) Clinical waste (bottle/vial) - dispose into yellow bag.
    c) Sharp objects (e.g., needle, syringe, ampoule) - dispose into “sharps bin”.

5.4 QUALITY CONTROL

5.4.1 Principles

Quality control ensures that all requirements related to quality are met. Quality control and release activities shall be independent of preparation activities.

5.4.2 General Requirements

i. Testing equipment shall be suitable for its intended use.
ii. All operations shall be performed in accordance with the defined procedures and recorded. Test records shall be retained for at least one year after the expiry date of the starting materials or of the finished product, whichever is the longest.

5.4.3 Sampling

i. Samples taken for analysis shall be representative of the material being tested.
ii. Samples shall be taken from the final container of the preparation prior to sealing of infusion port.

5.4.4 Testing of Finished Products

i. The risk assessment to define the testing of finished products shall especially consider product properties, the use of the product as well as risks associated with its preparation.
ii. No quality control testing is necessary for extemporaneously prepared products.
iii. Microbiological analysis is not necessary on each batch. Alternatively, a regular programme of microbiological analysis of the preparations produced over a certain period of time or a regular programme of media fills (i.e. process validation using broth) may be acceptable.

5.4.5 Product Release

i. All personnel shall adhere strictly to the standards of GPP and are equally accountable for the quality of all finished products. Finished products should be released or dispensed by Releasing Officer accordingly (refer 5.3.5 (iv) Dispensing).
ii. End-users should verify all finished products that they received. Proper record/ documentation of product release and receipt are required.

CHAPTER 6

STANDARD OPERATING PROCEDURE: RADIOPHARMACEUTICAL PREPARATIONS

Contents

CHAPTER 6

STANDARD OPERATING PROCEDURE: RADIOPHARMACEUTICAL PREPARATIONS

6.1 PERSONNEL

6.1.1 Principles

There shall be sufficient and competent personnel to execute all the tasks. Personnel's responsibilities shall be documented and clearly understood. All personnel must be well-informed on the principles of QA, GPP, safe handling of hazardous drugs and OSHA. Risk management approach shall be used on qualification and validation of personnel, while balancing GPP and radiation protection principle.

6.1.2 General Requirements

i. All personnel involved in production, analytical control and release of radiopharmaceuticals must be appropriately trained.
ii. All preparations should be carried out under the responsibility of personnel with competency in radiation protection.
iii. New personnel shall be trained in all necessary areas as in Checklist of Training Topics for Personnel in Sterile Pharmaceuticals Production Unit (*Appendix 1*). All new personnel must be supervised by a trained pharmacist.

6.1.3 Training and Continued Education

i. Upon job recruitment and on a continuous basis, personnel are required to receive vital training in all areas, which are crucial for the fulfilment of their duties.
ii. New personnel shall be adequately trained by pharmacist (on a continuous basis) and assessed for competency. All training shall be documented.
iii. All radiopharmacy staffs shall have appropriate training in National legislation relating to Ionising Radiation Regulations.

6.1.4 Hygiene

i. Hand Hygiene
Remove make-up, jewelleries and watch before gowning. Before donning sterile gown, hand washing is done by practicing the 7-step technique with appropriate disinfectant and clean water (*Appendix 2*).

ii. Personal Protective Equipment (PPE)
PPE is used to protect personnel from hazardous drug exposure, maintain cleanliness of clean rooms and ensure sterility of finished products. Hence, PPEs are to be selected based on location of work areas and risk of exposure (depends on the activities being performed). Sterile PPEs shall be worn when working in Grade A and B clean rooms.

a) Sterile Jumpsuit
- Non-linting/ non-shedding
- Minimum number of seams
- Closed front
- Hooded (hood attached to jumpsuit or available separately)
- Long sleeves with tight-fitting elastic or knitted cuffs
- Well-fitting

  Jumpsuit must be changed immediately if torn or contaminated.

b) Head Covers (bouffant cap and etc.) and Shoe Covers
- Disposable
- Non-linting/ non-shedding
- Head covers must be snug fit and able to contain all hairs

c) Boot Covers
- Made of low permeability fabric
- Non-linting/ non-shedding
- With shaft extended over bottom of the pant legs of jumpsuit
- Anti-skid soles

d) Sterile Gloves
- Non-linting
- Long enough to cover wrist cuffs of the garment and powder free

e) Surgical Mask
- Surgical mask shall be worn all the time to prevent droplets contamination.
- Beards shall be covered accordingly.

iii. Gowning procedure:
a) Put on shoe covers and cross the cross over bench.
b) Put on a head/ hair cover, making sure that hairs are tucked inside.

c) Put on a facemask and make sure that facial hairs are not exposed.
d) Wash hands according to the '7-step Hand Washing Technique' (*Appendix 2*) and aseptically wear a pair of gowning gloves.
e) Put on a sterile jumpsuit with sleeves that fit snugly around the wrists and enclosed at the neck. If reusable gowns are used, a clean gown must be donned daily. Ensure the garments do not touch the bench or floor.
f) Put on booties and pull the booties over the legs of gown.
g) Aseptically wear sterile gloves over the gowning gloves with ends fastened over the cuff of jumpsuit.
h) Use a full-length mirror to ensure that all clean room apparel is worn correctly and properly fitted.
i) Routinely apply sterile 70% alcohol to gloves and inspect the gloves for holes, punctures, radioactivity contamination, or tears.

iv. Gloving procedure:
a) Put on the right glove.
b) Do not uncover the folded sleeve.
c) Put on the left glove by inserting fingers of the right hand under the folded sleeve.
d) Uncover the folded sleeve of the left glove with the fingers without touching the arm.
e) Fold back the folded sleeve on the right glove in the same way (*Appendix 3*).

6.1.5 Procedures for Entry into the Clean Room

i. Before entering the Clean Room:
a) Remove accessories and make-up before entry. Radiation dosimetry devices are allowed.
b) Outdoor clothing should not be brought into changing rooms leading to Grade B and Grade C areas. Change into scrubs and clean shoes.
c) Wash hands and dry them.

ii. Inside the Changing Room: Follow the gowning and gloving procedure.

iii. Entry into Grade D:
a) Follow steps as explained in 6.1.5 (i) and 6.1.5 (ii).
b) Jumpsuit and booties may be replaced with appropriate alternative such as lab coat and clean room shoes.
c) Put on sterile non-powdered gloves.

iv. Entry into Grade C and Grade B Clean Room:
a) Follow steps as explained in 6.1.5 (i) and 6.1.5 (ii).
b) During gowning, care should be given to minimise contact on the outer layer of garments.
c) For booties, if cross over bench is used, transfer each foot to the clean side of

bench as boot is donned.

d) Double gloving should be practiced. Other than putting on a new pair of gloves over the gowning gloves, you may also replace it before putting on second pair of new gloves. Make sure the cuffs are fastened over the sleeve of jumpsuit.

v. During preparations: Routinely apply sterile 70% alcohol on gloves and whenever non-sterile surfaces are touched. Gloves should also consistently be inspected for holes, punctures, tears or radioactivity contamination.

vi. Exiting the clean room:

a) When personnel exit the clean room during a shift, the gowns may be retained in classified area for reuse during the same shift if not visibly soiled. However, shoe covers, hair covers, face masks and gloves must be replaced with new one before re-entering.

b) From clean room head directly to designated non-clean area or "exit gown room", remove all used protective clothing in reverse order of gowning procedure and discard into designated waste bin in the following sequence: outer gloves, booties, jumpsuits, hood, inner gloves, mask, hair cover, shoe covers.

c) Wash and dry hands.

6.1.6 Health Requirements

All personnel should undergo health assessment pre-placement, during and upon exit to evaluate their fitness to perform sterile compounding tasks and to monitor for adverse health effects of radiopharmaceutical preparation exposure. All personnel shall be registered as radiation worker and provided with a medical book.

i. Pre-placement

Pre-placement medical examination is to determine the person general state of health and it should also include all known previous exposures to ionizing radiation resulting from previous employment and medical condition (*Appendix 8*).

ii. Periodic Review of Health

The health of worker is reviewed at least once in three years to determine such worker remains fit to perform his duties. The nature of periodic reviews shall depend on the type and extent of exposure to ionizing radiation and the individual worker's state of health.

iii. Annual Health Review for Workers Involved in Sterile Preparations

The test shall include full blood count with white cell differential, biochemistry (renal profile & liver function test) and infectious disease (HIV, Hepatitis B and Tuberculosis).

iv. Personnel Exit Review
Medical examination shall be carried out upon personnel exit from Nuclear Pharmacy Service (*Appendix 9*). The medical practitioner may indicate any need to continue the medical surveillance even after their exit from Nuclear Pharmacy Service to safeguard the health of the personnel.

v. At discretion of authorised medical practitioner if deemed necessary
Contingency provisions for emergency situation (e.g. exposure to radiation spillage, sharp injury, radiation induced diseases, etc.) to enable urgent remedial action can be taken.

vi. Personnel monitoring
Personnel monitoring using approved dosimetry services shall be carried out to all permanent personnel or occasional workers who may receive significant occupational exposure and the monitoring results shall be informed to the personnel and documented in the exposure records. If exposure in excess of dose limits, investigation has to be carried out and report submitted to the appropriate authority.

6.1.7 Qualification and Validation

i. All permanent personnel directly involved in the compounding of radiopharmaceutical preparations shall be trained and qualified in aseptic technique and satisfy the following requirements:
   a) Fit to perform sterile compounding and other technical tasks as determined in medical examination by a physician.
   b) Undergone basic aseptic training.
   c) Adequate competency (assessed by Pharmacist In-Charge)
   d) Passed annual validation (inclusive of gloved fingertip sample and media fills).
   e) Credentialed or privileged.

ii. Every personnel involved in aseptic technique dispensing shall undergo validation test prior to working in the sterile unit

iii. Revalidation shall be performed at least once a year. Validation of personnel is adapted from the Universal Operator Broth Transfer Validation, UK Pharmaceutical Aseptic Services Committee.

6.2 PREMISES AND EQUIPMENT

6.2.1 Principles

Premises and equipment shall be suitable for the intended activities and they shall not present any hazard to the quality of the products.

6.2.2 General Requirements

i. Radiopharmaceuticals should be prepared in controlled (environmental and radiation) areas. The minimum expected standards for a range of activities is shown in Table 6.1.
ii. Premises and equipment shall be appropriately maintained and upgraded, ensuring that they are suitable for the intended activities and to minimise the risk of errors. There shall be appropriate workflow and segregation of activities.
iii. In order to reduce the risk of contamination and radiation exposure (e.g., by cross contamination or by the accumulation of dust and dirt), appropriately designed premises and equipment as well as careful and suitable working techniques shall be used. Special care shall be taken when samples are taken or when equipment is cleaned and, where applicable, disinfected after repair or maintenance.
iv. Appropriate controls should be in place to detect any radioactive contamination, either directly using radiation detectors or indirectly through a swabbing routine.
v. Adequate measures shall be taken against the entry of insects and other animals (pest control).
vi. Washing and cleaning activities shall not themselves be a source of contamination.
vii. Production, storage and quality control areas shall be accessible to authorised personnel only.
viii. Environmental conditions (temperature, humidity, light, sound, and pressure differential) during production, quality control and storage (including cold storage) shall be defined and monitored, if necessary, controlled.
ix. Monitoring results shall be documented, assessed and retained. When conditions fall outside the defined limits, adequate corrective action shall be promptly addressed.
x. All areas shall be clean, orderly and well lit.

Table 6.1 Minimum expected standards for radiopharmaceutical activities

Preparation Method	Open workstation	Closed (isolator)
Open aseptic	B*	D
Closed aseptic	C	D
Open terminally sterilised	D	D
Closed terminally sterilised	D	D

*Note: Immediate administration may allow a C grade area to be used, subject to a risk assessment.

6.2.3 Cleaning Procedure for Clean Room and Equipment

i. Principles
   a) The act of reducing or removing radioactivity (radioactive decontamination) from an object or surface must be balanced with the risk of spreading radioactive contamination. At times the best approach may be to shield the area until the radiation exposure levels are lower. Working areas should be checked for radioactive contamination prior to cleaning and disinfecting to prevent spreading radioactive contamination.
   b) All cleaning and disinfecting activities must be performed by trained and appropriately garbed personnel using facility approved agents and procedures that must be described in written SOPs.

ii. General Requirements
   a) Cleaning and disinfecting should be recorded by the Designated Person and verified by the Pharmacist In-Charge
   b) Cleaning log (refer *Appendix 10*) must be customised to meet local settings and maintained according to local policy

iii. Responsibilities
   a) The Pharmacist In-Charge shall oversee the cleaning and disinfecting of clean room and all equipment.
   b) Cleaning and disinfecting tasks can be assigned to Pharmacy and/ or Hospital Support Service personnel, provided that they are well-trained.
   c) The Pharmacist In-Charge or a Designated Person shall provide routine training to the cleaning and disinfecting personnel.
   d) The Pharmacist In-Charge or a Designated Person shall supervise and assess all cleaning procedures done.

iv. Equipment/ Materials
   a) Dedicated sterile low shedding mops (autoclavable)
   b) Dedicated multi-bucket mopping system (if required)

c) Sterile low lint wipes
d) Sterile disinfectant such as sterile alcohol 70%, etc (refer *Appendix 18*)
e) Sterile Water for Injection (WFI)
f) PPE

Note: Cleaning supplies and solutions used in the classified areas should be monitored for radioactive contamination after use and prior to disposal

v. Entry of Cleaning Materials and Equipment into Clean Room
   a) Ensure that all materials and equipment are in good condition and monitored for radioactive contamination.
   b) All materials entering clean room shall be disinfected with sterile alcohol 70%.
   c) Materials and equipment disinfected shall be brought into clean room through pass box, except for materials that are too bulky to be placed into the pass box.

vi. Cleaning Procedures
   Frequency of cleaning for equipment/ area is as shown in Table 6.2.
   Cleaning procedures for radiopharmaceutical facilities as shown in Table 6.3.

