MANUAL FOR
STERILE PREPARATIONS

PHARMACEUTICAL SERVICES DIVISION
MINISTRY OF HEALTH, MALAYSIA
First Edition | August 2010

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Published by

PHARMACEUTICAL SERVICES DIVISION
Ministry of Health Malaysia
Lot 36, Jalan Universiti
46350 Petaling Jaya, Selangor, Malaysia
Tel: 603-7841 3200   Fax: 603-7968 2222
Website: www.pharmacy.gov.my

Printed by

UNIVISION PRESS SDN BHD (473080-W)
Lot 46, 47 & 48, Jalan Serdang Raya, 43300 Seri Kembangan, Selangor
Foreword

The importance of ensuring the quality, safety and efficacy of sterile pharmaceutical preparations such as reconstituted cytotoxic drugs, parenteral nutrition solutions, intravenous admixtures and eye drops can never be overstated. The Pharmaceutical Services Division, Ministry of Health Malaysia has established the ‘Manual for Sterile Preparations’ to provide guidance on Good Practices in the preparation of such products for human use.

The contents of this manual comprehensively cover key aspects including quality assurance, personnel, premises and equipment, production and quality control as well as documentation and self audits to ensure quality, safety and efficacy of sterile pharmaceutical preparations. It also addresses the important aspect of safety to ensure protection for the personnel and environment.

In accordance with current international standards and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide for Good Preparation Practice (GPP), Malaysia as a member of PIC/S is committed towards implementing such guidelines, both in private and public healthcare settings. In line with this, the manual is intended to promote awareness amongst healthcare practitioners of the requirements in sterile preparation.

It is my sincere hope that this manual will serve as a useful reference to all relevant parties. Last but not least, I would like to congratulate and commend everyone involved for the tremendous support and invaluable contributions towards making the publication of this manual a reality.

Thank you.

EISAH BINTI A. RAHMAN
Senior Director of Pharmaceutical Services
Ministry of Health Malaysia
Preface

First of all, I would like to thank the working committee for their tireless efforts in developing the first edition of the ‘Manual for Sterile Preparations’. Due to the rapidly expanding sterile pharmaceutical preparation services nationwide, it is very timely and essential that the Pharmaceutical Services Division, Ministry of Health develops and publishes this manual.

The recommendations in this manual have been made by taking into consideration existing policies pertaining to the preparation of sterile products, requirements for working environment and personnel safety in accordance with the current international standards such as the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide for Good Preparation Practice (GPP). Therefore, it will ensure standardization, accuracy and effectiveness as well as consistency in performance.

I believe that the contents of this manual will be able to serve as a standard reference for all hospital pharmacists in handling and managing sterile preparation activities. I am confident that this manual will also provide useful information on ensuring quality, safety and efficacy of products. Updates on new topics, activities and procedures will be introduced in future editions in accordance with international practices.

Finally, I would like to congratulate all those who were involved directly or indirectly during the preparation of this manual.

Thank you

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# Table of Contents

**MANUAL FOR STERILE PREPARATIONS**

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Quality Assurance System</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>Documentation</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>Standard Operating Procedures</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>- Cytotoxic Drug Reconstitution</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>- Parenteral Nutrition</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>Work Contracted Out</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>Complaints &amp; Product Recalls</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>Self Audits</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>Safety</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Appendices</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>Glossary</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>103</td>
</tr>
</tbody>
</table>
Introduction

1. Preparation of sterile pharmaceutical products in hospital includes
   - The aseptic preparation of products
   - The preparation of terminally sterilized products

2. Sterile preparations are considered to be high risk category products due to:
   - The increased risk and higher level of microbiological contamination for products prepared in uncontrolled environments
   - The increased risk of systemic infections associated with products prepared in uncontrolled environments

3. Preparation should take place in well controlled environment using well established quality assurance-driven procedures. This considerably reduces the risks associated with these products

4. This operation manual is applicable to all products prepared aseptically for administration to patients, which includes Cytotoxic Drug Reconstitution (CDR), Parenteral Nutrition (PN), Intravenous Admixture and Eye Preparation

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. These procedures apply to all activities involved in preparing sterile products such as aseptic technique, documentation, quality control, cleaning, maintenance and transportation

Objectives

This operating procedure manual aims to:

1. Provide a basic understanding of the requirements in sterile preparation in line with PIC/S Good Preparation Practice (GPP)

2. Provide a general overview of the operations involved in preparing sterile products

3. Provide current understanding of standard procedures in maintaining the clean room and equipments

4. Address the importance of aseptic technique during preparation of the sterile products in order to eliminate or prevent the risk of contamination
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. This system shall be well documented with its effectiveness monitored, and it must be up-to-date according to the latest knowledge or techniques.

1.2 QUALITY ASSURANCE
Quality assurance ensures that:

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

b. Production and control operations are clearly specified and implemented according to the principles of Good Preparation Practice

c. The sterile preparations 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. Responsible Person or Releasing Officer)

d. Adequate measures are in place to ensure that sterile preparations are released, stored and handled in such a way that the required quality can be assured throughout their shelf-life and the in-use expiry date

e. Documentation systems are in place and maintained

1.3 DEVIATION FROM SPECIFICATION

a. Deviations can occur from time to time. It can occur during handling of starting and packaging materials and end products, and during maintenance and cleaning of premises and equipments

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

   i. Identification
      - Clearly define the problem

   ii. Investigation
      - Shall include objective, strategy and responsibility

   iii. Analysis
      - Every possible cause is identified and the data collected
      - Data is assessed and prioritized to identify the root cause
iv. Action Plan
- Create a list of required task, which includes corrective action and preventive action
- Corrective action refers to any action to remove the deviation
- 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 take
CHAPTER 2

DOCUMENTATION

1.1 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 a sterile preparation.

2.2 GENERAL REQUIREMENTS

a. All specifications, instructions and procedures shall be approved, signed and dated by the Responsible Person or by a person appointed by the Responsible Person.

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

c. The totality of these documents shall ensure the complete traceability of the preparation process of a sterile preparation.

d. 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.

e. Procedures and preparation instructions shall be retained for at least five years after their use.

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

2.3 TYPES OF DOCUMENTATION

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

b. There shall be Standard Operating Procedures for processing, packaging, quality control and release of product. Standard operating procedures shall be written in the imperative and include the following:

- Control of documentation systems
- Training of personnel (e.g., related to the realization of hygiene measures)
- Entering and exiting from clean areas including the correct use protective clothing
- Cleaning and disinfection
- Maintenance of equipment (e.g., Cytotoxic Drug Reconstitution (CDR) Cabinet, Laminar Air Flow (LAF) Cabinet, Isolator) and facilities
- Procedures for monitoring, including trending
- Calibration and qualification of equipment (e.g., autoclaves, thermometers)
- Operation of equipment, where applicable
- Receiving, sampling and releasing starting and packaging materials
- Counter-checking and release or rejection of finished products, including emergency release.
• Validation of processes
• Storage and distribution
• Procedure for actions to be taken in the case of deviations and complaints
• Recall of finished products
• Self audits

2.4 BATCH PREPARATION INSTRUCTIONS & RECORDS

a. 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.

b. 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 requirements given in the general requirements.

c. The processing and packaging records shall include:

• 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).
• Identification of the product (including batch number and preparation formula), the date of preparation and a specimen of the label used.
• Information on all operations and observations, such as documentation of cleaning, line clearance, calculations, as well as sampling.
• Initials or signature of the responsible operators for significant processing steps and controls.
• Any deviations from the approved processing instruction.
• Name of patient or identification, where applicable.

d. The final processing record shall be assessed and approved by the Responsible Person or Releasing Officer with a date and signature.

2.5 RECORDS

a. Records for the following activities shall be maintained for a period of time that satisfies legislation or local document control policies:

• Batch Preparation Records
• Quality control tests
• Monitoring
• Maintenance
• Education and training
• Validation
• Statistics
• Distribution

2.6 OTHER DOCUMENTS

a. Examples are the description of receipt of goods, sampling, products leaflets, references of prepared products, testing, release, rejection, calibration, performance of hygiene activities.
CHAPTER 3

STANDARD OPERATING PROCEDURE: CYTOTOXIC DRUG RECONSTITUTION

Contents

3.1 PERSONNEL
  3.1.1 Principles
  3.1.2 General Requirements
  3.1.3 Training & Continued Education
  3.1.4 Personal Hygiene
    a. Hand Washing
    b. Personnel Protective Equipment
  3.1.5 Procedure for Entry into the Clean Room
  3.1.6 Health Requirements
  3.1.7 Qualification and Validation

3.2 PREMISES & EQUIPMENT
  3.2.1 Principles
  3.2.2 General Requirements
  3.2.3 Cleaning Procedure for Clean Room & Equipment
  3.2.4 Maintenance Procedure for Clean Rooms & Equipment

3.3 PRODUCTION
  3.3.1 Principles
  3.3.2 General Requirements
  3.3.3 Pre-preparation
  3.3.4 During Preparation
    3.3.4.1 Cleaning of CDR Cabinet / Isolator
    3.3.4.2 Aseptic Processing
  3.3.5 Post-Preparation
    3.3.5.1 Cleaning
    3.3.5.2 Labelling and Packaging
    3.3.5.3 Storage
    3.3.5.4 Dispensing
    3.3.5.5 Rejected and Returned Materials and Products
  3.3.6 Disposal of Clinical Waste

3.4 QUALITY CONTROL
  3.4.1 Principles
  3.4.2 General Requirements
  3.4.3 Product Release
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. Personnel’s responsibilities shall be documented and clearly understood. All personnel shall be aware of the principles of Good Preparation Practice (GPP) and the system for quality assurance.

3.1.2 GENERAL REQUIREMENTS

RESPONSIBILITIES

a. Every personnel involved (Pharmacist, Provisionally Registered Pharmacist (PRP), Pharmacy Assistant, others) is to be responsible for the quality of all sterile preparations and adhere to GPP. Responsibilities of each personnel will depend on the duties and the requirement of the activities in the organisation. The responsibilities shall be put into the job function or description clearly.

b. New personnel shall be trained in all necessary areas according to the organisation. Training of new personnel shall be documented. Provisionally Registered Pharmacist (PRP) and trainee dispenser shall be trained and supervised by pharmacist at all times.

3.1.3 TRAINING & CONTINUED EDUCATION

a. 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.

b. New personnel shall be adequately trained by pharmacist and assessed for competency. All training shall be documented.

c. Training for all personnel shall be provided on a continuous basis. All training shall be recorded.

d. Required training for new personnel are as in Checklist: Training Module of Personnel in Aseptic Unit (Appendix 1).

3.1.4 PERSONAL HYGIENE

a. Hand Washing
   Before donning sterile gown, hand washing is done by practising the 7-step technique with appropriate disinfectant and clean water.
7-Step Technique:

i. Scrub palm to palm

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

iii. Palm to palm fingers interlaced

iv. Back of fingers to opposing palms with fingers interlocked

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

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

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

HAND WASHING TECHNIQUES

1. 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
b. Personnel Protective Equipment

Sterile garments shall be worn at all times when preparing and handling cytotoxic drugs.

- **Sterile Jumpsuit**
  The fabric used shall be low-linting, synthetic type (polyethylene coated - impervious to cytotoxic drugs) and have low electrostatic generating properties, sterilization compatibility (gamma ray), lightweight, easy to wear, have minimum seams, loose fitting, close front, hooded and long sleeves with knit or elastic cuffs. Jumpsuits must be changed immediately when damaged or contaminated

- **Head Cover**
  Head covering (e.g., bouffant cap) shall fit snugly around the head to contain hair and reduce contamination. It shall be made of disposable, low-linting material

- **Sterile Footwear**
  Footwear or booties shall be made of low permeability fabric and long enough to cover ankle cuffs. The soles shall be made from a skid resistant material

- **Sterile Gloves**
  Choices of gloves shall be non-linting, long enough to cover wrist cuffs of the garment and powder free (to prevent contamination and absorption of hazardous drugs contaminants by the powder). Permeability of disposable gloves has been shown to be dependent on the gloving material (neoprene, latex or nitrile), thickness of gloves and exposure time. Double gloving and wearing gloves no longer than 30 minutes are recommended

- **Respirator Mask**
  Disposable particulate respirators that filter out aerosols, powder and liquid spills are recommended (e.g., N-95, N-99). Surgical masks protect against the inhalation of powder only. Therefore, it is not recommended to use surgical mask only. Beards shall be covered accordingly

- **Protective Goggles**
  Goggles are recommended to be worn to prevent exposure of cytotoxic drugs to the eyes (e.g., protective goggles with side shields)

- **Sterile Chemo Gowns**
  Gowns are used to protect jumpsuits from splashes. It shall be made of impermeable material with long cuffed sleeves and closed back

c. Gowning

i. Remove make-up, jewellery and watch before gowning
ii. Put on a “bouffant” head cap, making sure that all hair is contained
iii. Put on a face mask and make sure that no facial hair is exposed
iv. Wash hands according to the ‘Seven - Step Hand Washing Technique’.
  Dry hands with electrical hand dryer
v. Wear sterile powder-free gloves before gowning
vi. Wear the hood on top of head cover (if the hood is a separate piece)
vii. Wear jumpsuit; make sure that the jumpsuit does not touch the ground.
  Zip all the way to the top
viii. Wear the particulate respirator mask
ix. Take a set of booties and place it over your feet
x. Dispose the first glove
xi. Wear a pair of chemo gloves aseptically. Place the gloves on your hands and pull the sleeve of the smock over the gloves

xii. Wear the disposable chemo gown

xiii. Wear a pair of surgical gloves aseptically. Pull the gloves over the cuffs of the disposable gown

xiv. Use the full-length mirror in the gowning room to ensure that all clean room apparel is worn correctly and properly fitted

d. Gloving

i. Put on the right glove

ii. Do not uncover the folded sleeve

iii. Put on the left glove by inserting fingers of the right hand under the folded sleeve

iv. Uncover the folded sleeve of the left glove with the fingers without touching the arm

v. Fold back the folded sleeve on the right glove in the same way

GLOVING TECHNIQUES

1. Pick up one glove with thumb and forefinger

2. Pull glove on hand

3. Slip partially gloved hand under cuff of second glove

4. Pull second glove over other hand and pull glove up to gowned wrist

5. Slip fingers of completely gloved hand under cuff of first hand, pull glove to gowned wrist

6. Gloving procedure completed
3.1.5 PROCEDURES FOR ENTRY INTO THE CLEAN ROOM

a. Before entering the Clean Room:
   i. Remove accessories and make-up before entry
   ii. Wash hands and dry them with hand towel

b. Inside the Changing Room:
   i. Wear shoe cover and cross-over
   ii. Wear head cover and mask
   iii. Wash hands with appropriate disinfectants using proper hand washing techniques
   iv. Dry hands under electrical hand-dryer

c. Entry into Grade C or Grade D Clean Room(except Changing Room):
   i. Follow steps as explained in a and b
   ii. Wear non-sterile garment
   iii. Put on sterile non-powdered gloves if not handling cytotoxic drugs
   iv. Put on sterile latex chemo gloves if handling cytotoxic drugs

d. Entry into Grade B Clean Room:
   i. Follow steps as explained in a and b
   ii. Put on sterile non-powdered gloves
   iii. Enter gowning room without touching the door handle
   iv. Wear sterile garments (hood, jumpsuit and boots), minimizing contact with outer layer of the garments
   v. 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
   vi. Throw away the first glove and wear sterile latex chemo gloves according to gloving techniques with the ends fastened under the sleeve cuffs
   vii. Put on a second sterile non-powdered gloves with the ends fastened over the sleeve cuffs

e. During Reconstitution:
   i. Check periodically to ensure that garments are in good condition and the seams are sealed
   ii. Gloves shall be regularly disinfected during compounding operations

f. Degowning:
   i. Remove outer layer of surgical gloves and disposable chemo gown. Dispose into cytotoxic waste bag in the clean room
   ii. Remove all used protective clothing in the following order/sequence and place them into the cytotoxic waste bin in the changing room
      • respirator mask
      • footwear
      • jumpsuit
      • head cover
      • inner pair of chemo gloves
   iii. Wash hands and dry
3.1.6 HEALTH REQUIREMENTS

a. Health assessment shall be carried out at least once a year to prevent possible product contamination from occurring and monitor exposure to cytotoxic drugs. However, there is currently no form of biological monitoring or health assessment technique, which is sensitive, specific and quantitative to adequately predict the effects of exposure to cytotoxic drugs.

b. Nevertheless, current developments for monitoring the health of personnel involved in the handling of sterile preparations shall be applied. All cytotoxic drug reconstitution personnel safety records shall be kept for at least 7 years.

3.1.6.1 Types of Health Assessment

i. Pre-placement Medical Examinations:
   • History (potential risk factors, occupational history)
   • HIV test, Hepatitis B, Tuberculosis
   • X-ray
   • Visual examination
   • Base line examination that includes Full Blood Count with white cell differential and biochemistry (Renal Profile, Liver Function Test and Electrolytes), physical observation (skin-related problem and neurological disorder, e.g., hand tremors)

ii. Health Advice and Counselling:
   a. Personnel involved in cytotoxic drug reconstitutions shall be advised and counselled on issues such as:
      • The potential health effects associated with exposure to cytotoxic drugs and related wastes
      • The optimum standard of control measures to expect in the workplace
      • The results of the health monitoring, including any abnormal findings
      • The potential risks to personnel planning parenthood or those who are breastfeeding or pregnant

iii. Periodic Medical Examinations:
   a. Periodic Medical Examination is recommended every year unless in emergency situations (spillage, sharps injury) when medical examination shall be done promptly.

   b. Types of test are listed as below:
      • HIV test, Hepatitis B, Tuberculosis
      • X-ray
      • Visual examination
      • Full Blood Count with white cell differential and biochemistry (Renal Profile, Liver Function Test and Electrolytes)

iv. Personnel Exit Review
   a. This review completes the information and documentation of the personnel’s medical, reproductive and exposure histories prior to exit from cytotoxic drug reconstitution service.

   b. The following data shall be collected:
      • Date of termination
      • Reason for termination
c. The final medical examination shall follow the format outlined in the pre-placement examination

d. All reports and records of each personnel shall be kept in their individual Health Record File

3.1.7 QUALIFICATION AND VALIDATION

a. All permanent personnel directly involved in the preparation of cytotoxic drugs shall be trained and qualified in aseptic technique

b. All permanent personnel directly involved in the preparation of cytotoxic drugs shall satisfy the following requirements:
   - Fulfill health requirements for recruitment as reviewed by physician
   - Undergone basic aseptic training
   - Assessed by Responsible Person
   - Performed and passed processing validation
   - Credentialing by Responsible Person
   - Revalidation shall be performed at least once a year

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

3.2.1 PRINCIPLES

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

3.2.2 GENERAL REQUIREMENTS

a. Premises and equipment shall be appropriately maintained and upgraded, ensuring that they are suitable for the intended activities and to minimize the risk of errors. There shall be a logical workflow and appropriate segregation of activities

b. 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

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

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

e. Production, storage and quality control areas shall be accessible to authorized personnel only
f. 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.

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

3.2.3 CLEANING PROCEDURE FOR CLEAN ROOM & EQUIPMENT

3.2.3.1 Responsibilities

a. The Responsible Person is responsible for all matters regarding cleaning of the clean room.

b. The Responsible Person could delegate the cleaning duties to any pharmacy personnel and/or any hospital personnel, provided that the delegated personnel are trained.

c. The Responsible Person shall provide training to the cleaning personnel to enable the personnel to perform cleaning duties.

d. The Responsible Person shall supervise the cleaning procedures done by the delegated personnel.