Table 6.2 Cleaning frequency for related area

Frequency	Equipment/Area
Before and after production	Safety cabinet/ Isolator
After production or daily	Stainless steel bench and trolley in preparation room, floor, window and door knobs, pass box and clinical waste bins.
Weekly	Safety cabinet/ Isolator, stainless steel bench and trolley, floor (including sporicidal), window and door knobs, pass box and clinical waste bins, walls and sinks, gowning cabinet, changing room cabinet.
Monthly	Safety Cabinet/ Isolator, stainless steel bench and trolley, floor, window and door knobs, pass box and clinical waste bins, walls and sinks, gowning cabinet, changing room cabinet, ceilings.

Table 6.3 Cleaning procedures for radiopharmaceutical facilities

	Site	Procedures
1.	Safety Cabinet	• Wear PPE before entering the preparation room. • The cabinet shall be cleaned at the start and the end of each work session. • The back of the cabinet shall be cleaned first, followed by the left and right side, the safety glass panel and lastly, the working bench. • The left, back and right side, the safety glass panel and working bench of the cabinet are wiped from the least contaminated area to the most contaminated area with overlapping strokes using sterile alcohol 70% as surface disinfectant to reduce any bioburden present. • All soiled wipes shall be thrown into the dedicated waste. • After the completion of radiopharmaceutical reconstitution, clean the cabinet accordingly.
2.	Isolator	• Wear PPE before entering the preparation room. • The isolator shall be cleaned at the start and the end of each work session. • Clean the external surfaces of the transfer chambers and front visor. • Wipe all internal surfaces with sterile alcohol 70% before the start of each work session. • Clean the inner surfaces of both transfer chambers. • Clean the back of the isolator, followed by the left and right side, the front visor, glove sleeves and lastly, the working bench, with overlapping wipes using sterile alcohol 70% as surface disinfectant to reduce any bioburden present. • Discard all used wipes into the dedicated waste. • After the completion of radiopharmaceutical reconstitution, clean the isolator accordingly.
3.	Stainless steel bench, trolley in preparation room, door knobs and clinical waste bins	• Wipe all equipment with low lint wipes and sterile alcohol 70%. • Ensure that all hard-to-reach areas are cleaned.
4.	Window	• Clean from top to bottom with low lint wipes and sterile alcohol 70%. • Ensure that all hard-to-reach areas are cleaned.
5.	Pass box	• Clean the inner surface of the pass box before transferring materials and equipment into the pass box for the first time on that day. • Begin with the top surface, followed by the left and right side, glass panels and lastly, the bottom surface with low lint wipes and sterile alcohol 70%.

	Site	Procedures
6.	Floor	• Clean the floor accordingly before applying disinfectant. • Use overlapping strokes from the cleanest area to the dirtiest.
7.	Walls	• Clean walls using low lint wipes or extendable mop with appropriate disinfectant (sterile alcohol 70%). • Clean from top to bottom (ceiling to floor) or side to side from the least contaminated area to the most contaminated area using overlapping strokes. • Ensure that all hard-to-reach areas are cleaned.
8.	Ceilings	• Clean ceilings using low lint wipes or extendable mop with appropriate disinfectant (sterile alcohol 70%) from the cleanest area to the dirtiest. • Avoid contact with HEPA filters while cleaning. • Ensure that all hard-to-reach areas are cleaned.

vii. Use of Disinfectants

a) Choice of disinfectants shall be based on the grade of clean room as well as the fauna of the clean room.
b) Disinfectants used shall be sterile (in grade A and B clean rooms) and rotated at specific interval based on manufacturer's recommendation.
c) Periodic use of sporicidal agents shall be considered to reduce contamination from spore forming microorganisms (eg. monthly).
d) Prepare or dilute disinfectant in clean containers as per manufacturer's recommendation in the clean room.
e) Label containers clearly with BUD and store as per manufacturer's recommendation.
f) Partly emptied containers shall not be topped up.

viii. Storage of Cleaning Materials

a) Facility with utility room: all cleaning materials shall be stored in the utility room.
b) Facility without utility room: all cleaning materials shall be stored in the component preparation room.

ix. Management of Used Cleaning Materials

a) All waste shall be disposed daily after each production.
b) Reusable cleaning materials shall be rinsed and sterilised before the next use.

x. Cleaning Procedure under Non-Routine Circumstances

Thorough cleaning must be done before any production activity in the event of which the cleanliness of classified room is deemed compromised;

a) Breakdown of Air Handling Unit (AHU)
b) High microbial count
c) Major and minor renovations
d) Repair and maintenance work
e) Deviation of room physical parameters (e.g. wet room environment and floors

due to high humidity & etc.)

f) Others

Refer to Maintenance Procedure for Clean Room and Equipment for further details.

xi. Cleaning and Disinfecting Items from Patient Care Areas

a) Radiation shielding and equipment used in classified/ clean areas that are exposed to patient care areas during the process of administration must be cleaned and disinfected before returning to any classified/ clean areas.

b) Used syringes must not be brought back into classified/ clean areas for re-assaying or disposal, unless it has been sealed inside an impervious and disinfected container.

c) Equipment that has been contaminated with blood-borne pathogens and radioactive materials are considered mixed waste. Mixed waste must be cleaned and disinfected with an appropriate agent(s) for blood.

6.2.4 Maintenance Procedure for Clean Room and Equipment

i. Responsibilities

a) Pharmacist In-Charge

- Monitor all performance testing/ recertification, maintenance and repair work.
- Monitor all physical and microbiological parameters.
- Analyse and verify all monitoring and testing reports.
- Ensure performance testing are conducted by qualified/ accredited third-party agent (e.g. NEBB or NATA certified).

b) Hospital Support Services (HSS)

- Carry out periodic maintenance and performance testing as scheduled.
- Appoint qualified/ accredited third-party agent (e.g. NEBB or NATA certified) for performance testing and recertification of clean room and equipment.
- Ensure performance tests are conducted and data collected in accordance with the appropriate standards.
- Analyse and verify all testing reports.
- Investigate and rectify deviation from specifications in timely manner.
- Present findings of testing report/ investigation on deviation and corrective action plan to the Pharmacist In-Charge.

ii. Equipment/ Materials
   a) All devices used for monitoring clean room and equipment parameters (pressure gauges, thermometer, hygrometer and etc.) require periodic maintenance and calibration.
   b) Equipment used for performance testing must be calibrated prior to testing done.

iii. Procedure for Monitoring
   a) Generally, the monitoring activities could be divided into:
      - Physical Monitoring
      - Microbiological Monitoring

   b) Planned Preventive Maintenance (PPM) could be divided into:
      - Planned Preventive Maintenance (PPM) by HSS according to facility schedule (check with hospital engineer for details)
      - Annual performance testing/ Recertification by qualified/accredited third party testing agent

   c) Physical monitoring parameter and frequency are listed in Table 6.4.

Table 6.4 Monitoring parameters and their frequency for facility maintenance

Parameter	BSC/ Isolator/ Hot Cell	Clean Room
1. Temperature		a) Before preparation. b) Every day if no preparation.
2. Humidity		a) Before preparation. b) Every day if no preparation.
3. Air Pressure Differential		a) Before preparation. b) Every day if no preparation.
4. Pressure Differential Across HEPA Filter or Airflow Velocity	Before preparation.	
5. Isolator Glove Integrity	Once a week (if any).	
6. Isolator Leak Test	Weekly. *depends on the brand and model of isolator (refer User Manual)	
7. Radiation monitoring	Before preparation.	Before preparation.

Note: Record the temperature and humidity reading in the Clean Room Temperature, Humidity and Pressure Differential Record (Appendix 11)

- Temperature and Humidity Monitoring
  - Record the temperature and humidity reading in the Clean Room Temperature, Humidity and Pressure Differential Record (Appendix 11).
  - Check, analyse and verify the records.
  - For deviation from specification, please refer to 6.2.4 (v) and also 1.3 under Chapter 1.

- Air Pressure Differential Monitoring
  - Record the air pressure differential reading in the Clean Room Temperature, Humidity and Pressure Differential Record (Appendix 11).
  - Check, analyse and verify the records.
  - For deviation from specification, please refer to 6.2.4 (v) and also 1.3 under Chapter 1.

d) Microbiological Monitoring
- Microbiological monitoring parameter and frequency are as listed in Table 6.5.
- Procedures for microbial monitoring are as shown in Table 6.6.

Table 6.5 Monitoring parameter and their frequency for microbiological monitoring

Parameter	BSC/ Isolator/ Hot Cell	Clean Room
1. Settle plate (90mm diameter)	a) Every working session. b) After major breakdown/ After major maintenance.	a) Once a week during preparation. b) After major breakdown/ After major maintenance.
2. Surface sample test (Contact plate -55 mm diameter / Swab test)	Once a week.	a) Once a month. b) After major breakdown/ After major maintenance.
3. Personnel monitoring – gloved finger dabs	At the end of each working session.	
4. Active air samples	a) Every 3 months. b) After major breakdown/ After major maintenance.	a) Every 3 months. b) After major breakdown/ After major maintenance.

Note: All the parameters mentioned above shall be monitored during in-operation.

- Microbial contamination from work environment is a potential risk for sterile radiopharmaceutical preparation. Air and surface monitoring programmes are developed to ensure maintenance of proper cleanliness in the classified areas. They are useful to evaluate the air quality, material handling procedures, cleaning and disinfecting procedures and also personnel competency in work practices.

- Initial air and surface sampling must be performed to establish baseline environmental quality for classified areas. After initial sampling, the classified areas should be monitored according to the minimum frequencies described in Table 6.5.

- Due to radiation exposure concerns for the workers involved, it is permissible for sampling to be carried out at the end of sterile radiopharmaceutical processing but prior to cleaning and disinfecting the surface area. In this case, simulated tasks that are reflective of the routine aseptic activities are performed.

- In addition to the specific sampling frequencies described in this section, sampling must be performed in any of the following circumstances:
  - Certification of new facilities and equipment
  - After any modification of facilities or equipment
  - Detection of problems or worrying trends
  - Detection of changes that could impact the controlled area environments

Table 6.6 Microbial monitoring procedures

(A) Settle Plate (TSA & SDA - 90mm diameter)	(B) Contact Plate* (TSA **& SDA** - 55mm diameter)	(C) Gloved fingertip sampling with contact plate
✓ **Before the start of operation/ production, gather the required quantity of agar plates.** ✓ **Label plates with location/ sample site, date (for all plates), time of sampling starts (for settle plates), names of personnel, left & right hand (for plates used for gloved fingertip sampling).** ✓ **Disinfect before transfer the plates into pass box.**		
a) Place the settle plate at the sample site. b) Remove its lid and leave it for 4 hours or less (if production ends earlier)#. c) Put its lid back, seal with parafilm and write the end time on its label.	a) Take samples upon completion of operation/ production. b) Remove the lid of contact plate. c) Press it lightly against the surface of sample site for 2-5 seconds. d) Put its lid back, seal with parafilm. e) Clean and disinfect sampled area immediately. f) Use a new plate for each sample site.	a) Take samples after the last dose of drug compounded. b) Do not disinfect gloves before sampling. c) Remove the lid of a contact plate. d) Hold the plate at an angle that will allow four fingers of one hand to first press on the agar and create a slight impression then followed by the thumb. e) Repeat with the opposite hand on the second plate. f) Put its lid back and seal with parafilm.
✓ **Send the plates to the laboratory immediately or handle as per microbiology laboratory protocol.**		

Incubate as follows:

- TSA plates- 48hrs at 30-35°C (for bacteria)
- SDA plates- 5 days at 26-30°C (for yeasts & mold)[19]

✓ **Analyse and verify all laboratory results and reports. Keep the reports systematically.**
✓ **For deviation from specification, please refer to 6.2.4 (v) and also 1.3 in Chapter 1.**

(Notes: Sampling must be done during normal operation/ production)

*Contact plate has a raised surface that allow the agar to be pressed on surfaces.

** Media used for surface- and fingertip sampling must contain added Lecithin and Polysorbate 80 (to neutralize the effects of disinfectants).

For exposure time less than 4 hours, result obtained should be extrapolated using the following equation: Count/ Time Exposed (min) X 240 = cfu/4 hr.

TSA: Tryptic Soy Agar; SDA: Sabouraud Dextrose Agar

- Identifying sample sites
  - Select critical zones and sites that are likely to capture the impact of personnel movement and work within the area. Other areas of concern to be monitored include entry points of materials/ equipment from a room with lower classification to another with higher classification, areas near doors and any other spots with air backwash turbulence. Sample sites selected shall remain constant as determined during facility qualification and well documented.

- Selecting culture media and diluents
  - The type of medium used (solid or liquid) for sampling microorganism may differ (depends on the procedure and equipment used). Alternatives to TSA and SDA can be used as long as they are suitable for the intended purpose. Soybean casein digest medium is considered equivalent to TSA and malt extract agar can be used to detect yeasts and molds in the environment.

- Swabbing method (surface swabs) can be done for irregular surfaces to supplement contact plate method for surface sampling but there is no microbial limit can be recommended. Check with microbiology laboratory for proper sampling procedure and refer to reliable references (e.g. USP 797 & etc.) for guide on interpretation of results.

- Microbiological monitoring is essential for quality assurance of finished products, evaluation of effectiveness of cleaning and disinfecting procedures and personnel adherence to aseptic work practice.

iv. PPM by Hospital Support Services (HSS) and Recertification by Third Party Testing Agent

PPM schedule should be made available to pharmacy and appointment should be made beforehand to facilitate proper arrangement for maintenance activities. PPM must include the below:

a) Changing of all primary and secondary filters as scheduled in timely manner (AHU, BSC and isolator).
b) Calibration of pressure gauges, thermometer and hygrometer.
c) Inspection of emergency push button, interlocking button and alarm button (if applicable).
d) Performance testing by third party agent on clean room and major equipment.
e) Performance testing and recertification by Third Party Testing Agent should include parameters listed in Table 6.7.

Table 6.7 Validation activities by third party agent

Parameter	BSC/ Isolator/ Hot Cell	Clean Room
1. Airborne Particle Counts	a) Every 6 months. b) After major breakdown/ After major maintenance.	a) Every 6 months (Grade A & B)/ Once a year (Grade C & D). b) After major breakdown/ After major maintenance.
2. HEPA Filter Integrity Tests	a) Once a year. b) After major breakdown/ After major maintenance.	a) Once a year. b) After major breakdown/ After major maintenance.
3. Air Pressure Differential Test		a) Once a year. b) After major breakdown/ After major maintenance.
4. Air Change Rate Test		a) Once a year. b) After major breakdown/ After major maintenance.
5. Air Flow Velocities (Grade A)	a) Once a year. b) After major breakdown/ After major maintenance.	
6. Air Flow Pattern Test (Grade A)	a) Once a year. b) After major breakdown/ After major maintenance.	
7. Isolator Alarm Functional Tests	Once a year.	
8. Isolator Leak Test	a) Once a year. b) After major breakdown/ After major maintenance.	
9. Isolator Pressure Hold Test	a) Once a year. b) After major breakdown/ After major maintenance.	

Note: All the parameters mentioned above shall be monitored during at-rest.

- Ensure all personnel from Third Party Agents adhere to proper hand washing and clean room entry procedures.
- Ensure maintenance and corrective works are complete before annual performance testing or recertification.

v. Deviation from Specifications

Deviations of physical and microbiological monitoring parameters from specifications are indicators of compromised clean/ safe environment. Immediate actions are warranted:

a) Lodge report to HSS and follow up closely.
b) Identify cause of problems and take the necessary corrective actions soonest possible.

vi. Records and Documentation
   a) All reports/ records of physical and microbiological parameters monitoring, repair and maintenance work, performance testing and recertification must be verified by Pharmacist In-Charge.
   b) All reports/ records of physical and microbiological parameters monitoring, repair and maintenance work, performance testing and recertification must be kept systematically or as per facility protocol (examples of records refer *Appendix 11* and *Appendix 12*).

6.3 PRODUCTION

6.3.1 Principles

i. The preparation of radiopharmaceuticals should be organized in such a way to prevent cross-contamination.
ii. Process validation, in process controls and monitoring of process and environment parameters are particularly important in case where decision has to be made to release or reject a batch or a product before all tests are completed.
iii. Prepared or compounded radiopharmaceuticals must comply with applicable standards.

6.3.2 General Requirements

i. Production shall be performed by trained personnel. Products and materials shall be protected from microbial and other contamination at all times through sanitising the materials prior to use and strict adherence to aseptic technique.
ii. Appropriate flow, segregation and adequate line clearance of materials shall be practiced to prevent accidental cross-contamination or mix-up of preparations.
iii. Only sterile materials shall be taken into Grade A and B areas.
iv. Radiation protection programme or local rules must be followed to ensure the safety of personnel.

6.3.3 Pre-Production

Before the start of production, the pharmacist shall ensure that:
i. Worksheets and labels are prepared, counterchecked and verified.
ii. Starting materials are gathered and counterchecked.
iii. Worksheets and labels are brought in using plastic covers.
iv. Starting materials are sprayed and sanitised with alcohol 70% prior to placing into pass box or air lock.
v. Personnel dosimeter shall be worn appropriately.

vi. BSC/ Isolator/ Hot Cell is intact and operational by checking on the display panel and isolator glove integrity.

6.3.4 During Production

i. Cleaning of BSC/ Isolator/ Hot Cell
Refer to the cleaning procedures for further details.

ii. Quality Control (QC) of Dose Calibrator
Physical inspection for damage, background response/ contamination check and daily constancy test on radionuclide dose calibrators using long-lived radioactive source shall be performed at the beginning of the day of use.

iii. Aseptic Processing
   a) For risk management, a minimum of 2 personnel shall be involved in production at all times. These personnel shall countercheck each other on the process involved.
   b) For kit based radiopharmaceutical preparation such as Technetium-99m (^{99m}Tc) radiopharmaceutical, Lutetium-177 (^{177}Lu) peptides and Samarium-153 (^{153}Sm) EDTMP, a biosafety cabinet or isolator equipped with appropriate shielding is recommended.
   c) For PET radiopharmaceuticals such as Fluorin-18 (^{18}F) FDG (Fluorodeoxyglucose), ^{18}F- FDOPA and Carbon-11 (^{11}C) Methionine a hot cell equipped with appropriate shielding is recommended.
   d) For radiolabeled blood preparation, a BSC or isolator equipped with appropriate shielding is recommended. If BSC is used, the room must not be shared with other BSC used for kit based radiopharmaceutical preparation.

iv. Basic Aseptic processing:
   a) Fixing needle to syringe
      - Half unwrap the syringe and the needle pack.
      - Fix syringe onto the needle with special precaution not to touch the critical sites.
      - Put the assembled syringe and needle aside to be used later.

   b) Fixing filter and needle to syringe
      - Half unwrap the syringe, 5µm filter and the needle pack.
      - Fix the filter onto the syringe and onto the needle with special precaution not to touch the critical sites.
      - Put the assembled syringe, filter and needle aside to be used later.

   c) Withdrawing solution from a vial:
      - Place the vial on the bench. Remove the plastic/ aluminium cap of the vial.
      - Swab the rubber bung with alcohol 70%.

- Place the vial upright in a vertical position and hold firmly.
- Position the syringe at 45° and place the needle (attached to the syringe) on the rubber bung with the bevel pointing upward.
- Push the needle down and at the same time, pierce the needle through the rubber bung.
- Invert the whole set with the vial on top of the syringe.
- Pull the plunger slightly downwards and then, push upwards slowly to withdraw drug solution into the syringe. Repeat this 'pulse technique' until the entire solution is transferred into syringe.
- Place the vial on the working cabinet bench top and pull out the needle from the vial.
- If the vial is to be reused, a second hole shall be made at the same site.
- Remove air bubbles and adjust to the required volume.

d) Adding solution to a vial containing powder/ solution:

- Place the vial on the bench. Remove the plastic/ aluminium cap of the vial.
- Swab the rubber bung with alcohol 70%.
- Position the syringe at 45° and place the needle (attached to the syringe) on the rubber bung of the vial with the bevel pointing upward.
- Push the needle down and at the same time, pierce the needle through the rubber bung.
- Push the plunger down slowly until the entire solution is transferred into the vial.
- Pull the plunger to its initial position. This will ensure that there is negative pressure in the vial and to avoid the generation of radioactive aerosols.
- Pull the needle slowly out of the rubber.
- Discard the needle into the sharps bin.
- Let the vial stand and swirl for a few minutes in order to dissolve the powder.

v. Procedure for Kit Based Radiopharmaceuticals: ^{99m}Tc based radiopharmaceuticals

a) Elution of ^{99m}Tc elutes from generator

- Place a Sterile Evacuated Vial (SEV) on the work bench.
- Remove the flip-top from SEV and swab the vial closure using an alcohol swab uni-directionally and allow to dry.
- Put the SEV into a dedicated elution vial shield.
- Remove the needle protector from the elution port and discard.
- Insert the shielded SEV into the elution port.
- Wait for at least three minutes to ensure the elution is complete. After three minutes, carefully remove the shielded SEV containing the ^{99m}Tc eluate. Replace the shielded SEV containing ^{99m}Tc eluate with a needle protector.
- Proceed for quality control of ^{99m}Tc eluate. Refer to Quality Control procedure.

Note: Procedure may vary depending on type of ^{99m}Tc Sterile Generator used. Refer product leaflet for the accurate procedure.

b) Preparation of ^{99m}Tc based radiopharmaceuticals

- Place the 'cold kit' vial on the work bench.
- Ensure the vial is free from defects before use.
- Remove the flip-top on the vial, wipe the rubber septum using alcohol swab uni-directionally and allow to dry.
- Place the vial inside a vial shield and close the vial shield.
- Determine activity of ^{99m}Tc pertechnetate and calculate the volume of ^{99m}Tc pertechnetate needed.
- Withdraw the required volume of ^{99m}Tc pertechnetate into the syringe.
- Take the syringe out of the syringe shield and immediately transfer into the dose calibrator for measurement.
- Take the syringe out of the dose calibrator and immediately place back into the syringe shield.
- If the measured activity is incorrect, re-adjust the volume of ^{99m}Tc-pertechnetate in the syringe either by withdrawing more ^{99m}Tc-pertechnetate or injecting the solution back into the eluate vial.
- Once the correct ^{99m}Tc-pertechnetate activity (± 10% of required activity) is obtained, withdraw the required volume of 0.9%w/v Sodium Chloride to make up to final volume using the same syringe otherwise use a new sterile syringe for the 0.9%w/v Sodium Chloride solution alone.
- Expel any air bubbles from the syringe by holding the syringe with the needle capped. Draw the plunger slightly downwards to remove any residual solution from the needle and then push the plunger upwards.
- Transfer the contents of the syringe(s) into the kit vial. To avoid build-up of pressure in the vial during this step, transfer the solution 2 – 3 ml at a time and allow excess gas in vial to escape into the syringe. If adding pertechnetate and saline separately, add the saline first (unless instructed otherwise in monograph). This is to avoid addition of pertechnetate at an excessively high radioactivity concentration.
- Before removing the needle, create negative pressure in the kit vial by withdrawing slightly more than equivalent volume of air into the syringe to avoid generation of radioactive aerosols. Gently mix the preparation.
- Carefully open the vial shield containing the labelled radiopharmaceutical. Visually inspect for particulates and/or discoloration. Take the vial out of the vial shield using tong and quickly place into the dose calibrator. Measure the activity in the vial.
- Print the label and return the vial into the vial shield and close the vial shield.
- Complete the Batch Processing Record of ^{99m}Tc- Based Radiopharmaceutical and/ or in the IT system.
- Withdraw a sample from the preparation using 1 ml syringe for quality control analysis.

Note: Procedure may vary depend on type of kit radiopharmaceuticals. Refer product leaflet for the accurate procedure.

vi. Procedure for Kit Based Radiopharmaceuticals: ^{177}Lu Peptide

a) Preparation of ^{177}Lu-Peptide:

- Place all starting materials inside the BSC.
- Open the ^{177}Lu container and take out the vial inside the container using a tong, measure the activity in a radionuclide dose calibrator.
- Print the label and insert the vial to the vial shield.
- Turn on heating block and set at 80°C.
- Remove the flip-top on the peptide vial and ^{177}Lu vial. Wipe the rubber septum using alcohol swab uni-directionally and allow to dry.
- Place the vial inside a vial shield and close the vial shield.
- Withdraw whole volume of Dotatate cold kit using 3ml syringe. Expel any excess air from the syringe.
- Transfer the content of the syringe into ^{177}Lu vial. Make sure that the needle does not touch ^{177}Lu solution inside the vial.
- Measure the activity of ^{177}Lu peptide in a radionuclide dose calibrator and print label.
- Gently mix the preparation.
- Place ^{177}Lu vial in the heating block for 30 minutes. For every 10 minutes, shake ^{177}Lu vial gently.
- After 30 minutes, the reaction has completed, place ^{177}Lu vial into vial shield and let it cool to room temperature for 15 minutes.
- Add 3.6 mL of Water for Injection into ^{177}Lu peptide preparation.
- Withdraw 0.1 ml of ^{177}Lu peptide using 1 ml syringe for quality control analysis.
- Complete the Batch Processing Record.