3.2.3.2 Equipment/Materials

- Dedicated sterile low shedding mops (autoclavable)
- Dedicated bucket system (if required)
- Sterile low lint wipes
- Sterile disinfectant
- Sterile water
- Personnel Protective Equipment (PPE)

3.2.3.3 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 alcohol 70%.

c. Materials and equipment disinfected shall be brought into the clean room through pass box, except for materials that are too bulky to be placed into the pass box.
### 3.2.3.4 Cleaning Procedures

#### a. Frequency of Cleaning

- **Qualified Clean Room**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Equipment/Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before and after production</td>
<td>CDR Safety Cabinet/ Isolators</td>
</tr>
<tr>
<td>After production or daily</td>
<td>Stainless steel bench and trolley in preparation room</td>
</tr>
<tr>
<td></td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td>Weekly</td>
<td>Stainless steel bench and trolley</td>
</tr>
<tr>
<td></td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td></td>
<td>Walls and sinks</td>
</tr>
<tr>
<td></td>
<td>Gowning cabinet, changing room cabinet</td>
</tr>
<tr>
<td></td>
<td>CDR Safety Cabinet/ Isolators</td>
</tr>
<tr>
<td>Monthly</td>
<td>Stainless steel bench and trolley</td>
</tr>
<tr>
<td></td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td></td>
<td>Walls and sinks</td>
</tr>
<tr>
<td></td>
<td>Gowning cabinet, changing room cabinet</td>
</tr>
<tr>
<td></td>
<td>Ceilings</td>
</tr>
<tr>
<td></td>
<td>CDR Safety Cabinet/ Isolators</td>
</tr>
</tbody>
</table>

- **Non-Qualified Clean Room**
  - Facility with daily production

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Equipment/Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before and after production</td>
<td>CDR Safety Cabinet/ Isolators</td>
</tr>
<tr>
<td></td>
<td>Stainless steel bench and trolley in preparation room</td>
</tr>
<tr>
<td></td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td>Weekly</td>
<td>Stainless steel bench and trolley</td>
</tr>
<tr>
<td></td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td></td>
<td>Walls and sinks</td>
</tr>
<tr>
<td></td>
<td>Gowning cabinet, changing room cabinet</td>
</tr>
<tr>
<td></td>
<td>CDR Safety Cabinet/ Isolators</td>
</tr>
<tr>
<td>Monthly</td>
<td>Stainless steel bench and trolley</td>
</tr>
<tr>
<td></td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td></td>
<td>Walls and sinks</td>
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<tr>
<td></td>
<td>Gowning cabinet, changing room cabinet</td>
</tr>
<tr>
<td></td>
<td>Ceilings</td>
</tr>
<tr>
<td></td>
<td>CDR Safety Cabinet/ Isolators</td>
</tr>
</tbody>
</table>
**Manual for Sterile Preparations**

- Facility without daily production

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Equipment/Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before and after production</td>
<td>CDR Safety Cabinet/ Isolators</td>
</tr>
<tr>
<td></td>
<td>Stainless steel bench and trolley</td>
</tr>
<tr>
<td></td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td></td>
<td>Walls and sinks</td>
</tr>
<tr>
<td></td>
<td>Gowning cabinet, changing room cabinet</td>
</tr>
<tr>
<td></td>
<td>Ceilings</td>
</tr>
</tbody>
</table>

**b. Procedures**

- **CDR Safety Cabinet**
  i. Wear PPE before entering the preparation room
  ii. The cabinet shall be cleaned at the start and the end of each work session
  iii. Wipe all internal surfaces with sterile alcohol 70% before the start of each work session
  iv. 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
  v. 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 using overlapping strokes
  vi. All soiled wipes shall be thrown into the cytotoxic waste bag
  vii. After the completion of cytotoxic reconstitution, clean the cabinet according to the above procedure using decontaminant, followed by sterilized water and then, sterile alcohol 70%

- **Isolator**
  i. Wear PPE before entering the preparation room
  ii. The isolator shall be cleaned at the start and the end of each work session
  iii. Clean the external surfaces of the transfer chambers and front visor
  iv. Wipe all internal surfaces with sterile alcohol 70% before the start of each work session
  v. Clean the inner surfaces of both transfer chambers
  vi. Clean the back of the isolator, followed by the left and right side, the front visor, glove sleeves and lastly, the working bench. Use overlapping strokes to wipe
  vii. Discard all used wipes into the cytotoxic waste bin placed in the transfer chamber
  viii. After the completion of cytotoxic reconstitution, clean the isolator according to the above procedure using decontaminant, followed by sterilized water and then, sterile alcohol 70%

- **Stainless steel bench, trolley in preparation room, door knobs and clinical waste bins**
  i. Wipe all equipment with low lint wipes and sterile alcohol 70%
  ii. Ensure that all hard-to-reach areas are cleaned
• Window
  i. Clean from top to bottom with low lint wipes and sterile alcohol 70%
  ii. Ensure that all hard-to-reach areas are cleaned

• Pass box
  i. Clean the inner surface of the pass box before transferring materials and equipment into the pass box for the first time on that day
  ii. 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%

• Floors
  i. Wipe (mop) the floor using appropriate disinfectant
  ii. Use overlapping strokes from the cleanest area to the dirtiest

• Walls
  i. Clean walls using low lint wipes or extendable mop with appropriate disinfectant (sterile alcohol 70%)
  ii. 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
  iii. Ensure that all hard-to-reach areas are cleaned

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

3.2.3.5 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)
  c. Disinfectants used shall be rotated every 6 months to prevent resistance
  d. Disinfectants shall be diluted in the clean room and the expiry date must be labelled clearly

3.2.3.6 Storage of Cleaning Materials

  a. All cleaning materials shall be stored in the utility room (for facility with utility room) or component preparation room (for facility without utility room)

3.2.3.7 Management of Used Cleaning Materials

  a. All waste shall be disposed daily after each production
  b. Reusable cleaning materials shall be rinsed and sterilized before the next use
3.2.3.8 Cleaning Procedure Under Special Circumstances

a. In the event of out of specification or serious problems such as Air Handling Unit (AHU) breakdown, high count of microbiological reading, or major renovation of clean room that jeopardizes the cleanliness of the room, thorough cleaning shall be done before any aseptic activity

b. Monitoring of clean room control parameters shall be done to ensure effectiveness of the thorough cleaning. Should the monitored control parameters exceed the permitted limit, another round of thorough cleaning shall be done followed by monitoring until the results are within specified limit

c. Minor renovation and/or maintenance activity that does not require shutting down the AHU unit shall be followed by a round of thorough cleaning before commencement of aseptic activity

d. Refer to Maintenance Procedure for Clean Room & Equipment for further details

3.2.3.9 Documentation

a. All cleaning done shall be recorded. The Responsible Person shall verify all the documentations

b. All records shall be maintained according to Hospital Documentation Procedure

c. List of Forms:
   Cleaning Forms (Appendix 2)

3.2.4 MAINTENANCE PROCEDURE FOR CLEAN ROOM & EQUIPMENT

This procedure is applicable in the maintenance activity of both qualified and non-qualified cytotoxic drug reconstitution rooms. However, for non-qualified clean room, this procedure shall be applied wherever possible

3.2.4.1 Responsibilities

Pharmacist in-charge:

a. Performing the environmental monitoring of the clean room and equipment during the preparation process
b. Sending out settle plate and contact plate for testing
c. Approving of environmental monitoring results by third party
d. Analyzing, checking and verifying the monitoring and testing report
e. Obtaining the accreditation status of third party (testing agent)

Hospital Support Services (HSS) and Third Party Testing Agent:

a. Ensure that the third party testing agent have appropriate accreditation
b. Execution of the test and data collection
c. Submit the test report to person in-charge
3.2.4.2 Equipment/Materials

- Thermometer
- Hygrometer (for humidity)
- Pressure Gauge
- Settle Plates-TSA/SDA (90 mm)
- Contact Plate-TSA (55 mm)
- All relevant maintenance equipment used by Third Party Testing Agent and HSS

*Note: All devices used in performing testing need to be calibrated*

3.2.4.3 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:
   - PPM by HSS
   - PPM by Third Party Testing Agent

c. Physical Monitoring
   For physical monitoring, the monitoring parameter and frequency are listed as below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cabinet (CDR Safety Cabinet or Isolator)</th>
<th>Clean Room</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Temperature</td>
<td></td>
<td>a) Before preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Every day if no preparation</td>
</tr>
<tr>
<td>2. Humidity</td>
<td></td>
<td>a) Before preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Every day if no preparation</td>
</tr>
<tr>
<td>3. Air Pressure Differential</td>
<td></td>
<td>a) Before preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Every day if no preparation</td>
</tr>
<tr>
<td>4. Pressure Differential Across HEPA Filter</td>
<td>Before preparation</td>
<td></td>
</tr>
<tr>
<td>5. Isolator Glove Integrity</td>
<td>Once a week (if any)</td>
<td></td>
</tr>
</tbody>
</table>
• Temperature and Humidity Monitoring
  i. Record the temperature and humidity reading in the Temperature, Humidity and Air Pressure Differential Monitoring for Clean Room Form (Appendix 3)
  ii. Check, analyse and verify the records
  iii. For deviation from specification, please refer to 3.2.4.4 and also 1.3 under Chapter 1

• Air Pressure Differential Monitoring
  i. Record the air pressure differential reading in the Temperature, Humidity and Air Pressure Differential Monitoring for Clean Room Form (Appendix 3)
  ii. Check, analyse and verify the records
  iii. For deviation from specification, please refer to 3.2.4.4 and also 1.3 under Chapter 1

d. Microbiological Monitoring
   For microbiological monitoring, the monitoring parameter and frequency are listed as below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cabinet (CDR Safety Cabinet or Isolator)</th>
<th>Clean Room</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Settle plate</td>
<td>a) Every working session</td>
<td>a) Once a week during preparation</td>
</tr>
<tr>
<td><em>(90mm diameter)</em></td>
<td>b) After major breakdown or After major maintenance</td>
<td>b) After major breakdown or After major maintenance</td>
</tr>
<tr>
<td>2. Surface sample test</td>
<td>a) Once a week</td>
<td>a) Once a month</td>
</tr>
<tr>
<td><em>(Contact plate/Swab test)</em></td>
<td>b) After major breakdown or After major maintenance</td>
<td>b) After major breakdown or After major maintenance</td>
</tr>
<tr>
<td><em>(55 mm diameter)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Personnel monitoring - glove</td>
<td>a) At the end of each working session</td>
<td></td>
</tr>
<tr>
<td>finger dabs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Active air samples</td>
<td>a) Every 3 months</td>
<td>a) Every 3 months</td>
</tr>
<tr>
<td></td>
<td>b) After major breakdown or After major maintenance</td>
<td>b) After major breakdown or After major maintenance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: All the parameters mentioned above shall be monitored during in-operation.*
### (A) Settle Plate Microbiological Environment (TSA and SDA)

- Place the settle plates. Remove the cover of the settle plate and place next to it. Expose the agar for several hours. Do not leave the settle plate open for more than 4 hours.
- Record the time when the settle plates are opened and closed.

### (B) Contact Plate Microbial Surface (55mm diameter)

- Press the contact plate agar onto the surface of the dedicated location.
- Use IPA (isopropyl alcohol) to thoroughly wipe the stains of agar from the surface.

### (C) Swab Test Microbial Surface

- Swab the surface at the intended location.
- Place the swab back into the tube.

### (D) Glove Finger Dabs

- Operator need to press firmly on the respective settle plate.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Incubation Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Settle Plate</td>
<td>TSA plates - 48hrs at 30 - 35˚ C (for bacteria) SDA plates - 5 days at 20 - 25˚ C (for yeasts and mould)</td>
</tr>
<tr>
<td>(B) Contact Plate</td>
<td>TSA plates - 48hrs at 30 - 35˚ C (for bacteria)</td>
</tr>
<tr>
<td>(C) Swab Test</td>
<td>For bacterial colony culture.</td>
</tr>
<tr>
<td>(D) Glove Finger Dabs</td>
<td>Incubate as follows: TSA plates - 48hrs at 30 - 35˚ C (for bacteria) SDA plates - 5 days at 20 - 25˚ C (for yeasts and mould)</td>
</tr>
</tbody>
</table>

#### Additional Instructions:

- Obtain plates or swab kit
- Label plates or tubes
- Replace the plates’ or tubes’ covers and seal them with laboratory parafilm
- Send the plates or tubes to the laboratory immediately
- Record, analyse, check and verify the records

### Notes:

- PPM by Hospital Support Services (HSS) or Third Party Testing Agent
  - i. Obtain the PPM schedule from HSS and make appropriate arrangement to facilitate maintenance activities. These would include:
    - Washing / changing of primary and secondary filter
    - Calibration of pressure gauges, thermometer and hygrometer
    - Testing by third party agent on clean room and major equipment
PPM by Third Party Testing Agent are listed as below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cabinet (CDR Safety Cabinet or Isolator)</th>
<th>Clean Room</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Airborne Particle Counts</td>
<td>a) Once a year</td>
<td>a) Once a year</td>
</tr>
<tr>
<td></td>
<td>b) After major breakdown /</td>
<td>b) After major breakdown /</td>
</tr>
<tr>
<td></td>
<td>After major maintenance</td>
<td>After major maintenance</td>
</tr>
<tr>
<td>2. HEPA Filter Integrity Tests</td>
<td>a) Once a year</td>
<td>a) Once a year</td>
</tr>
<tr>
<td></td>
<td>b) After major breakdown /</td>
<td>b) After major breakdown /</td>
</tr>
<tr>
<td></td>
<td>After major maintenance</td>
<td>After major maintenance</td>
</tr>
<tr>
<td>3. Air Pressure Differential Test</td>
<td>a) Once a year</td>
<td>a) Once a year</td>
</tr>
<tr>
<td></td>
<td>b) After major breakdown /</td>
<td>b) After major breakdown /</td>
</tr>
<tr>
<td></td>
<td>After major maintenance</td>
<td>After major maintenance</td>
</tr>
<tr>
<td>4. Air Change Rate Test</td>
<td>a) Once a year</td>
<td>a) Once a year</td>
</tr>
<tr>
<td></td>
<td>b) After major breakdown /</td>
<td>b) After major breakdown /</td>
</tr>
<tr>
<td></td>
<td>After major maintenance</td>
<td>After major maintenance</td>
</tr>
<tr>
<td>5. Air Flow Velocities (Grade A)</td>
<td>a) Once a year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) After major breakdown /</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After major maintenance</td>
<td></td>
</tr>
<tr>
<td>6. Air Flow Pattern Test (Grade A)</td>
<td>a) Once a year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) After major breakdown /</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After major maintenance</td>
<td></td>
</tr>
<tr>
<td>7. Isolator Alarm Functional Tests</td>
<td>a) Once a year</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Isolator Leak Test</td>
<td>a) Once a year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) After major breakdown /</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After major maintenance</td>
<td></td>
</tr>
<tr>
<td>9. Isolator Pressure Hold Test</td>
<td>a) Once a year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) After major breakdown /</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After major maintenance</td>
<td></td>
</tr>
</tbody>
</table>

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

ii. Ensure that all Third Party Testing Agents involved in maintenance adhere to proper hand washing and gowning procedures before entering the clean room (if required)

iii. Before testing is done, the following need to be checked:
   - Check the accreditation status of the Third Party Testing Agent
   - Check the equipment calibration status
   - Confirm and verify the list of testing parameters that need to be carried out by Third Party Testing Agent

iv. Obtain the testing report from the Third Party Testing Agent

v. Analyse, check and verify the testing report

vi. For deviation from specification, please refer to 3.2.4.4 and also 1.3 in Chapter 1
3.2.4.4 Action to be taken if there is deviation from specification

a. In the event of out of specification or serious problems such as Air Handling Unit (AHU) breakdown, high count of microbiological reading, or major renovation of clean room that jeopardizes the cleanliness of the room, the following actions shall be taken:
   i. Inform immediately HSS or Third Party Testing Agent for further action
   ii. Perform investigation immediately and take corrective action

3.2.4.5 Documentation

a. All records and reports shall be maintained according to Hospital Documentation Procedure
b. List of Forms and Specifications:
   • Temperature, Humidity and Air Pressure Differential Monitoring For Clean Room (Appendix 3)
   • Particle Count Limit, Microbial Limit & Temperature, Humidity and Air Pressure Differential Limit (Appendix 4)

3.3 PRODUCTION

3.3.1 PRINCIPLES

Production operations shall guarantee the required quality, and be performed and supervised by competent people

3.3.2 GENERAL REQUIREMENTS

a. Production shall be performed by trained personnel. Products and materials shall be protected from microbial and other contamination at all times through swabbing of materials prior to use and strict adherence to aseptic technique
b. Appropriate flow of materials, segregation and adequate line clearance shall be practised to prevent accidental cross-contamination or mix-up of preparations
c. Only sterile materials shall be taken into Grade A and B areas

3.3.3 PRE-PREPARATION

a. Before entering the clean room, the pharmacist shall ensure that:
   • Worksheets and labels are done and counterchecked
   • Starting materials are gathered and counterchecked
   • Worksheets and labels are brought in plastic covers
   • Starting materials are sprayed and swabbed with alcohol 70% when put into pass box or air lock

3.3.4 DURING PREPARATION

3.3.4.1 Cleaning of CDR Safety Cabinet / Isolator

   i. The CDR Safety Cabinet/ Isolator shall be left running for a minimum of 20-30 minutes
   ii. Refer to the cleaning procedures for further details
3.3.4.2 Aseptic Processing

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.

a. Withdrawal of Cytotoxic Drug Solution from Ampoule
   - Clearing and Preparation of Ampoule
     i. Make sure that the ampoule and contents of the ampoule are in good condition, i.e., intact, not expired, clear and no foreign particles
     ii. 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 are present (a little tap might be able to remove the bubbles). Swing the ampoule in inverted ‘J’ pattern
     iii. With the ampoule in upright position, ensure that no more solution or bubble is trapped at the ampoule neck
   - Fixing Needle to Syringe
     i. Half unwrap the syringe, 5µm filter and the needle pack
     ii. Fix the filter onto the syringe and onto the needle with special precaution not to touch the critical sites
     iii. Put the assembled syringe, filter and needle aside to be used later
   - Breaking the Ampoule
     i. Swab the neck of the ampoule with alcohol 70%
     ii. Snap the ampoule neck by pulling it slightly towards self and pull it upward
     iii. Discard the ampoule neck with gauze immediately into the sharp bin
   - Withdrawing Solution from Ampoule
     i. Insert the needle into the ampoule cautiously, avoiding contact between the needle and the ampoule neck. Position the needle in the shoulder area of the ampoule so that the bevel tip is facing downwards
     ii. 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 the ‘non touch’ technique
     iii. Remove air from the syringe and measure the volume of the content withdrawn. Be careful so as not to expel the drug solution into the syringe cap

b. Adding Diluent to a Vial Containing Powder
   i. Place the vial on the bench. Swab the rubber bung with alcohol 70%
   ii. 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
   iii. Push the needle down and at the same time, pierce the needle through the rubber bung
   iv. Push the plunger down slowly until the entire diluent is transferred into the vial
v. Pull the plunger to its initial position. This will ensure that there is no pressure difference within and outside the vial
vi. Pull the needle slowly out of the rubber
vii. Discard the needle into the sharp bin
viii. Let the vial stand and swirl for a few minutes in order to dissolve the powder

c. Withdrawing Drug Solution from a Vial
   i. Remove the plastic/aluminium cap of the vial
   ii. Swab the rubber bung with alcohol 70%
   iii. Pull in the required volume of air into the syringe
   iv. Place the vial upright in a vertical position and hold firmly
   v. Position the syringe at 45° and place the needle (attached to the syringe) on the rubber bung with the bevel pointing upward
   vi. Push the needle down and at the same time, pierce the needle through the rubber bung
   vii. Invert the whole set with the vial on top of the syringe
   viii. 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
   ix. Do not push too much air into the vial. This is to avoid positive pressure being developed in the vial, which could lead to aerosolization of the cytotoxic drug
   x. Place the vial on the working cabinet bench top and pull out the needle from the vial
   xi. If the vial is to be reused, a second hole shall be made at the same site
   xii. Remove air bubbles and adjust to the required volume

d. Transferring Drug Solution from Syringe to Infusion Bottle
   i. Position the syringe at 45° and place the needle (attached to the syringe) on the rubber bung with the bevel pointing upward
   ii. Push the needle down and at the same time, pierce the needle through the rubber bung
   iii. Push the plunger down slowly until the entire drug is transferred into the infusion bottle
   iv. Pull the needle slowly out of the rubber bung to avoid the drug being spilled onto the bottle cap
   v. Discard the needle into the sharp bin
   vi. Swab the rubber bung and reseal the rubber bung of the infusion bottle with a sealing film
   vii. Inspect for presence of any foreign material in the infusion bottle. If there is presence of foreign particles, ensure that the infusion set used contains a filter