Note: Procedure may vary depend on brand and type of kit radiopharmaceuticals. Refer product leaflet for the accurate procedure.

vii. Procedure for PET Radiopharmaceuticals: Gallium-68 (^{68}Ga) peptide

a) Preparation of ^{68}Ga peptide:

- Inspect the buffer vial and peptide for any particulate or damage on the container. If found, discard the vial immediately.
- Prepare the reaction vial and the buffer vial by wiping the rubber bung with an alcohol swab.
- Aseptically, syringe out the buffer and transfer it into the reaction vial.
- Carefully transfer the peptide into the reaction vial.
- Fix a filtered venting needle to the reaction vial.
- Insert the outlet line from the Germanium-68/ Gallium-68 (^{68}Ge/ ^{68}Ga) generator to the reaction vial.

b) Elution of $^{68}Ge/^{68}Ga$ Generator and radiolabelling of ^{68}Ga peptide

- Inspect the eluent vial for any particulate or damage on the container. If found, discard the vial immediately.
- Wipe the eluent vial using an alcohol swab.
- Using a Luer-lock syringe, aseptically withdraw the eluent according to the recommended volume.
- Fix the syringe containing the elution solution to the inlet line of the $^{68}Ge/^{68}Ga$ generator.
- With the outlet line inserted in the reaction vial containing the peptide and buffer, slowly push the content inside the syringe to elute $^{68}Ge/^{68}Ga$ generator into the reaction vial.
- Record the time of elution and let react.
- If heating is required, place the reaction vial inside a heating block and set the temperature accordingly. Make sure to let the reaction vial cool down before the filtration and purification process.
- In the case where HEPES buffer is used for the preparation of ^{68}Ga peptide, remove the HEPES buffer by following the purification step.
- Add in a suitable base to neutralize the pH if necessary.

c) Filtration of ^{68}Ga peptide

- Prepare the sterile product vial by wiping the rubber bung with an alcohol swab. Inspect the product vial for any damage or contamination.
- Using a syringe, withdraw the content inside the reaction vial.
- Fix a 0.22µm PVDF filter onto the syringe and aseptically transfer the product into the sterile product vial.
- Using a 1 ml syringe, withdraw 0.1 ml for quality control analysis.

d) Purification of ^{68}Ga peptide:

- Condition the SPE C18 cartridge with ethanol followed by sterile water for injection.
- Load the radiolabeled product into the SPE C18 cartridge and wash with 10 ml sterile water for injection.
- Elute the radiolabeled product with ethanol followed by sterile water for injection.

  Note: The concentration of ethanol inside the final product must not exceed 10%.

viii. Dispensing of Radiopharmaceuticals

a) Attach a fresh needle to a Luer-lock syringe and place into a syringe shield. (needle and syringe size may differ depends on type of radiopharmaceuticals).

b) Withdraw the required volume of radiopharmaceutical solution using the syringe. Take the syringe out of the syringe shield and immediately transfer into the calibrator. Measure the activity. If the measured activity is incorrect, remove the syringe from the dose calibrator and re-adjust the volume of radiopharmaceutical in the syringe either by withdrawing more solution or

injecting the solution back into the radiopharmaceutical vial.

c) Once the correct radiopharmaceutical activity is obtained, print the label.
d) Remove the syringe from the dose calibrator.
e) Using the same syringe, withdraw the required volume of 0.9%w/v Sodium Chloride to make up to the final volume.
f) Expel any air bubbles from the syringe by holding the syringe upright with the needle capped. Draw the plunger slightly downwards to remove any residual solution from the needle and then push the plunger upwards. Attach patient's label and radiopharmaceutical label on the syringe shield.
g) Supply the radiopharmaceutical in a shielded syringe carrier to the technologist or medical officer in-charge through pass box.

ix. Decontamination Procedure for Radioactive Spillage[46]

a) Contaminated area should be decontaminated using decontamination solution and disposable absorbent towel/ paper towel or any absorbent material. Allow several minutes for the decontamination solution to settle on the contaminated area before proceed with decontamination process.
b) If the contamination occurred on top of an absorbent material, remove the contaminated material and put it into plastic bag and dispose it as radioactive waste. Small objects such as tongs and glassware can be cleaned by agitated submersion in hot water.
c) Inform RPO of the contamination incident as soon as possible.

6.3.5 Post-Production

i. Cleaning

a) Remove all used vial, ampule, needles and syringes from the workbench and floor, and dispose them into a shielded sharps bin.
b) Start swabbing the BSC as detailed in the cleaning procedure.

ii. Labelling and Packaging for product – Labels should include:

a) Product name
b) Volume
c) Radioactivity
d) Batch number
e) Calibration date and time
f) Expiry date and time

iii. Storage

a) All preparations shall be stored according to manufacturer's recommendation.
b) Radiopharmaceutical shall be stored in appropriate conditions (e.g., leaded shielding, controlled temperature and humidity). Radiation warning sign shall be displayed on the door of storage area.
c) The storage conditions shall be recorded. Storage area shall be monitored regularly to detect the presence of possible contamination, perform leakage

test if necessary.

d) Separate storage areas shall be assigned for quarantined, rejected, returned or recalled materials until the decision on their future use has been taken unless there is an alternative system to prevent unintentional or unauthorised usage of such materials.

e) Only Designated Person(s) are allowed to mobilise the radioactive materials from the storage area.

iv. Rejected and Returned Materials and Products

a) All errors, defects and complaints related to starting materials, commercial drug products and CSP shall be investigated, remediated and documented.

b) For deviation from specifications in CSP, refer to Chapter 1. Check if other preparations are affected and cease supply until cause(s) of problem solved.

c) Product complaints and recalls of starting materials or commercial drug products by manufacturers shall be managed in accordance with MOH policy.

d) Rejected or recalled starting materials, commercial drug products and CSP shall be stored in a secure, segregated area while their disposition is decided.

e) Where any doubt arises over the quality of a commercial drug product or CSP, it shall not be considered suitable for re-issue or re-use.

f) Unused products/ preparations returned by end users from wards/ daycare units should be disposed, unless its quality can be assured:

- Check expiry date and inspect for any sign of instability
- Consider stability and possible microbial contamination under actual handling conditions (storage, transportation) by end users
- Determine reason(s) for medication return
- Records of re-use must be kept (identifications, assignment of new expiry date, new label, worksheet & re-dispensing)

g) Products/ preparations that have been released to a patient, or into the community, should **NEVER** be reused for other patients.

6.3.6 Disposal of Clinical/ Radioactive Waste

i. Principles

a) Disposal procedure shall follow the requirements set by the Atomic Energy Licensing (Radioactive Waste Management) Regulations 2011 monitor by Radiation Protection Officer (RPO).

b) These are the main approaches for disposal of radioactive waste:

- Dilute and Disperse: Radioactive material in aqueous or gaseous form can be diluted and distributed over a large volume before release into environment so that the final concentration of radionuclides is low.
- Delay and Decay: This principle is usually applicable to wastes containing short half-live radionuclide. The radioactive waste is kept in safe containers at dedicated area until it decays to the permitted release level set by the regulatory body.

- Return to manufacturer: This approach involves returning the used long half-life radioactive source to the vendor or supplier.

c) Containers used for disposal of radioactive waste shall be properly labelled, sealed, covered and handled by trained personnel only. Such personnel shall take necessary precautions to ensure personal, public and environmental safety.

d) All radioactive waste, including those generated after cleaning of spillage, must be segregated, packaged and disposed of in a manner that will not contaminate personnel and the environment.

ii. Materials Required for the Disposal of Clinical/ Radioactive Waste

a) Inches thick (minimum) lead shield
b) Calibrated survey meter
c) Plastic bags
d) Inventory form

iii. Procedure

a) Radioactive waste includes all materials that have come into contact with radiopharmaceuticals during the process of preparation and administration.

b) Radioactive waste generated in the BSC

- All contaminated sharp materials such as vial/ ampoule which are empty or with unused portions of drugs, needles and syringes shall be discarded in the shielded sharps bin.
- Used materials (non-sharp) such as gauze, wrappers and infusion bottles that are potentially contaminated with radiopharmaceuticals residues must be discarded into the shielded waste bin.

c) Gowns and Gloves

- Disposable gowns and outer gloves must be placed into the radioactive waste bag before leaving the clean room at the end of the working session. The radioactive waste bag is then kept in the Radioactive Waste Room.
- Personnel must not leave the room while still wearing the gown and outer gloves that have been used for radiopharmaceutical preparation.

d) Radioactive Waste Bins

- Shielded waste bins shall be made available in the radiopharmaceutical preparation units and areas where radiopharmaceuticals are administered to patients.
- Bins must be rigid and puncture resistant.
- All radioactive waste bins and bags shall be labelled with radioactivity hazard symbol (trefoil).

e) Disposal of Bins/ Bags

- Bins and bags must not be more than two-third full before discarded.
- Removal of contaminated waste bags from the radiopharmaceutical preparation room is the responsibility of the Authorised Personnel.

f) Each waste bin or bag shall be securely sealed. Authorised Personnel shall place a label at the waste bin containing following information:

- Bin/ Bag No

- Location/ Type of Waste
- State
- Closed Date
- Disposed Date
- Performed By

g) Authorised Personnel will transfer the sealed bin or bag into the Radioactive Waste Room for storage and decay.

h) After sufficient period of storage and decay, Authorised Personnel shall measure the dose rate of the waste before Hospital Support Service (HSS) collects it for disposal.

6.4 QUALITY CONTROL

6.4.1 Principles

Quality control (QC) ensures that all requirements related to quality are met. Quality control and release activities shall be independent of the preparation activities. Labelling kits that are prepared at a manufacturers facility and released for sale only after all prescribed quality control tests are completed. Therefore, the composition, chemical purity, apyrogenicity, sterility and particle size (where applicable) are guaranteed by the producer.

6.4.2 General Requirements

The instructions for use accompanying radiopharmaceutical kits should strictly be followed when performing the labelling procedures. Any deviation from these instructions must be validated. Verification of the effectiveness of the applied labelling procedure is done by checking the final activity (at a stated time), the labelling yield and/ or radiochemical purity of the preparation as well as particulate contamination.

i. Quality control procedures for prepared radiopharmaceutical include tests for radiochemical, radionuclidic, and chemical purity as well as checks for pharmaceutical concerns (such as physical characteristics, biologic purity, particle size, particle number, and pH).

ii. The specifications and quality control testing procedures for most of the currently used radiopharmaceuticals are given in the European Pharmacopoeia or other Pharmacopoeia (BP, USP etc).

iii. Some radiopharmaceuticals may need to be distributed and used on the basis of assessment of batch documentation before all chemical and microbiology tests have been completed.

iv. Radiopharmaceutical product release may be carried out in two or more stages, before and after full analytical testing:

a) Assessment by a Designated Person of batch processing records

b) Assessment by the Pharmacist In-Charge of the final analytical data

v. Clearly state the period of validity with regard to the radioactive shelf-life.
vi. All tests including the sterility test should be performed as soon as possible. Samples can be stored to allow sufficient radioactivity decay.
vii. Corrective measures must be taken by Pharmacist In-Charge if unsatisfactory test results (Out-of-Specification) are obtained after dispatch and before expiry.
viii. A traceability system for radiopharmaceuticals should be made available in order to relay any information to the clinical responsible persons.
ix. Injectable compounded from non-certified pyrogen-free components must undergo bacterial endotoxin testing prior to dispensing.

6.4.3 Quality Control Parameters of the Eluates of Tc-99m Generators

i. Radionuclidic purity (e.g. Molybdenum-99 breakthrough)
ii. Radioactivity (e.g. eluate)
iii. Chemical purity (e.g. aluminium ion breakthrough)
iv. pH level

6.4.4 Quality Control Parameters of Radiolabelled Preparation Kit

i. Radiochemical purity (RCP)
ii. pH level
iii. Particle size (e.g. Macro aggregated albumin)

6.4.5 Radiochemical Purity (Thin Layer Chromatography Method)

i. Materials & Reagents
   a) Stationary phases (e.g. Instant thin-layer chromatography, silica gel [ITLC-SG], Whatman 3MM chromatography paper [3MM], etc).
   b) Mobile Phases (e.g. 0.9% Sodium Chloride, 20% Sodium Chloride, Acetone, Methyl Ethyl Ketone [2-Butanone], etc).

ii. Quality control Procedures for ^{99m}Tc kit based radiopharmaceuticals
   a) Setup for Thin Layer Chromatography
      - Use commercially available chromatography strips whenever possible. Alternatively prepare the strips based on manufacturer's recommendations.
      - Prior to preparing the strips, make sure to wear gloves when handling the strips.
      - Place adsorbent paper on designated work area.
      - Prepare forceps, scissors, ruler and pencil.

- Using forceps and scissors, cut the strips in dimensions as mentioned in the manufacturer recommendation.
- Mark a line with pencil at 1.0 cm from each end (origin line and solvent front line).
- If the cut and count technique is to be used, mark a line with pencil based on the RF (retention factor) of the radiopharmaceuticals.
- Store all strips in sealed containers.
- When setting up the mobile phase for Thin Layer chromatography, please choose the mobile phase based on reference from Tec–Control Chromatography, or manufacturer's recommendation.
- Prepare chromatography tanks by using glass vials or test tubes.
- Add solvent to depth of approximately 5mm (approximately 0.5mL to 0.8mL).
- Check solvent level before performing the Thin Layer Chromatography.

b) Sampling of radiopharmaceutical product

- Set up the quality control workspace by placing absorbent papers on the top of dedicated tray.
- Attach a fresh 23G or 25G needle to a Luer-lock syringe.
- Mark the name of the product on the syringe.
- Time for sampling is immediately after incubation time following the preparation. Note: Please refer to manufacturer's recommendations for incubation time of each product.
- Place the syringe inside a syringe shield and withdraw approximately 0.05ml of sample solution from the prepared kit vial.

c) Quality control procedure

- Select the solvent (mobile phase) and glass vials.
- Rinse the vials with the related mobile phase.
- Place approximately 0.5mL to 0.8mL of mobile phase in a developing vial.
- Select the appropriate type of strip (stationary phase).
- Use the forceps to take the strip and placed it onto the absorbent paper on the dedicated tray.
- Ensure the correct radiopharmaceutical sample is taken prior to performing the QC procedure.
- Place a drop of the radiopharmaceutical sample on the origin line located at the bottom of the strip (Figure 1).
- Using forceps, place the strip in the developing vial containing the mobile phase with the origin line placed downwards first into the vial (Figure 1).
- Ensure that the bottom of the strip is immersed in the solvent but the solvent does not reach the origin line (Figure 1).
- Allow to develop until the solvent reaches the solvent front line (Figure 1).