3.3.5 POST-PREPARATION

3.3.5.1 Cleaning
   i. Remove all broken ampoules, needles and syringes from the working bench and floor, and dispose them into a sharps bin
   ii. Spread water for injection liberally on the bench and wipe with wipers until dry
   iii. Wipe any spillage on the wire mesh and side panel with water
   iv. Start swabbing the CDR cabinet as detailed in the cleaning procedure
3.3.5.2 Labelling and Packaging

a. The packaging materials used for cytotoxic reconstitution shall provide sufficient protection from external influences and possible contamination as well as protect personnel and environment from exposure to cytotoxic substances.

b. Labels shall include:
   - Patient name
   - Product name
   - Final volume
   - Content and amount
   - Batch number (if required)
   - Date of preparation
   - Expiry date
   - Storage instructions

3.3.5.3 Storage

a. All preparations shall be stored appropriately as instructed in the product information leaflet.

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

c. Records of these conditions shall be maintained as they are critical for the preservation of material characteristics.

d. Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned or recalled materials, separate storage areas shall be assigned for their temporary storage until the decision on their future use has been taken.

3.3.5.4 Dispensing

a. Countercheck to ensure that all labels are complete with the patient’s particulars.

b. To ensure that cytotoxic drugs are transported in a manner that does not adversely affect their quality, they 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.

3.3.5.5 Rejected and Returned Materials and Products

- Rejected Products
  a. Rejected materials and products shall be marked as such and stored in separate areas.

- Returned products
  a. Dispensed products that was returned and had left the control of the preparation establishment shall be destroyed; unless there is no doubt that their quality is satisfactory.
b. Where any doubt arises over the quality of the product, it shall not be considered suitable for re-issue or re-use. Any action taken shall be appropriately recorded.

c. For deviation from specification of final product, please refer to chapter 1

3.3.6 DISPOSAL OF CLINICAL WASTE

3.3.6.1 Principles

a. Materials that have been used in the preparation and administration of cytotoxic drugs may present a source of exposure or injury to personnel not involved in the preparation and administration if the disposal is not properly handled.

b. Containers used for disposal of cytotoxic 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 protection.

c. All cytotoxic waste, including those generated after cleaning of spills, must be segregated, packaged and disposed off in a manner that will not contaminate personnel and the environment.

d. Disposal procedure shall follow the requirements set by the Department of Environment. Incineration is recommended with a minimum residence time of one second at 1100°C to ensure adequate degradation of all cytotoxic drugs.

3.3.6.2 Materials

- Cytotoxic waste bins
- Cytotoxic waste bags
- Spill kit: Content of Spill Kit (Appendix 5)

3.3.6.3 Procedure

Cytotoxic waste includes all materials that have come into contact with cytotoxic drugs during the process of reconstitution and administration.

- Cytotoxic waste generated in the CDR Cabinet
  a. All contaminated materials such as vial/ampoule which are empty or with unused portions of drugs, needles and syringes shall be discarded in the sharp bin.
  b. Used materials such as gauze, 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 alcohol 70% before removing it from the cabinet for future use.*

- Gowns and Gloves
  a. Disposable gowns and outer layer of gloves must also be placed into the cytotoxic waste bag before leaving the cytotoxic drug reconstitution room at the end of the working session.
  b. Personnel must not leave the room whilst wearing the gown and outer layer gloves that have been worn throughout a cytotoxic preparation procedure.
3.4 QUALITY CONTROL

3.4.1 PRINCIPLES

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

3.4.2 GENERAL REQUIREMENTS

Testing of finished products is not necessary for extemporaneously prepared products. Furthermore, as cytotoxic drugs are hazardous to the environment, testing of final product is not recommended. However, a regular programme of media fills (i.e., process validation using broth) may be acceptable.

3.4.3 PRODUCT RELEASE

a. The Responsible Person is ultimately responsible for the quality of the products prepared and released. The actual release can be delegated to another appropriately competent person (i.e., Releasing Officer).

b. Product release shall include verification that the products comply with valid specifications and that they have been prepared in accordance with valid procedures and the principles of Good Preparation Practice.

c. Counterchecking for the finished product shall be performed as per specification.

d. Products 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., Responsible Person or Releasing Officer).
CHAPTER 3

STANDARD OPERATING PROCEDURE: PARENTERAL NUTRITION

Contents

3.1 PERSONNEL
3.1.1 Principles
3.1.2 General Requirements
3.1.3 Training & Continued Education
3.1.4 Personal Hygiene
  a. Hand Washing
  b. Personnel Protective Equipment
3.1.5 Procedure for Entry into the Clean Room
3.1.6 Health Requirements
3.1.7 Qualification and Validation

3.2 PREMISES & EQUIPMENT
3.2.1 Principles
3.2.2 General Requirements
3.2.3 Cleaning Procedure for Clean Room & Equipment
3.2.4 Maintenance Procedure for Clean Rooms & Equipment

3.3 PRODUCTION
3.3.1 Principles
3.3.2 General Requirements
3.3.3 Pre-preparation
3.3.4 During Preparation
  3.3.4.1 Cleaning of LAF Cabinet / Isolator
  3.3.4.2 Aseptic Processing
3.3.5 Post-Preparation Procedure
  3.3.5.1 Cleaning
  3.3.5.2 Packaging & Labelling of Parenteral Nutrition Preparation
  3.3.5.3 Disposal of PN Waste
  3.3.5.4 Storage
  3.3.5.5 Dispensing
  3.3.5.6 Rejected and Returned Materials and Products

3.4 QUALITY CONTROL
3.4.1 Principles
3.4.2 General Requirements
3.4.3 Sampling
3.4.4 Testing of Finished Products
3.4.5 Product Release
CHAPTER 3

STANDARD OPERATING PROCEDURE: PARENTERAL NUTRITION

3.1 PERSONNEL

3.1.1 PRINCIPLES

There shall be sufficient and competent personnel to execute all the tasks. Personnel's responsibilities shall be documented and clearly understood. All personnel shall be aware of the principles of Good Preparation Practice (GPP) and the system for quality assurance.

3.1.2 GENERAL REQUIREMENTS

RESPONSIBILITIES

a. Every personnel involved (Pharmacist, Provisionally Registered Pharmacist (PRP), Pharmacy Assistant, others) is to be responsible for the quality of all sterile preparations and adhere to GPP. Responsibilities of each personnel will depend on the duties and the requirement of the activities in the organisation. The responsibilities shall be put into the job function or description clearly.

b. New personnel shall be trained in all necessary areas according to the organisation. Training of new personnel shall be documented. Provisionally Registered Pharmacist (PRP) and trainee dispenser shall be trained and supervised by pharmacist at all times.

3.1.3 TRAINING & CONTINUED EDUCATION

a. 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.

b. New personnel shall be adequately trained by pharmacist and assessed for competency. All training shall be documented.

c. Training for all personnel shall be provided on a continuous basis. All training shall be recorded.

d. Required training for new personnel are as in Checklist: Training Module of Personnel in Aseptic Unit (Appendix 1).

3.1.4 PERSONAL HYGIENE

a. Hand Washing

Before donning sterile gown, hand washing is done by practising the 7-step technique with appropriate disinfectant and clean water.
7-Step Technique:
i. Scrub palm to palm
ii. Right palm over left dorsum and left palm over right dorsum
iii. Palm to palm fingers interlaced
iv. Back of fingers to opposing palms with fingers interlocked
v. Rotational rubbing of right thumb clasped in left palm and vice versa
vi. Rotational rubbing, backwards and forwards with clasped fingers of right hand in left palm and vice versa
vii. Rotational rubbing of right wrist and vice versa. Rinse and dry thoroughly
b. Personnel Protective Equipment
Sterile garments shall be worn at all times when preparing parenteral nutrition (PN)

- Sterile Jumpsuit
  The fabric used shall be low-linting and have low electrostatic generating properties, sterilization compatible (gamma ray), lightweight, easy to wear, have minimum seams, loose fitting, close front, hooded and long sleeves with knit or elastic cuffs. Jumpsuits must be changed immediately when damaged or contaminated.

- Head Cover
  Head covering (e.g., bouffant cap) shall fit snugly around the head to contain hair and reduce contamination. It shall be made of disposable, low-linting material.

- Sterile Footwear
  Footwear or booties shall be made of low permeability fabric and long enough to cover ankle cuffs. The soles shall be made from a non-slip material.

- Sterile Gloves
  Choices of gloves shall be non-linting, long enough to cover wrist cuffs of the garment and powder free. Double gloving is recommended.

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

c. Gowning
i. Remove make-up, jewellery and watch before gowning
ii. Put on a “bouffant” head cap, making sure that all hair is contained
iii. Put on a face mask and make sure that no facial hair is exposed
iv. Wash hands according to the ‘Seven - Step Hand Washing Technique’. Dry hands with electrical hand dryer
v. Wear sterile powder-free gloves before gowning
vi. Wear the hood on top of head cover (if the hood is a separate piece)
vii. Wear jumpsuit; make sure that the jumpsuit does not touch the ground. Zip all the way to the top
viii. Take a set of booties and place it over your feet
ix. Wear gloves according to the gloving procedure (please refer to 4.2.7)
x. Use the full-length mirror in the gowning room to ensure that all clean room apparel is worn correctly and properly fitted.

d. Gloving
i. Put on the right glove
ii. Do not uncover the folded sleeve
iii. Put on the left glove by inserting fingers of the right hand under the folded sleeve
iv. Uncover the folded sleeve of the left glove with the fingers without touching the arm
v. Fold back the folded sleeve on the right glove in the same way
GLOVING TECHNIQUES

1. Pick up one glove with thumb and forefinger
2. Pull glove on hand
3. Slip partially gloved hand under cuff of second glove
4. Pull second glove over other hand and pull glove up to gowned wrist
5. Slip fingers of completely gloved hand under cuff of first hand, pull glove to gowned wrist
6. Gloving procedure completed

3.1.5 PROCEDURES FOR ENTRY INTO THE CLEAN ROOM

a. Before entering the Clean Room:
   i. Remove accessories and make-up before entry
   ii. Wash hands and dry them with hand towel

b. Inside the Changing Room:
   i. Wear shoe cover and cross-over
   ii. Wear head cover and mask
   iii. Wash hands with appropriate disinfectants using proper hand washing techniques
   iv. Dry hands under electrical hand-dryer
   v. Enter the gowning room without touching the door handle

c. Entry into Grade C or Grade D Clean Room (except Changing Room):
   i. Follow steps as explained in a and b
   ii. Wear non-sterile garment
   iii. Put on sterile non-powdered gloves
d. Entry into Grade B Clean Room:
i. Follow steps as explained in a and b
ii. Put on sterile non-powdered gloves
iii. Enter gowning room without touching the door handle
iv. Wear sterile garments (hood, jumpsuit and boots), minimizing contact with outer layer of the garments
v. 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
vi. Wear double sterile gloves according to gloving techniques with ends fastened over the sleeve cuffs
e. During Aseptic Compounding:
i. Check periodically to ensure that garments are in good condition and the seams are sealed
ii. Gloves shall be regularly disinfected during compounding operations

3.1.6 HEALTH REQUIREMENTS

Health assessment shall be carried out at least once a year to prevent possible product contamination to occur

3.1.6.1 Types of Health Assessment

i. Pre-placement Medical Examinations:
   • History (potential risk factors, occupational history)
   • HIV test, Hepatitis B, Tuberculosis
   • X-ray
   • Visual examination
   • Base line examination that includes Full Blood Count with white cell differential and biochemistry (Renal Profile, Liver Function Test and Electrolytes), physical observation (skin-related problem and neurological disorder, e.g., hand tremors)

ii. Periodic Medical Examinations:
   • HIV test, Hepatitis B, Tuberculosis
   • X-ray
   • Visual examination
   • Full Blood Count with white cell differential and biochemistry (Renal Profile, Liver Function Test and Electrolytes)

3.1.7 QUALIFICATION AND VALIDATION

a. All permanent personnel directly involved in the preparation of parenteral nutrition solutions shall be trained and qualified in aseptic technique

b. All permanent personnel directly involved in the preparation of parenteral nutrition solutions shall satisfy the following requirements:
   • Fulfill health requirements for recruitment as reviewed by physician
   • Undergone basic aseptic training
   • Assessed by Responsible Person
   • Performed and passed processing validation
   • Credentialing by Responsible Person
   • Revalidation shall be performed at least once a year
c. Every personnel involved in aseptic technique dispensing shall undergo validation test prior to working in the sterile unit. 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 & EQUIPMENT

3.2.1 PRINCIPLES

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

3.2.2 GENERAL REQUIREMENTS

a. Premises and equipment shall be appropriately maintained and upgraded, ensuring that they are suitable for the intended activities and to minimize the risk of errors. There shall be appropriate workflow and segregation of activities.

b. 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.

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

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

e. Production, storage and quality control areas shall be accessible to authorized personnel only.

f. 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.

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

3.2.3 CLEANING PROCEDURE FOR CLEAN ROOM & EQUIPMENT

3.2.3.1 Responsibilities

a. The Responsible Person is responsible for all matters regarding cleaning of the clean room.

b. The Responsible Person could delegate the cleaning duties to any pharmacy personnel and/or any hospital personnel, provided the delegated personnel are trained.

c. The Responsible Person shall provide training to the cleaning personnel to enable the personnel to perform cleaning duties.

d. The Responsible Person shall supervise the cleaning procedures done by the delegated personnel.
3.2.3.2 Equipment/Materials

- Dedicated sterile low shedding mops (autoclavable)
- Dedicated bucket system (if required)
- Sterile low lint wipes
- Sterile disinfectant
- Sterile water
- Personnel Protective Equipment (PPE)

3.2.3.3 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 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

3.2.3.4 Cleaning Procedures

a. Frequency of Cleaning

- Qualified Clean Room

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Equipment/Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before and after production</td>
<td>Laminar Air Flow Cabinet (LAFC), isolator</td>
</tr>
<tr>
<td>After production or daily</td>
<td>Stainless steel bench and trolley in preparation room</td>
</tr>
<tr>
<td></td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td></td>
<td>Stainless steel bench and trolley</td>
</tr>
<tr>
<td>Weekly</td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td></td>
<td>Walls and sinks</td>
</tr>
<tr>
<td></td>
<td>Gowning cabinet, changing room cabinet</td>
</tr>
<tr>
<td></td>
<td>Laminar Air Flow Cabinet (LAFC), isolator</td>
</tr>
<tr>
<td></td>
<td>Stainless steel bench and trolley</td>
</tr>
<tr>
<td>Monthly</td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td></td>
<td>Walls and sinks</td>
</tr>
<tr>
<td></td>
<td>Gowning cabinet, changing room cabinet</td>
</tr>
<tr>
<td></td>
<td>Ceilings</td>
</tr>
<tr>
<td></td>
<td>Laminar Air Flow Cabinet (LAFC), isolator</td>
</tr>
</tbody>
</table>
- **Non-Qualified Clean Room**
  - Facility with daily production

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Equipment/Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before and after production</td>
<td>Laminar Air Flow Cabinet (LAFC), Isolator&lt;br&gt;Stainless steel bench and trolley in preparation room&lt;br&gt;Floor, window and door knobs&lt;br&gt;Pass box and clinical waste bins</td>
</tr>
<tr>
<td>Weekly</td>
<td>Stainless steel bench and trolley&lt;br&gt;Floor, window and door knobs&lt;br&gt;Pass box and clinical waste bins&lt;br&gt;Walls and sinks&lt;br&gt;Gowning cabinet, changing room cabinet</td>
</tr>
<tr>
<td>Monthly</td>
<td>Stainless steel bench and trolley&lt;br&gt;Floor, window and door knobs&lt;br&gt;Pass box and clinical waste bins&lt;br&gt;Walls and sinks&lt;br&gt;Gowning cabinet, changing room cabinet&lt;br&gt;ceilings</td>
</tr>
</tbody>
</table>

- Facility without daily production

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Equipment/Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before and after production</td>
<td>Laminar Air Flow Cabinet (LAFC), Isolator&lt;br&gt;Stainless steel bench and trolley&lt;br&gt;Floor, window and door knobs&lt;br&gt;Pass box and clinical waste bins&lt;br&gt;Walls and sinks&lt;br&gt;Gowning cabinet, changing room cabinet&lt;br&gt;ceilings</td>
</tr>
</tbody>
</table>
b. Procedures

- Laminar Air Flow Cabinet (LAFC)
  i. Wear PPE before entering the clean room
  ii. The cabinet shall be cleaned at the start and the end of each work session
  iii. Wipe all internal surfaces with sterile alcohol 70% before the start of each work session
  iv. The top surface of the cabinet shall be cleaned first, followed by the left and right side and lastly, the working bench
  v. 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 using overlapping strokes
  vi. All soiled wipes shall be thrown into the clinical waste bag
  vii. After the completion of aseptic preparation, clean the cabinet according to the above procedure using sterile alcohol 70%

- Isolator
  i. Wear PPE before entering the preparation room
  ii. The isolator shall be cleaned at the start and the end of each work session
  iii. Clean the external surfaces of the transfer chambers and front visor
  iv. Wipe all internal surfaces with sterile alcohol 70% before the start of each work session
  v. Clean the inner surfaces of both transfer chambers
  vi. Clean the back of the isolator, followed by the left and right side, the front visor, glove sleeves and lastly, the working bench. Use overlapping strokes to wipe
  vii. Discard all used wipes into the waste bin placed in the transfer chamber
  viii. After the completion of sterile preparation, clean the isolator according to the above procedure using sterilized water, followed by sterile alcohol 70%

- Stainless steel bench, trolley in preparation room, door knobs and clinical waste bins
  i. Wipe all equipment with low lint wipes and sterile alcohol 70%
  ii. Ensure that all hard-to-reach areas are leaned

- Window
  i. Clean from top to bottom with low lint wipes and sterile alcohol 70%
  ii. Ensure that all hard-to-reach areas are cleaned

- Pass box
  i. Clean the inner surface of the pass box before transferring materials and equipment into the pass box for the first time on that day
  ii. 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%

- Floors
  i. Wipe (mop) the floor using appropriate disinfectant
  ii. Use overlapping strokes from the cleanest area to the dirtiest
• Walls
  i. Clean walls using low lint wipes or extendable mop with appropriate disinfectant (sterile alcohol 70%)
  ii. 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
  iii. Ensure that all-hard-to-reach areas are cleaned