- Using forceps, remove the strip from the vial. Cut the strip in (generally) two portions at the cut point indicated (RF) and place in separate tubes.
- If the radiopharmaceutical testing needs to be done with two different strips, repeat steps above (Figure 2).
- Measure the radioactivity in the two portions of the strip separately using dose calibrator and document the measured activity.
- Radiochemical purity is calculated based on percentage of radioactivity present in the desired chemical form in a radiopharmaceutical preparation.
- The preparation can be released for usage after achieved the required radiochemical purity.
- Discard used adsorbent paper, strips and solvents into their respective shielded/ designated waste bins.

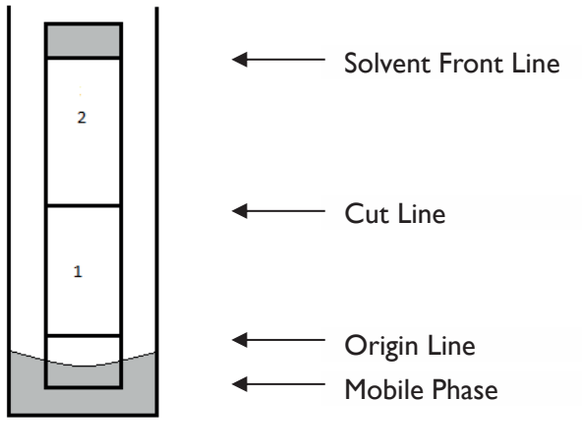


Figure 1. Single strip procedure

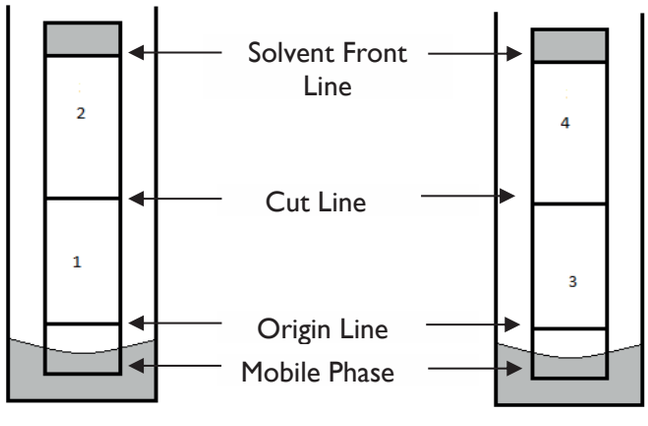


Figure 2. Two strip procedure

iii. Quality control procedure for PET radiopharmaceuticals (e.g. ^{68}Ga peptide radiopharmaceuticals)
   a) Prepare 1 cm x 8 cm ITLC-SG paper and mark origin line at 1 cm. Mark a second line at 6 cm above the origin line.
   b) Prepare 1M Ammonium acetate: Methanol inside the developing chamber until approximately 5 mm depth.
   c) Using a pipette, withdraw 2 µl of ^{68}Ga-peptide and spot at the origin line.
   d) Carefully place the ITLC-SG paper inside the developing chamber and close the lid. Allow the solvent to develop until it reaches the solvent front line.
   e) Remove the ITLC-SG paper and let dry.
   f) Place the ITLC-SG paper on the plate of TLC-scanner and scan the plate at 1 mm/sec.
   g) Once the scan is complete, integrate the chromatogram and record the % ROI and RF.

Table 6.8 Quality control acceptance criteria for ^{68}Ga labelled peptide radiopharmaceuticals

Peptide	[^{68}Ga]**Ga-PSMA-HBED-CC**	[^{68}Ga]**Ga-DOTATATE,** [^{68}Ga]**Ga-DOTATOC,** [^{68}Ga]**Ga-DOTANOC**
pH	4-8	4-8
Radiochemical purity (%)	95	90
Radionuclidic Purity ($t_{1/2}$)	62-74 minutes	62-74 minutes

6.4.6 Product Release

i. All personnel shall adhere strictly to the standards of GPP and are equally accountable for the quality of all finished products. Finished products should be released or dispensed by Releasing Officer accordingly.
ii. End-users should verify all finished products that they received. Proper record/ documentation of product release and receipt are required.

CHAPTER 7

WORK CONTRACTED OUT

7.1 PRINCIPLES

7.1.1 Depending on the local situation and on national legislation, the work contracted out by a healthcare establishment may include activities, which are directly involved with preparation, such as processing, packaging or quality control, and also services, which are not directly involved with preparation, but that can nevertheless have a significant effect on the quality of the products prepared, or on any quality control results produced.

7.1.2 Such services, which are contracted out to another department may include:

- Maintenance of the air handling system, water systems or other utility systems.
- Maintenance of key equipment such as LAFC, BSC, Isolator, sterilisers and balances.
- Sterilisation of components and consumables such as mops, clothing, trays.
- Environmental monitoring services.
- Supply of microbiological consumables (e.g., settle plates).
- Handling of waste.
- Pest control.

7.1.3 Any work, which could affect the quality of the products prepared, and which is contracted out to a third party, shall be the subject of a written technical agreement.

7.1.4 In an emergency, an individual, extemporaneously prepared product may be obtained without a written contract. This shall be an exceptional occurrence.

7.2 GENERAL REQUIREMENTS

7.2.1 A technical service level agreement (contract) shall specify the details of the work to be done, the specification that shall be met and the responsibilities of each party (*Appendix 17*).

7.2.2 The contract shall be authorised and signed by the contract acceptor (i.e. third party contractor) and by the Responsible Person of the contract giver.

7.3 CONTRACT GIVER

7.3.1 In the contract, the contract giver shall specify exactly what level of service is required and to what specification.

7.3.2 The contract giver shall make sure that the contract acceptor is competent and complies with the legal requirements (e.g. GPP, Good Laboratory Practice).

7.3.3 Any reports produced by the contract acceptor, summarizing results or work carried out, shall be formally reviewed and accepted by the contract giver as complying with the required specification.

7.4 CONTRACT ACCEPTOR

7.4.1 Any work shall be performed in accordance with the contract.

7.4.2 Any service or results not complying with the required specification shall be notified to the Responsible Person of the contract giver.

7.4.3 The contract acceptor shall not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.

7.5 SHARING OF FACILITIES

7.5.1 In the event of the same facilities being shared by another party apart from the owner due to breakdown/ renovation of facility, a mutual agreement shall exist between both parties, to prevent conflicts and misunderstandings.

7.5.2 The mutual agreement shall be in the form of a written technical agreement, authorised and signed by the Responsible Person of both parties.

7.6 PREPARING FOR OTHER USERS

7.6.1 It is the responsibility of the service provider to establish the rules and regulations pertaining to the acquisition of the services by the users.

7.6.2 The users shall specify the level of services required and shall comply with requirements from the service provider.

7.6.3 The mutual agreement shall be in the form of a written technical agreement, authorised and signed by the Responsible Person of both parties.

CHAPTER 8

COMPLAINTS AND PRODUCT RECALLS

8.1 PRINCIPLES

All errors, defects, complaints and other signs of quality problems shall be reviewed carefully according to a written procedure. In order to be able to promptly and effectively recall finished products that have severe deficiencies, a suitable procedure shall be developed.

8.2 QUALITY PROBLEMS

8.2.1 Errors, defects, complaints and other signs indicating quality problems shall be investigated. Appropriate measures shall be in place to ensure that effective remedial action is taken. The source and content of deficiencies, remedial measures taken and tests performed shall be documented in writing and added to the preparation record.

8.2.2 When a product defect is reported, consideration shall be given to check if other products could be affected and to cease supply until the problem is fully investigated.

8.3 RECALLS

8.3.1 When deficiencies are potentially harmful to health, a product recall shall be initiated immediately and the competent authority shall be informed without delay.

8.3.2 A written procedure for a recall shall be in place.

8.3.3 Recalled products shall be marked as such and stored in segregated areas. It shall be guaranteed that they cannot be supplied in error.

8.3.4 The progress of the recall shall be recorded. A final report shall be issued, including reconciliation between the delivered and recovered quantities of the products. The report shall be retained for five years, if national regulations do not require other retention times.

8.4 DISPOSAL OF RETURNED/ RECALLED PRODUCTS

8.4.1 In the event of a product recall initiated by the manufacturing company from where the affected product is acquired, the affected batch shall be returned to the company.

8.4.2 If the recalled/ returned preparations are prepared by sterile preparation unit, these preparations shall be disposed according to procedure for disposal upon confirmation of the defect.

CHAPTER 9

SELF-AUDITS

9.1 PRINCIPLES

9.1.1 The quality assurance system, including personnel matters, premises, equipment, documentation, production, QC, distribution of the medicinal products, arrangements for dealing with complaints and work contracted out, shall be examined at regular intervals in order to verify their conformity with the principles of GPP.

9.1.2 A self-audit programme, which considers the type and complexity of operations performed and includes an annual self-audit plan with records and evidence that adequate corrective actions are undertaken, shall be established.

9.1.3 Self-audits shall be conducted in an independent and detailed way by designated competent people.

9.1.4 All GPP-relevant changes and deletions should be documented for the purpose of 'audit trail' and regularly reviewed.

CHAPTER 10

SAFETY

10.1 PRINCIPLES

10.1.1 Occupational Safety and Health (OSH) issues such as needle-prick injury and fire safety in this manual are regarded as a general guide that is applicable to all aseptic services. Safety and health issues should be adapted according to the institution's OSH unit, OSHA, and local fire and safety policy.

10.1.2 Standard procedure and techniques for the handling of cytotoxic drugs and radiopharmaceuticals shall be followed. They are necessary to limit the generation of aerosols and spills and thereby, protect the personnel and environment.

10.2 FIRE SAFETY AND DISASTER

10.2.1 In the event of fire **OCCURRING OUTSIDE** the clean room, the following procedure could be adopted:

i. Received notification of fire or disaster.
ii. Remain calm.
iii. Stop all current activities.
iv. Press the interlocking emergency button, De-gown (if possible).
v. Leave the clean room.
vi. Run to the nearest emergency exit, according to hospital in house policy and guidelines.

10.2.2 If the fire or disaster **OCCURS IN** the clean room:

i. Remain calm.
ii. Stop all current activities.
iii. Press the interlocking emergency button.
iv. Leave the clean room immediately.
v. De-gown (if possible).
vi. Run to the nearest emergency exit, according to hospital in house policy and guidelines.

10.3 NEEDLE PRICK INJURY

10.3.1 Needle-prick injury is defined as the accidental puncture of the skin by a needle during a medical intervention including compounding of sterile pharmaceutical preparations. This injury is especially dangerous if involves cytotoxic drugs or radiopharmaceutical preparations.

10.3.2 In the incident of a needle-prick injury:

i. Stop all current activities immediately.
ii. Retreat to Changing Room.
iii. Discard the gloves.
iv. Cleanse the wound thoroughly with water.
v. Disinfect the wound using disinfectant.
vi. Dry the hands and inspect the wound.
vii. If the injury is serious, do not continue with preparation. Leave the clean room.
viii. If the injury is mild, cover the wound with plaster (if necessary). Perform hand washing and gloving. Continue preparation.
ix. Report all injury to Occupational Safety and Health Administration (OSHA) committee of the hospital.

10.4 RADIATION SAFETY CONSIDERATIONS

10.4.1 Aseptic handling practices must be balanced with radiation safety considerations to ensure all exposure levels for the workers involved is kept As Low As Reasonably Achievable (ALARA). Techniques and materials that can be used to achieve the principles of radiation safety include, but not limited to, the following:

i. Work quickly in a controlled and safe manner.
ii. Utilize techniques to increase distance, such as using remote handling tools, including within Grade A area.
iii. Use of shielding when required throughout the radiopharmaceuticals handling process.
iv. Any techniques and materials that can be used to minimise radioactive contaminations. For example, container contents are maintained at neutral or negative pressure, policies for handling biohazardous radioactive sharps while minimising contamination, etc.

10.4.2 All necessary equipment located inside Grade A area should be placed in a manner that minimises disruptions of airflow. Radiation workers who directly handles radioactive materials must wear body and, extremity dosimeters for long-term monitoring of personnel radiation exposure. The body and extremity dosimeters are to be worn underneath the gown and gloves, respectively.

Appendices

Appendix 1

CHECKLIST OF TRAINING TOPICS FOR PERSONNEL IN STERILE PHARMACEUTICALS PRODUCTION UNIT

Name of Trainee :

No.	Topics	Trained by	Assessed by	Date
1.	*Basic pharmaceutical microbiology*			
2.	*Principles of clean room*			
3.	*Cleaning and maintenance of clean room and equipment (BSC, Isolator & etc)*			
4.	*Aseptic technique*			
5.	*Hand washing*			
6.	*Gloving*			
7.	*Gowning and/or de-gowning*			
8.	*Cytotoxic drug spill management (if applicable)*			
9.	*Others*			

Appendix 2

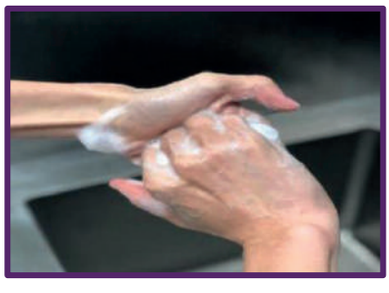
7-STEP HAND WASHING TECHNIQUES

Remove make-up, jewellery and watch before hand washing. Hand washing is done by practising the 7-step technique with appropriate sanitiser and clean water.

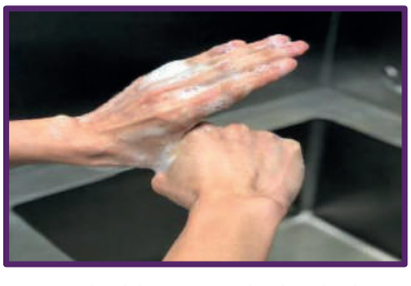
1. Scrub palm to palm.

2. Right palm over left dorsum and left palm over right dorsum.

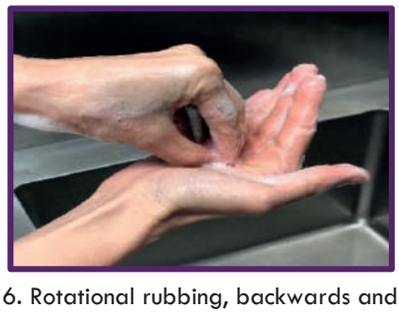
3. Palm to palm fingers interlaced.



4. Back of fingers to opposing palms with fingers interlocked.



5. Rotational rubbing of right thumb clasped in left palm and vice versa.



6. Rotational rubbing, backwards and forwards with clasped fingers of right hand in left palm and vice versa.

7. Rotational rubbing of right wrist and vice versa. Rinse and dry thoroughly.

Appendix 3

GLOVING TECHNIQUES

1. Pick up the first glove with thumb and index finger of one hand. Slip the opposite hand into the glove. Do not touch external surfaces of sterile gloves with bare fingers/hands.

2. Fit all fingers and thumb into the glove and pull it down.

3. Slip gloved fingers underneath the folded cuff of the second glove to pick it up.

4. Fit the opposite hand into the second glove, unfold its cuff & pull it up to the wrist.

5. Slip gloved fingers of the opposite hand underneath the folded cuff of the first glove, unfold and pull it up to the wrist.

6. Gloving procedure completed.

Appendix 4

ASEPTIC GOWNING PROCEDURES

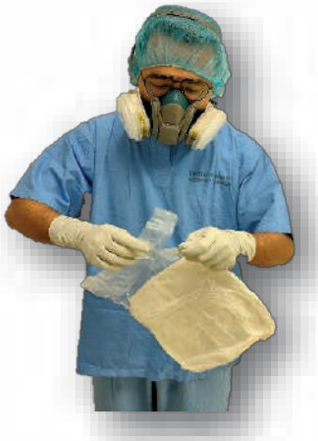
1

Don shoe cover, head cover (bouffant cap) and respirator before hand washing.

2

Don first pair of sterile gloves.

3



Open the pack and take the sterile jumpsuit out by grabbing the inside of its neck. Let it unfold without touching the floor. Unzip and hold the jumpsuit at the waist from the inside (if it is ready folded by manufacturer) or roll top of the jumpsuit with sleeves inside the roll to the waist.

4

Insert one foot into the jumpsuit leg and pull it up to the thigh. Repeat with the other foot.

5

Unfold/ unroll the top part of the jumpsuit and insert one arm into the sleeve. Bring the jumpsuit over shoulder and back to fit in the other arm.

6

Put on the hood by touching only the inside of the hood.

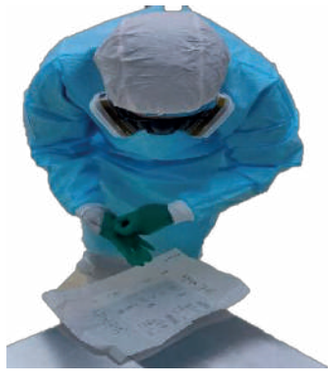
7

Cross legs, straighten back and zip up jumpsuit.

8

Don boot covers and then chemo gown by touching only the inside of the apparels. Put on goggle lastly (if required).

9



Don second pair of sterile gloves.

10

Inspect and ensure all PPE are properly donned.

Basics of donning and doffing of PPE for sterile hazardous drug compounding:

1. Avoid touching the external surfaces of apparels and gloves throughout donning and doffing
2. Do not let sterile PPE come into contact with the floor (except soles of footwear) or other surrounding surfaces
3. All used PPE are considered contaminated

* Procedures may vary by facility or site protocols

Disclaimer:

This poster is created by CDR Unit of Hospital Wanita dan Kanak-Kanak Sabah to be used as a general guide.

Appendix 5

DE-GOWNING PROCEDURES

1



Remove the *outer layer of chemo glove* by grasping the outside of the glove with the opposite gloved hand and pull it off inside out. Slide index finger underneath the cuff of the glove on the opposite hand and roll the glove down, turning it inside out to avoid touching its external surface.

2



Remove *chemo gown*. Begin by pulling the gown at the hips to dislodge the fastener holding the neck closed. Slowly begin removing the gown inside out while holding it away from your body and folding it in on itself.

3

Remove *goggle*.

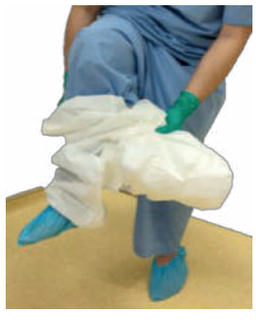
4

Remove *boot covers* without letting the upper parts touch the floor.

5





Remove the *jumpsuit*. Unzip the jumpsuit until the waist. Pull hood away from head. Touching the inside of the jumpsuit only, pull one sleeve down and off the shoulder of one arm and extract the arm. Extract the other arm from within the jumpsuit. Turn the jumpsuit inside out, fold it while rolling it down the body to the feet. Then take it off from the ankles and feet. Do not touch the external surface of the jumpsuit. Do not let the jumpsuit comes into contact with surrounding surfaces (e.g. floor, crossover bench and etc.).

6


Remove *respirator*, *head cover (bouffant cap)* and *shoes covers*.

7

Remove the *inner chemo gloves* by grasping the outside of the first glove with the opposite gloved hand, pull it off inside out and hold it in the palm of the opposite gloved hand. Slide index finger underneath the second glove and pull the second glove off inside out (keeping the first glove wrapped in the second glove).

8

Wash hand with soap and water.

Basics of donning and doffing of PPE for sterile hazardous drug compounding:
1. Avoid touching the external surfaces of apparels and gloves throughout donning and doffing.
2. Do not let sterile PPE come into contact with the floor (except soles of footwear) or other surrounding surfaces.
3. All used PPE are considered contaminated.

* Procedures may vary by facility or site protocols.

Disclaimer:
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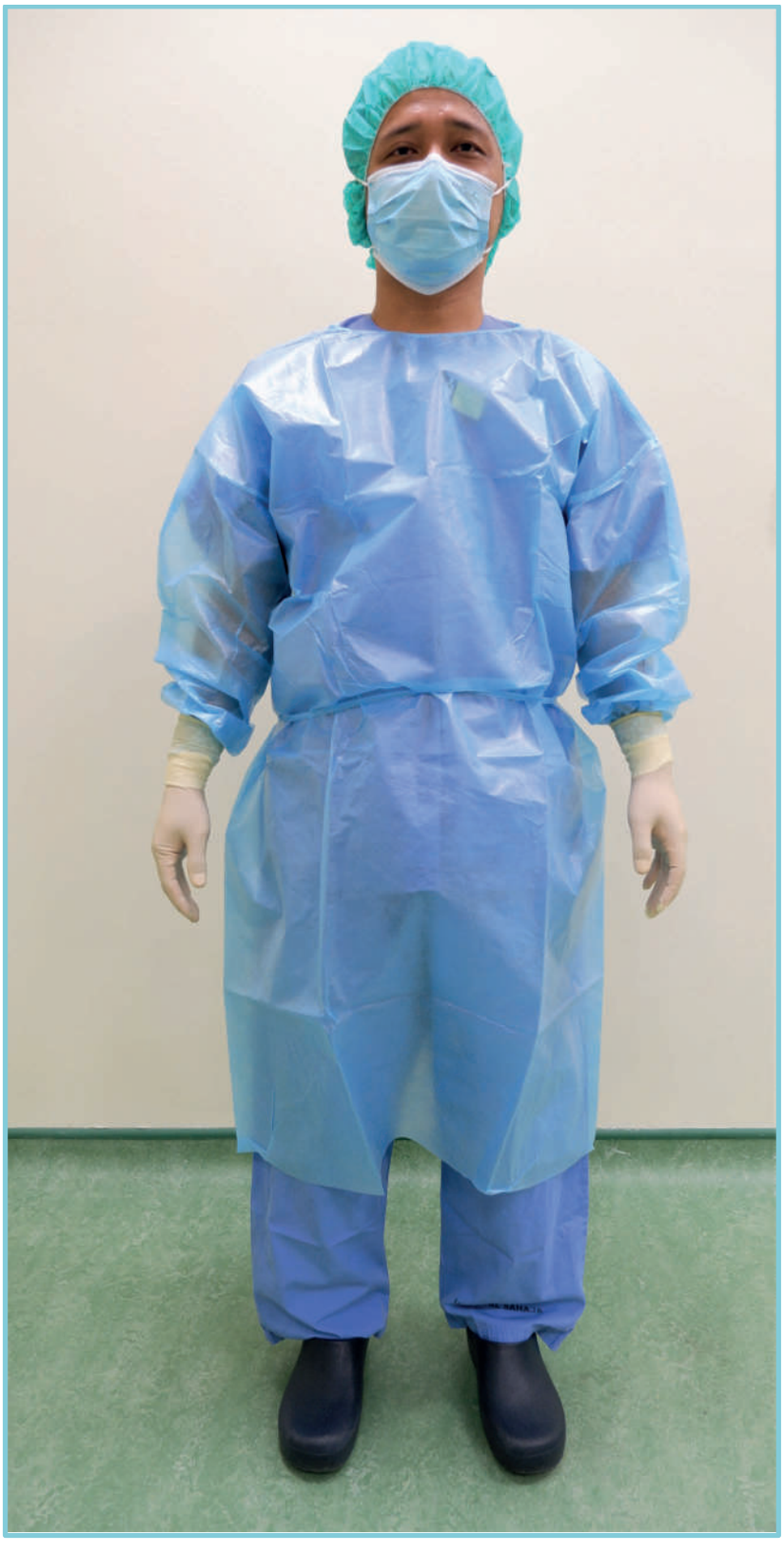
Appendix 6

PERSONNEL PROTECTIVE EQUIPMENT IN GRADE A OR B CLEAN ROOM

Appendix 7

PERSONNEL PROTECTIVE EQUIPMENT IN GRADE C OR D CLEAN ROOM



Appendix 8

MEDICAL EXAMINATION REPORT

PERSONNEL DETAILS	
Name:	**IC no:**
Gender: **Age:**	**Height:** **Weight:**
Designation:	**Date of Entry into Sterile Production Service:**
Purpose of Medical Examination (please circle)	**Entry into Service/ Routine Monitoring/ Exit Service**

HEALTH CONDITION	
Past Medical History	**Social History**
	Social / **Yes** / **No** / **Remark** (if any) **Smoking** **Alcohol Intake** **Pregnant**
Current Medical Condition	**Family History of Malignancy**
	Malignancy / **Yes** / **No** / **Remark** (if any) ➢ **1st Degree** ➢ **2nd Degree**
Allergy (including latex allergy and others)	

INFECTIOUS DISEASE AND HEALTH SCREENING			
Infectious Disease Screening			
Type	**Results** (please circle)		**Remark** (if any)
HIV	Positive	Negative	
Hepatitis B	Positive	Negative	
Tuberculosis	Positive	Negative	
Laboratory Investigations			
Type	**Results** (please circle)		**Remark** (if any)
Full Blood Count (with Differential Count)	Normal	Out of range	
Renal Profile	Normal	Out of range	
Liver Profile	Normal	Out of range	
Others (if any eg. tumour marker)	Normal	Out of range	

Physical Exam	
Type	**Findings**
Visual Examination	
Skin-related problems	
Neurological problems (eg. hand tremors)	
Others (eg. joint-related problem affecting dexterity & etc)	

Recommendation (please choose one)**:**

- ○ I hereby certify that I have examined the above named person & that he is **fit / unfit for work** involving preparation of sterile pharmaceutical products (hazardous & non-hazardous substances).

- ○ I hereby certify that I have examined the above named person & that he **has / doesn't have** apparent **adverse health effects** from his previous involvement in handling of hazardous substances upon **exit of service**.