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

3.2.3.5 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)

c. Disinfectants used shall be rotated every 6 months to prevent resistance

d. Disinfectants shall be diluted in the clean room and the expiry date must be labelled clearly

3.2.3.6 Storage of Cleaning Materials

a. All cleaning materials shall be stored in the utility room (for facility with utility room) or component preparation room (for facility without utility room)

3.2.3.7 Management of Used Cleaning Materials

a. All waste shall be disposed daily after each production

b. Reusable cleaning materials shall be rinsed and sterilized before next use

3.2.3.8 Cleaning Procedure Under Special Circumstances

a. In the event of out of specification or serious problems such as Air Handling Unit (AHU) breakdown, high count of microbiological reading, or major renovation of clean room that jeopardizes the cleanliness of the room, thorough cleaning shall be done before any aseptic activity

b. Monitoring of clean room control parameters shall be done to ensure effectiveness of the thorough cleaning. Should the monitored control parameters exceed the permitted limit, another round of thorough cleaning shall be done followed by monitoring until the results are within specified limit
c. Minor renovation and/or maintenance activity that does not require shutting down the AHU unit shall be followed by a round of thorough cleaning before commencement of aseptic activity

d. Refer to Maintenance Procedure for Clean Room & Equipment for further details

3.2.3.9 Documentation

i. All cleaning done shall be recorded. The Responsible Person shall verify all the documentations

ii. All records shall be maintained according to Hospital Documentation Procedure

iii. List of Forms:
   Cleaning Forms (Appendix 2)

3.2.4 MAINTENANCE PROCEDURE FOR CLEAN ROOMS & EQUIPMENT

This procedure is applicable in the maintenance activity of both qualified and non-qualified parenteral nutrition clean rooms. However, for non-qualified clean room, this procedure shall be applied wherever possible

3.2.4.1 Responsibilities

- Pharmacist in-charge:
  a. Performing the environmental monitoring of the clean room and equipment during the preparation process
  b. Sending out settle plate and contact plate for testing
  c. Approving of environmental monitoring results by third party
  d. Analyzing, checking and verifying the monitoring and testing report
  e. Obtaining the accreditation status of third party (testing agent)

- Hospital Support Services (HSS) and Third Party Testing Agent:
  a. Ensure that the third party testing agent have appropriate accreditation
  b. Execution of the test and data collection
  c. Submit the test report to person in-charge

3.2.4.2 Equipment/Materials

- Thermometer
- Hygrometer (for humidity)
- Pressure Gauge
- Settle Plates-TSA/SDA (90 mm)
- Contact Plate- TSA (55 mm)
- All relevant maintenance equipment used by Third Party Testing Agent and HSS

*Note: All devices used in performing testing need to be calibrated*
3.2.4.3 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:
   - PPM by HSS
   - PPM by Third Party Testing Agent

c. Physical Monitoring
   For physical monitoring, the monitoring parameter and frequency are listed as below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Laminar Air Flow Cabinet/Isolator</th>
<th>Clean Room</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Temperature</td>
<td></td>
<td>a) Before preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Every day if no preparation</td>
</tr>
<tr>
<td>2. Humidity</td>
<td></td>
<td>a) Before preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Every day if no preparation</td>
</tr>
<tr>
<td>3. Air Pressure Differential</td>
<td></td>
<td>a) Before preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Every day if no preparation</td>
</tr>
<tr>
<td>4. Pressure Differential Across HEPA Filter</td>
<td>Before preparation</td>
<td></td>
</tr>
<tr>
<td>5. Isolator Glove Integrity</td>
<td>Once a week (if any)</td>
<td></td>
</tr>
</tbody>
</table>

- Temperature and Humidity Monitoring
  i. Record the temperature and humidity reading in the Temperature, Humidity and Air Pressure Differential Monitoring for Clean Room Form (Appendix 3)
  ii. Check, analyse and verify the records
  iii. For deviation from specification, please refer to 3.2.4.4 and also 1.3 under Chapter 1

- Air Pressure Differential Monitoring
  i. Record the air pressure differential reading in the Temperature, Humidity and Air Pressure Differential Monitoring for Clean Room Form (Appendix 3)
  ii. Check, analyse and verify the records
  iii. For deviation from specification, please refer to 3.2.4.4 and also 1.3 under Chapter 1
d. Microbiological Monitoring
For microbiological monitoring, the monitoring parameter and frequency are listed as below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Laminar Air Flow Cabinet/Isolator</th>
<th>Clean Room</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Settle plate (90mm diameter)</td>
<td>a) Every working session</td>
<td>a) Once a week during preparation</td>
</tr>
<tr>
<td></td>
<td>b) After major breakdown or</td>
<td>b) After major breakdown or</td>
</tr>
<tr>
<td></td>
<td>After major maintenance</td>
<td>After major maintenance</td>
</tr>
<tr>
<td>2. Surface sample test (Contact plate/ Swab test) (55 mm diameter)</td>
<td>a) Once a week</td>
<td>a) Once a month</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) After major breakdown or</td>
</tr>
<tr>
<td>3. Personnel monitoring - glove finger dabs</td>
<td>a) At the end of each working session</td>
<td>b) After major maintenance</td>
</tr>
<tr>
<td>4. Active air samples</td>
<td>a) Every 3 months</td>
<td>a) Every 3 months</td>
</tr>
<tr>
<td></td>
<td>b) After major breakdown or</td>
<td>b) After major breakdown or</td>
</tr>
<tr>
<td></td>
<td>After major maintenance</td>
<td></td>
</tr>
</tbody>
</table>

Note: All the parameters mentioned above shall be monitored during in-operation.
Procedure for microbial monitoring is as follows:

<table>
<thead>
<tr>
<th>(A) Settle Plate Microbiological Environment (TSA and SDA)</th>
<th>(B) Contact Plate Microbial Surface (55mm diameter)</th>
<th>(C) Swab Test Microbial Surface</th>
<th>(D) Glove Finger Dabs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain plates or swab kit</td>
<td>Label plates or tubes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Place the settle plates. Remove the cover of the settle plate and place next to it. Expose the agar for several hours. Do not leave the settle plate open for more than 4 hours</td>
<td>Press the contact plate agar onto the surface of the dedicated location</td>
<td>Swab the surface at the intended location</td>
<td>Operator need to press firmly on the respective settle plate</td>
</tr>
<tr>
<td>Record the time when the settle plates are opened and closed</td>
<td>Use IPA (isopropyl alcohol) to thoroughly wipe the stains of agar from the surface</td>
<td>Place the swab back into the tube</td>
<td>-</td>
</tr>
<tr>
<td>Replace the plates' or tubes' covers and seal them with laboratory parafilm</td>
<td>Send the plates or tubes to the laboratory immediately</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incubate as follows: TSA plates - 48hrs at 30 - 35˚C (for bacteria) SDA plates - 5 days at 20 - 25˚C (for yeasts and mould)</td>
<td>Incubate as follows: TSA plates - 48hrs at 30 - 35˚C (for bacteria)</td>
<td>For bacterial colony culture</td>
<td>Incubate as follows: TSA plates - 48hrs at 30 - 35˚C (for bacteria) SDA plates - 5 days at 20 - 25˚C (for yeasts and mould)</td>
</tr>
<tr>
<td>Record, analyse, check and verify the records</td>
<td>For deviation from specification, please refer to 3.6.3.4 and also 1.3 in Chapter 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
e. PPM by Hospital Support Services (HSS) or Third Party Testing Agent
i. Obtain the PPM schedule from HSS and make appropriate arrangement to facilitate maintenance activities. These would include:
   • Washing / changing of primary and secondary filter
   • Calibration of pressure gauges, thermometer and hygrometer
   • Testing by third party agent on clean room and major equipment

Procedure for microbial monitoring is as follows:

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

Note: All the parameters mentioned above shall be monitored during at-rest.
ii. Ensure that all Third Party Testing Agents involved in maintenance adhere to proper hand washing and gowning procedures before entering the clean room (if required)
iii. Before testing is done, the following need to be checked:
   • Check the accreditation status of the Third Party Testing Agent
   • Check the equipment calibration status
   • Confirm and verify the list of testing parameters that need to be carried out by Third Party Testing Agent
iv. Obtain the testing report from the Third Party Testing Agent
v. Analyse, check and verify the testing report
vi. For deviation from specification, please refer to 3.2.4.4 and also 1.3 in Chapter 1

3.2.4.4 Action to be taken if there is deviation from specification

   a. In the event of out of specification or serious problems such as Air Handling Unit (AHU) breakdown, high count of microbiological reading, or major renovation of clean room that jeopardizes the cleanliness of the room, the following actions shall be taken:
      i. Inform immediately HSS or Third Party Testing Agent for further action
      ii. Perform investigation immediately and take corrective action

3.2.4.5 Documentation

   a. All records and reports shall be maintained according to Hospital Documentation Procedure
   b. List of Forms and Specifications:
      • Temperature, Humidity and Air Pressure Differential Monitoring For Clean Room (Appendix 3)
      • Particle Count Limit, Microbial Limit & Temperature, Humidity and Air Pressure Differential Limit (Appendix 4)

3.3 PRODUCTION

3.3.1 PRINCIPLES

   Production operations shall guarantee the required quality, and be performed and supervised by competent people

3.3.2 GENERAL REQUIREMENTS

   a. Production shall be performed by trained personnel. Products and materials shall be protected from microbial and other contamination at all times through swabbing of materials prior to use and strict adherence to aseptic technique
   b. Appropriate flow of materials, segregation and adequate line clearance shall be practised to prevent accidental cross-contamination or mix-up of preparations
   c. Only sterile materials shall be taken into Grade A and B areas
3.3.3 PRE-PREPARATION

a. Before entering the clean room, the pharmacist shall ensure that:
   - Worksheets and labels are done and counterchecked
   - Starting materials are gathered and counterchecked
   - Worksheets and labels are brought in plastic covers
   - Starting materials are sprayed and swabbed with alcohol 70% when put into pass box or air lock