Further Comments/Recommendations (if any)**:**

*Please attach laboratory reports with this Medical Examination Report

REPORT APPROVED BY PHYSICIAN/MEDICAL OFFICER
Physician/Medical Officer Name : Registration No. : Signature : Official Stamp :   Date :

Appendix 9

PERSONNEL EXIT REVIEW

PERSONNEL DETAILS			
Name		**Date of Entry**	
Identity Card Number		**Date of Exit**	
Designation		**Duration of Service**	
Job Description(s): (please tick) ○ Cytotoxic drugs preparation ○ Non-cytotoxic drugs preparation ○ Radiopharmaceuticals preparation ○ Other hazardous substances related activities If other, please state:		**Reason(s) for Exit:**	

PERSONNEL HEALTH/MEDICAL CONDITION (Please attach Medical Examination & Laboratory Investigations Reports with this review)	
Date of Health/Medical Examination	
Results of Medical Examination upon Exit: 1) Is there any hazardous drugs exposure-related health effects being reported? (please tick) o No o Yes Please describe actions to be taken: 2) Other comm**ents:** (if any)	

REVIEWED BY PHARMACIST IN-CHARGE	VERIFIED BY HEAD OF DEPARTMENT
Name : Signature : Official Stamp : Date :	Name : Signature : Official Stamp : Date :

Appendix 10

CLEANING LOG

Day & date : / *Location :*	M	T	W	T	F		M	T	W	T	F		M	T	W	T	F		M	T	W	T	F		M	T	W	T	F	Cleaning Agent
Daily *(i) LAFC/BSC* *(ii) Bench & Chair* *(iii) Pass Box* *(iv) Door knob*																														Alcohol 70% (sterile) Batch No.: Expiry Date:
(v) Floor																														Disinfectant Batch No.: Expiry Date:
(b) Wall (Weekly)	*Cleaner:* *Checked by:*						*Cleaner:* *Checked by:*						*Cleaner:* *Checked by:*						*Cleaner:* *Checked by:*						*Cleaner:* *Checked by:*					
(c) Ceiling (Monthly)	*Cleaner:* *Checked by:*																													
Daily *(i) LAFC/BSC* *(ii) Bench & Chair* *(iii) Pass Box* *(iv) Door knob*																														Alcohol 70% (sterile) Batch No.: Expiry Date:
(v) Floor																														Disinfectant Batch No.: Expiry Date:
(b) Wall (Weekly)	*Cleaner:* *Checked by:*						*Cleaner:* *Checked by:*						*Cleaner:* *Checked by:*						*Cleaner:* *Checked by:*						*Cleaner:* *Checked by:*					
(c) Ceiling (Monthly)	*Cleaner:* *Checked by:*																													

Appendix 11

CLEAN ROOM TEMPERATURE, HUMIDITY AND PRESSURE DIFFERENTIAL RECORD

Parameter / Date	Temperature (20 ± 2°C)	RH (55 ± 5%)	Compounding Room to -ve Airlock / Gowning Room (10 - 15 Pa)	Change Room to Outside (10 - 15 Pa)	Component room to Change room (10 - 15 Pa)	Gowning to Change Room (10 - 15 Pa)	Monitored by	Approved by

Appendix 12

LIMITS FOR CLEAN ROOM CONTROL PARAMETERS

a) Particle Count Limit

Grade	At Rest		In Operation	
	Maximum permitted number of particles/m3 equal to or above			
	> 0.5µm	> 5µm	> 0.5µm	> 5µm
A	3 520	20	3 520	<5
B	3 520	20	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not Defined	Not Defined

b) Microbial Limit

Grade	Recommended limits for microbial contamination			
	Air sample (Active air sampling)	Settle plates (Passive air sampling) (diam. 90 mm)	Contact plates (diam. 55 mm)	Glove print (5 fingers)
	cfu/m^3	cfu/4 hours	cfu/plate)	cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

c) Temperature, Humidity and Air Pressure Differential Limit:

- *Non-CDR [Parenteral Nutrition (PN), IV Admixture, Ophthalmic & other sterile preparation]*

Room	Temperature (°C)	RH (%)	Adjacent Room	Differential Pressure (Pa)
Compounding	20 ± 2	55 ± 5	Gowning	+ (10 – 15)
Component	20 ± 2	55 ± 5	Changing	+ (10 – 15)
Gowning	20 ± 2	55 ± 5	Changing	+ (10 – 15)
Changing	20 ± 2	55 ± 5	Outside	+ (10 – 15)

- *CDR :*

Room	Temperature (°C)	RH (%)	Adjacent Room	Differential Pressure (Pa)
Compouding	20 ± 2	55 ± 5	Airlock (negative)	+ (10 – 15)
-ve Airlock	20 ± 2	55 ± 5	Gowning	- (10 – 15)
Component	20 ± 2	55 ± 5	Changing	+ (10 – 15)
Gowning	20 ± 2	55 ± 5	Changing	+ (10 – 15)
Changing	20 ± 2	55 ± 5	Outside	+ (10 – 15)

** For room designs without –ve Airlock: Compounding Room pressure must be in *NEGATIVE 10 – 15 Pascal to the adjacent room.*

Appendix 13

PRODUCT RECALL / RETURN FORM

CYTOTOXIC DRUG PREPARATION(S) RECALL / RETURN FORM

(To be completed and returned to CDR Unit on the day of recall/return)

No	Content of Preparation(s)	Batch Number	Preparation Date	Expiry Date	Remarks (if any) *Duration without refrigeration for fridge items

Reason for Recall / Return	Please Tick [√]
Wrong Drug / Dose / Diluent / Volume / Infusion Rate	
Particles / Precipitation / Discoloration observed	
Patient withhold chemo / change chemo regimen	
Others (please state):	
Further details on recall/return (please describe) -	

Signature	
Name	
Designation	
Ward/Unit/Department	
Date	

For Pharmacy Use	
Date returned:	Received by:
Comment(s): Action taken: ☐ Reused Patient Name : _____ Date : _____	☐ Discard Date:_____

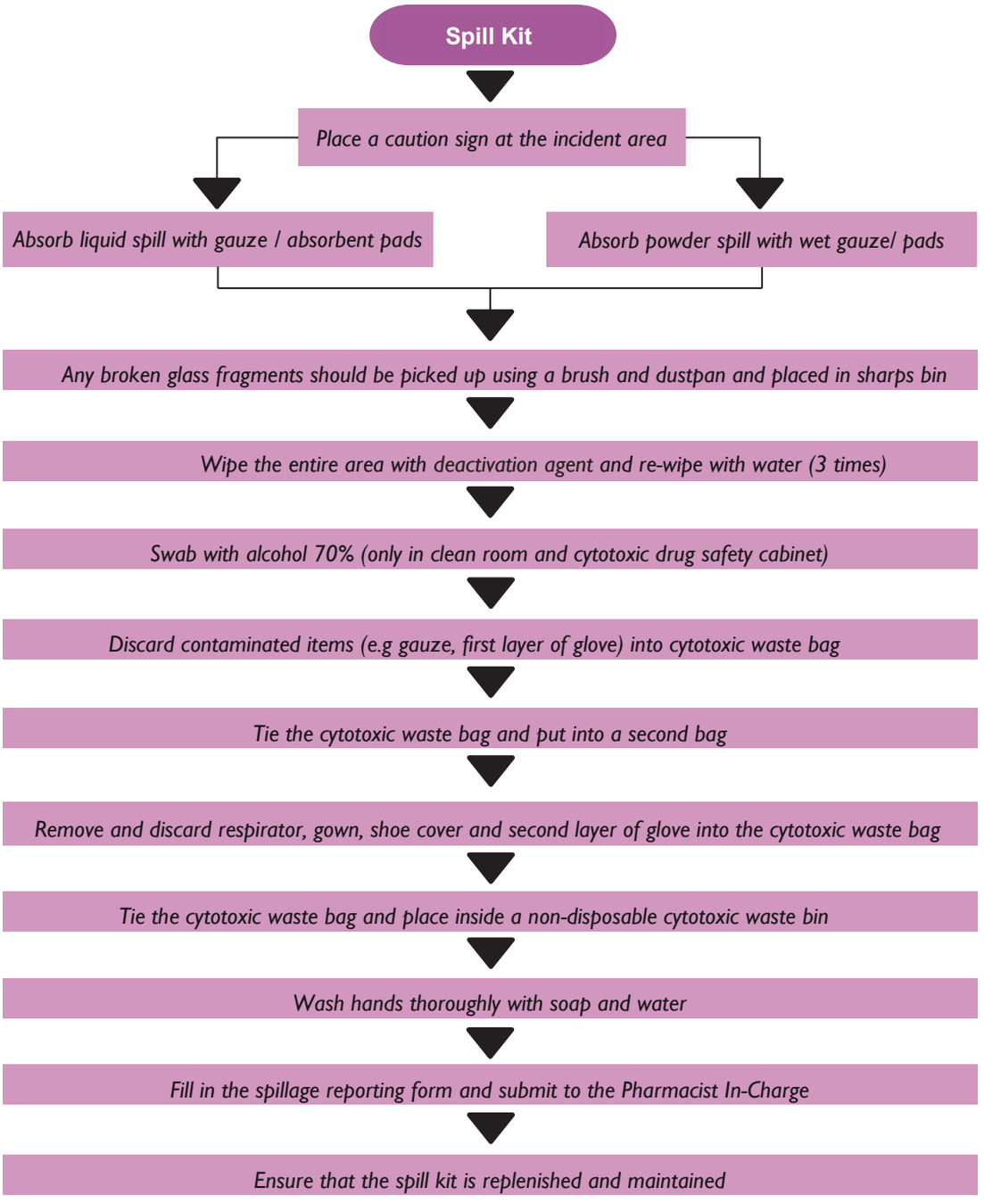
Appendix 14

CONTENT OF SPILL KIT

No.	Content of Spill Kit	Quantity
1.	*Disposable Gown*	*1 piece*
2.	*Surgical Glove*	*1 pair*
3.	*Chemo Glove*	*1 pair*
4.	*Shoe Cover*	*1 pair*
5.	*Head Cover*	*1 piece*
6.	*Respirator Mask N95*	*1 piece*
7.	*Sharps Container*	*1 bin*
8.	*Brush and Dustpan*	*1 set*
9.	*Cytotoxic Waste Bag*	*2 piece*
10.	*Gauze and Absorbent Pads*	*10 pieces each*
11.	*Deactivation Agent*	*120ml*
12.	*Water*	*500ml*
13.	*Spill Handling Procedure*	*1*
14.	*Spill Reporting Form*	*1*
15.	*Caution Sign*	*1 piece*

Appendix 15

FLOW CHART ON THE MANAGEMENT OF CYTOTOXIC SPILL



Appendix 16

SPILLAGE REPORTING FORM

Return to Pharmacy on day of incident

Drug involved	*Ward/Clinic/area*
What form was drug supplied in?	
• *liquid - vial/ ampoule* • *dry powder - vial/ ampoule* • *syringe* • *plastic bag*	• *vol/amp of drug supplied .....* • *vol/amp of drug supplied .....* • *vol/amp of drug supplied .....* • *vol/amp of drug supplied .....
Date:	*Time of incident:*
Cause of spill	Location of incident
• *Container supplied leaking* • *Container dropped* • *Container faulty* • *Container pierced* • *IV line disconnected* • *Pump problem* • *Others (describe)*	• *Patient area* • *Corridor* • *Nursing staff/area* • *Pharmacy area* • *Others .....*

Description of incident - what happened ? To whom ? Any precipitating cause ?

Name of witness: _____

Pharmacist notified at ext.: _____

Spill kit returned to the pharmacy: _____

Signature of person completing report: _____

Name (in block letters): _____

Date of kit returned:
Comment on incident:

Checked by (signature):
Date:

Appendix 17

EXAMPLE OF WORK CONTRACTED OUT AGREEMENT FOR CYTOTOXIC DRUG RECONSTITUTION SERVICE

Panduan Kriteria Perjanjian/ Kontrak Perkhidmatan Rekonstitusi Ubat Sitotoksik antara Jabatan Farmasi/ Unit CDR, Hospital A dengan Jabatan Farmasi/ Unit CDR, Hospital B

i. Panduan ini adalah sebagai cadangan bagi perkara-perkara yang perlu diteliti dan dipersetujui antara kedua-dua hospital yang terlibat dalam aktiviti *outsourcing* perkhidmatan rekonstitusi ubat sitotoksik.

ii. Perjanjian/ kontrak ini menjelaskan tanggungjawab dan peranan kedua-dua pihak yang terlibat agar perkhidmatan ini berjalan dengan lancar tanpa sebarang permasalahan. Sebarang maklumat/ kandungan adalah tertakluk kepada pindaan dari masa ke semasa.

   a) Hospital Yang Merujuk: HOSPITAL B
   b) Hospital Yang Dirujuk: HOSPITAL A

1. TANGGUNG JAWAB HOSPITAL YANG MERUJUK

1.1 Hospital Yang Dirujuk melakukan rekonstitusi untuk Hospital Yang Merujuk

1.1.1 Saring semua borang permohonan rekonstitusi ubat sitotoksik (*Request Form*) untuk memastikan semua permohonan adalah betul.

1.1.2 Sediakan senarai lengkap jumlah pesakit dan sediaan ubat sitotoksik yang perlu direkonstitusi (contoh: *Despatch Form*).

1.1.3 Hantar *Despatch Form* berserta *Request Form* melalui e-mel/faks ke unit CDR, Hospital A (A@moh.gov.my) sebelum jam 10.00 pagi. Unit CDR, Hospital A tidak akan memproses permohonan yang tidak lengkap dan permohonan yang diterima selepas jam 10.00 pagi.

1.1.4 Hubungi unit CDR, Hospital A dengan segera sekiranya terdapat perubahan pada permohonan yang dihantar, contohnya pertukaran dos, pembatalan dan sebagainya. Segala intervensi perlu direkod secara bertulis.

1.1.5 Uruskan pengangkutan untuk kutipan sediaan ubat sitotoksik yang telah siap direkonstitusi di Unit CDR, Hospital A selepas jam 10.00 pagi.

1.1.6 Sediaan ubat sitotoksik hanya boleh diambil oleh anggota yang terlatih dalam pengendalian ubat sitotoksik sahaja.

1.1.7 Periksa sediaan ubat sitotoksik yang diambil dan pastikan sediaan tersebut adalah betul.

1.1.8 Prosedur dan aliran kerja untuk pengambilan sediaan ubat sitotosik perlu mematuhi Manual For Sterile Preparations, KKM dan Garis Panduan Pengendalian Semasa Pengangkutan Sediaan Steril.

1.1.9 Bagi sediaaan yang perlu dilupuskan atas sebab-sebab tertentu, borang "Pemulangan Ubat Kemoterapi" perlu diisi dan dihantar ke Hospital A.

1.1.10 Perolehan dan pengendalian ubat/ bahan bukan ubat bagi aktiviti rekonstitusi ubat

sitotoksik ini adalah menjadi tanggungjawab hospital yang merujuk/ dirujuk (bergantung kepada persetujuan antara dua hospital).

1.1.11 Rekonstitusi perlu dilakukan oleh hospital yang merujuk bagi:
- i) Ubat yang tidak termasuk dalam senarai *Hazardous Drugs*
- ii) kes-kes kecemasan selepas waktu bekerja biasa
- iii) permintaan baru pada hujung minggu dan cuti umum
- iv) lain-lain; perlu disenaraikan.

1.1.12 Menggunakan sistem PHIS sekiranya modul CDR dapat digunakan.

1.2 Hospital Merujuk melakukan rekonstitusi di Hospital Yang Dirujuk

1.2.1 Hospital Yang Dirujuk bertanggungjawab menyediakan fasiliti bilik bersih Cytotoxic Drug Reconstitution (CDR) bagi penyediaan atau rekonstitusi ubat sitotoksik.

1.2.2 Hospital Yang Merujuk bertanggungjawab untuk melakukan rekonstitusi sediaan sitotoksik pada hari dan masa yang telah dipersetujui sahaja.

1.2.3 Anggota yang terlibat bagi penyediaan atau rekonstitusi ubat sitotoksik ini adalah anggota terlatih dalam pengendalian ubat sitotoksik dari Hospital Yang Merujuk.

1.2.4 Anggota Hospital Yang Merujuk perlu memastikan kebersihan bilik bersih CDR Hospital Yang Dirujuk selepas aktiviti rekonstitusi ubat sitotoksik selesai.

1.2.5 Sekiranya berlaku kontigensi yang menyebabkan fasiliti bilik bersih CDR Hospital Yang Dirujuk tidak dapat digunakan untuk rekonstitusi ubat sitotoksik, adalah menjadi tanggungjawab anggota dari Hospital Yang Merujuk untuk melaksanakan rekonstitusi ubat sitotoksik di hospital lain.

1.2.6 Hospital Yang Merujuk bertanggungjawab bagi menguruskan aktiviti pengambilan dan pengangkutan sediaan ubat sitotoksik.

1.2.7 Prosedur dan aliran kerja untuk pengambilan sediaan ubat sitotosik perlu mematuhi Manual For Sterile Preparations, KKM dan Garis Panduan Pengendalian Semasa Pengangkutan Sediaan Steril.

1.2.8 Pelupusan sisa sitotoksik hasil rekonstitusi adalah tanggungjawab Hospital Yang Merujuk/Dirujuk (bergantung kepada persetujuan antara dua hospital).

1.2.9 Perolehan dan pengendalian ubat/ bukan ubat adalah tanggungjawab Hospital Yang Merujuk/Dirujuk (bergantung kepada persetujuan antara dua hospital).

1.2.10 Semua anggota yang melakukan rekonstitusi sediaan ubat sitotoksik perlu mematuhi garispanduan Good Preparation Practice (GPP) PIC/S dan Manual For Sterile Preparations, KKM.

1.2.11 Persediaan sitotoksik perlu mematuhi Standard Operating Procedure (SOP) Hospital Yang Dirujuk.

1.2.12 Anggota yang dihantar dari Hospital yang Merujuk perlu terlatih dan lulus ujian validasi teknik aseptik.

1.2.13 Satu salinan rekod latihan/laporan validasi teknik aseptik perlu diserahkan kepada Hospital Yang Dirujuk untuk tujuan audit.

2. TANGGUNG JAWAB HOSPITAL YANG DIRUJUK

2.1 Hospital Yang Dirujuk melakukan rekonstitusi untuk Hospital Yang Merujuk

2.1.1 Rekonstitusi ubat sitotoksik sepertimana yang terkandung dalam *Despatch Form* pada waktu pejabat.
2.1.2 Pastikan sediaan dilabel dan dipek dengan betul.
2.1.3 Pastikan kualiti semua sediaan sitotoksik yang dibekal adalah terjamin.
2.1.4 Beri maklumbalas berkaitan proses rekonstitusi dan produk akhir apabila diminta.
2.1.5 Pantau dan elakkan pembaziran ubat dan barangan pakai buang.
2.1.6 Sediaan sitotoksik didispens oleh Pegawai Farmasi atau Penolong Pegawai Farmasi.
2.1.7 Hubungi Hospital yang merujuk jika ada sebarang pertanyaan.
2.1.8 Untuk perekodan dalam PF6.4, Hospital Yang Dirujuk perlu merekod bilangan persediaan yang dibuat untuk kegunaan Hospital Yang Merujuk.

2.2 Hospital Merujuk melakukan rekonstitusi di Hospital Yang Dirujuk

2.2.1 Untuk perekodan dalam PF6.4, Hospital Yang Merujuk perlu merekod bilangan persediaan yang dibuat di Hospital Yang Dirujuk.
2.2.2 Pelupusan sisa sitotoksik hasil rekonstitusi adalah tanggungjawab Hospital Yang Merujuk/Dirujuk (bergantung kepada persetujuan antara dua hospital).
2.2.3 Perolehan dan pengendalian ubat/bukan ubat adalah tanggungjawab Hospital Yang Merujuk/Dirujuk (bergantung kepada persetujuan antara dua hospital).
2.2.4 Semua anggota yang melakukan rekonstitusi sediaan ubat sitotoksik perlu mematuhi garispanduan Good Preparation Practice (GPP) PIC/S dan Manual For Sterile Preparations, KKM.
2.2.5 Persediaan sitotoksik perlu mematuhi Standard Operating Procedure (SOP) Hospital Yang Dirujuk.
2.2.6 Satu salinan rekod latihan/laporan validasi teknik aseptik perlu diserahkan kepada Hospital Yang Dirujuk untuk tujuan audit.

"BERKHIDMAT UNTUK NEGARA"

_____
Nama:
Jawatan:
Jabatan/Hospital Merujuk:
Tarikh:

Pihak kami bersetuju dengan terma-terma yang telah ditetapkan oleh pihak tuan/ puan.

_____
Nama:
Jawatan:
Jabatan/Hospital Dirujuk:
Tarikh:

Appendix 18

CLASSIFICATION OF DISINFECTANTS

CHEMICAL GROUP	CLASSIFICATION	EXAMPLE
Aldehydes	Sporicidal agent	2% Glutaraldehyde
Alcohols	Disinfectant	Alcohol 70% Isopropyl Alcohol 70%
Chlorine and sodium hypochlorite	Sporicidal agent	0.5% Sodium Hypochlorite
Phenolics	Disinfectant	500 µg per g Chlorocresol, 500 µg per g Chloroxylenol
Hydrogen Peroxide	Sporicidal agent	10% – 25% solution
Peracetic Acid	Liquid sterilant	0.2% Peracetic Acid
Quaternary Ammonium Compounds	Disinfectant	Concentration depends on application, Benzalkonium Chloride
β-Propiolactone	Sporicidal agent	100 µg per g β-Propiolactone

Notes:

1) Refer Material Safety Data Sheet (MSDS) or product information sheet for surface compatibility.

2) Above list is non-exhaustive, kindly refer to USP Compounding Compendium Chapter <1072> for further information.[20]

GLOSSARY

Aseptic processing or preparation A process whereby separate sterile components are mixed together under conditions that maintain their sterility.

Aseptic technique Aseptic technique refers to carrying out a procedure under controlled conditions in a manner that will minimise the chance of contamination.

As low as reasonably achievable (ALARA) The effort to maintain exposures to ionizing radiation as below the dose limits as practical.

Chemical purity The fraction of the total chemical species present in the radiopharmaceutical as the specified chemical component(s). A chemical impurity is the presence of an unwanted non-radioactive chemical.

Classified area/ room An area/ room that maintains an air quality classification based on the ISO guidelines (i.e., ante-room, buffer area).

Clean Room A room in which the number and concentration of viable and non-viable airborne particles are controlled. The room is constructed and used in a manner to minimise the introduction, generation and retention of particles inside the room and to control other relevant parameters (e.g., temperature, humidity) as necessary.

Contamination The undesired introduction of impurities of chemical, microbial, or radioactive in nature; or of foreign matter, into or onto starting material or intermediate, during production, sampling, packaging or repackaging, storage, or transport.

Counterchecking To check a second time for verification.

Designated Person One or more individuals assigned to be responsible and accountable for the performance and operation of the aseptic processing facility and for personnel who prepare, compound, dispense, and repackage sterile preparations.

Disinfectant A chemical/ physical agent used on inanimate surfaces and objects to destroy microbiological contamination when used in the appropriate concentrations and for the appropriate contact times.

GMP Grade The air-cleanliness levels in the "at rest" occupancy state for the manufacture of sterile medicinal products from the Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-Operation Scheme.

Hard to reach areas Critical areas that are unreachable by mop and potentially overlooked, i.e., door closer, outer pass box surfaces, outer cabinet surfaces etc.

High Efficiency Particulate Air (HEPA) filter A tested, and certified air filter designed to remove 99.97% of airborne particles of 0.3-micron or greater in diameter from the air passing through it.

Hot cell A shielded workstation for manufacture and handling of radioactive materials. Hot cells are not necessarily designed as an isolator. A hot cell may also be referred to by other designations (e.g., shielded isolator with laminar flow, PET dispensing station, manipulator hot-cell, shielded isolators for dispensing, radiopharmaceutical dispensing isolator).

In-use expiry date The end of the application period, in which a medicinal product may be taken or applied after the package has been opened, respectively after a first dose of the medicinal product has been taken from the package.

ISO class A quality classification from the International Organization for Standardization based on quantity and size of particles per volume of air.

Isolator A containment device that utilizes barrier technology for the enclosure of a controlled workspace.

Kit Conventionally manufactured package containing all ingredients required to prepare a radiopharmaceutical with the exception of the radionuclide.

Laminar Air Flow Laminar airflow or unidirectional airflow is a rectified airflow over the entire cross-sectional of a clean area with a steady velocity and approximately parallel streamlines (modern standards no longer refer to laminar airflow but have adopted the term unidirectional airflow).

Media-fills A simulation used to qualify processes and personnel engaged in sterile radiopharmaceutical processing to ensure that the processes and personnel can prepare radiopharmaceuticals without microbiological contamination.

Personal Protective Equipment (PPE) Equipment include sterile jumpsuit, sterile hood, sterile booties, sterile chemo gown, head cover, shoe cover, face mask, respirator and sterile gloves.

Pharmacist In-Charge The pharmacist responsible for all aspects of the services within an aseptic preparation unit, has the necessary basic scientific and technical background and experience. The duties include the approval of all system of work and documentation used in the unit.

Preparation The act of mixing, reconstituting, combining, diluting, or repackaging a conventionally manufactured product following manufacturer's recommended instructions or in accordance with directions contained in the FDA-approved labelling.

Primary engineering control (PEC) A device or zone that provides an ISO Class 5 air quality environment for sterile processing.

Production Part of preparation. It involves all processes and operations in the preparations of a product from receipt of materials, through processing and packaging, to its completion as a finished product.

Qualified clean room Clean room facility that has been inspected and qualified by auditors from the Pharmacy Practice & Development Division, Ministry of Health Malaysia after complying with required standard.

Quality assurance (QA) The system of procedures, activities, and oversight that ensures that aseptic processing consistently meets quality standards.

Quality control (QC) The sampling, testing, and documentation of results, which ensure that specifications have been met before release of the product.

Radiochemical purity The ratio, expressed as a percentage, of the radioactivity of the intended active radiopharmaceutical ingredient to the total radioactivity of all radioactive ingredients and impurities present in the radiopharmaceutical preparation.

Radionuclidic purity The ratio, expressed as a percentage, of the radioactivity of the intended radionuclide to the total radioactivity of all radionuclides in the radiopharmaceutical preparation.

Radiopharmaceutical/ radiopharmaceutical preparation/ radioactive drug A finished dosage form that consist of a radioactive substance and other ingredient(s), which is intended to diagnose, stage, monitor, or provide therapy.

Shielding: Barriers of appropriate radiation attenuating material, used for radiopharmaceuticals, to protect the personnel.

Sporicidal agent: An agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Sterilant: An agent that destroys all forms of microbial life including fungi, viruses, and all forms of bacteria and their spores. Sterilants are liquid or vapor-phase agents.

Sterility: The absence of viable microorganisms.

Thorough cleaning: Cleaning in thorough manner, including ceilings, walls, floors and all equipment in the clean room that equates to monthly cleaning, after any event that jeopardizes the cleanliness of the clean room.

Unclassified area/space: A space not required to meet any GMP grade or ISO class air cleanliness classification.

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