3.3.4 DURING PREPARATION

3.3.4.1 Cleaning of Cabinet / Isolator

i. The Laminar Air Flow Cabinet/Isolator shall be left running for a minimum of 20-30 minutes
ii. LAF Cabinet/Isolator shall be cleaned prior to commencement of production, using sterile alcohol with caution to prevent spraying directly into the HEPA filter

3.3.4.2 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. 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 zig-zag arrangement to allow filtered air to pass through

3.3.4.3 Withdrawal of Solution from Ampoule

   - Cleaning and Preparation of Ampoule
     i. Make sure that the ampoule and contents of the ampoule are in good condition, i.e., intact, not expired, clear and no foreign particles
     ii. 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
     iii. With the ampoule in upright position, ensure that no more solution or bubble is trapped at the ampoule neck

   - Fixing Needle to Syringe
     i. Half unwrap the syringe pack and the needle pack
     ii. Hold both the needle and the syringe in one hand
     iii. Fix the syringe to needle with special precaution not to touch the critical sites
     iv. Put the syringe and needle aside to be used later
• Breaking the Ampoule
  i. Swab the neck of the ampoule with alcohol 70%
  ii. Snap the ampoule neck by pulling it slightly towards self and pull it upward
  iii. Discard the ampoule neck immediately into the sharps bin

• Withdrawing Solution from Ampoule
  i. Insert the needle into the ampoule cautiously, avoiding contact between the needle and the ampoule neck. Position the needle in the shoulder area of the ampoule so that the bevel tip is facing downwards
  ii. Hold the ampoule in one hand and syringe in the other. Pull the plunger back with the thumb and index finger to withdraw the required volume of drug solution into the syringe using the 'non touch' technique
  iii. Remove air from the syringe and measure the volume of the contents withdrawn

d. Adding Diluent to a Vial Containing Powder
  i. Place the vial on the bench. Swab the rubber bung with alcohol 70%
  ii. 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
  iii. Push the needle down and at the same time, pierce the needle through the rubber bung
  iv. Push the plunger down slowly until the entire diluent is transferred into the vial
  v. Pull the plunger to its initial position. This will ensure that there is no pressure difference within and outside the vial
  vi. Pull the needle slowly out of the rubber and discard the needle into the sharps bin
  vii. Let the vial stand and swirl for a few minutes in order to dissolve the powder

e. Withdrawing Drug Solution from a Vial
  i. Swab the rubber bung with alcohol 70%
  ii. Pull in the required volume of air into the syringe
  iii. Place the vial upright in a vertical position and hold firmly
  iv. Position the syringe at 450 and place the needle (attached to the syringe) on the rubber bung with the bevel pointing upward
  v. Push the needle down and at the same time, pierce the needle through the rubber bung
  vi. Invert the whole set with the vial on top of the syringe
  vii. 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 the syringe
  viii. Place the vial on the working cabinet bench top and pull out the needle from the vial
  ix. Remove air bubbles and adjust to the required volume
f. Procedure for Compounding of Paediatric PN
   i. Prepare PN bags one by one
   ii. Affix a transfer set to the infusion port if necessary. Close all the clamps of the transfer set
   iii. Open the clamp and infuse amino acid, dextrose and water for injection into the bag through the transfer set
   iv. Fix the injection port with 0.2 µm filter
   v. Infuse electrolytes through the injection port in the order of stability, e.g., Phosphate, Sodium chloride, Magnesium sulphate, Acetate, Kalium chloride, Calcium, Trace elements
   vi. Infuse other necessary additives into the bag
   vii. Agitate the bag from time to time
   viii. Flush the filter. Make sure that the filter is intact throughout the process
   ix. If preparing all-in-one bag, infuse lipid emulsion as the last component
   x. If preparing two-in-one bag, prepare the lipid separately
   xi. When all components have been filled into the bag, remove the filter and close the opening
   xii. 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
   xiii. Check the bag visually
   xiv. Label the bag

   g. Procedure for Compounding of Adult PN
   i. Remove caps of amino acid, glucose or dextrose and water for injection vials and swab the rubber bungs with alcohol
   ii. Run all the components from the vials according to the required quantity to a PN bag via transfer set
   iii. Attach a 5.0µm filter to 0.2 µm filter (if required) with a new needle into the injection port of the PN bag
   iv. Withdraw required amount of micronutrients and inject into PN bag via the filter connected
   v. Mix the solution until homogeneous and check for foreign particles
   vi. If there is presence of foreign particle, infuse required amount of lipid emulsion into the PN bag via transfer set
   vii. Inject required amount of multivitamin into the PN bag
   viii. Mix the solution until homogeneous
   ix. Discard air bubbles and clamp the infusion port. Sample if required
   x. Label the bag

   h. Preparation of Lipid Emulsion for Paediatrics
   i. Withdraw lipid emulsion into a syringe according to the amount stated on the label
   ii. Withdraw multivitamin using a 5.0µm filter
   iii. With a needle, mix multivitamin into the lipid syringe
   iv. Mix the mixture until homogenous. Discard air from the lipid syringe. Cover and tighten the stopper
   v. Label the syringe
j. Procedure for Addition into Ready-Mix Bag
   i. Mix the Ready-Mix PN
   ii. Swab the injection port of the Ready-Mix PN
   iii. Attach a 5.0µm filter to 0.2 µm filter (if required) with a new
        needle into the injection port of the PN bag
   iv. Detach the needle with the filters from the injection port
   v. Mix the solution until homogeneous and check for foreign
       particles
   vi. Swab the injection port with sterile alcohol
   vii. Recap the injection port

3.3.5 POST-PREPARATION

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

3.3.5.2 Packaging & Labeling of Parenteral Nutrition Preparation
   a. The packaging material used for parenteral nutrition 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
      • Final volume
      • Content and amount
      • Batch number (if required)
      • Date of preparation
      • Expiry date

3.3.5.3 Disposal of PN Waste
   a. 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
   b. 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
   c. Materials
      • Clinical waste disposable - dispose into plastic bag
      • Clinical waste (bottle/vial) - dispose into yellow bag
      • Sharp objects (e.g. needle, syringe, ampoule) - dispose into
        sharps bin
3.3.5.4 Storage

a. All PN preparations shall be stored in the refrigerator (2-8°C)

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 unauthorized use of quarantined, rejected, returned or recalled materials, separate storage areas shall be assigned for their temporary storage until the decision on their future use has been taken

3.3.5.5 Dispensing

a. Countercheck to ensure that all labels are complete with the patient’s particulars

b. To ensure that PN bags are transported in a manner that does not adversely affect 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

3.3.5.6 Rejected and returned Materials and Products

- Rejected products
  a. Rejected materials and products shall be marked as such and stored in separate areas

- Returned products
  a. Dispensed products that was returned and had left the control of the preparation establishment shall be destroyed
  b. Where any doubt arises over the quality of the product, it shall not be considered suitable for re-issue or re-use. Any action taken shall be appropriately recorded
  c. For deviation from specification of final product, please refer to Chapter 1

3.4 QUALITY CONTROL

3.4.1 PRINCIPLES

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

a. Testing equipment shall be suitable for its intended use

b. 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

3.4.3 SAMPLING

a. Samples taken for analysis shall be representative of the material being tested

b. Samples shall be taken from the final container of the preparation prior to sealing of infusion port

3.4.4 TESTING OF FINISHED PRODUCTS

a. 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

b. No quality control testing is necessary for extemporaneously prepared products

c. 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

3.4.5 PRODUCT RELEASE

a. The Responsible Person is ultimately responsible for the quality of the products prepared and released. The actual release can be delegated to another appropriately competent person (i.e., Releasing Officer)

b. Product release shall include verification that the products comply with the valid specifications and that they have been prepared in accordance with valid procedures and the principles of Good Preparation Practice
CHAPTER 3

STANDARD OPERATING PROCEDURE:
IV ADMIXTURE & EYE PREPARATION

Contents

3.1 PERSONNEL
3.1.1 Principles
3.1.2 General Requirements
3.1.3 Training & Continued Education
3.1.4 Personal Hygiene
   a  Hand Washing
   b  Personnel Protective Equipment
3.1.5 Procedure for Entry into the Clean Room
3.1.6 Health Requirements
3.1.7 Qualification and Validation

3.2 PREMISES & EQUIPMENT
3.2.1 Principles
3.2.2 General Requirements
3.2.3 Cleaning Procedure for Clean Room & Equipment
3.2.4 Maintenance Procedure for Clean Rooms & Equipment

3.3 PRODUCTION
3.3.1 Principles
3.3.2 General Requirements
3.3.3 Pre-preparation
3.3.4 During Preparation
   3.3.4.1 Cleaning of LAF Cabinet / Isolator
   3.3.4.2 Aseptic Processing
3.3.5 Post-Admixing Procedure
   3.3.5.1 Cleaning
   3.3.5.2 Packaging & Labelling IV Admixture & Eye Preparation
   3.3.5.3 Disposal of IV Admixture & Eye Preparation Waste
   3.3.5.4 Storage
   3.3.5.5 Dispensing
   3.3.5.6 Rejected and Returned Materials and Products

3.4 QUALITY CONTROL
3.4.1 Principles
3.4.2 General Requirements
3.4.3 Sampling
3.4.4 Testing of Finished Products
3.4.5 Product Release
CHAPTER 3

STANDARD OPERATING PROCEDURE: IV ADMIXTURE & EYE PREPARATION

3.1 PERSONNEL

3.1.1 PRINCIPLES

There shall be sufficient and competent personnel to execute all the tasks. Personnel’s responsibilities shall be documented and clearly understood. All personnel shall be aware of the principles of Good Preparation Practice (GPP) and the system for quality assurance.

3.1.2 GENERAL REQUIREMENTS

RESPONSIBILITIES

a. Every personnel involved (Pharmacist, Provisionally Registered Pharmacist (PRP), Pharmacy Assistant, others) is to be responsible for the quality of all sterile preparations and adhere to GPP. Responsibilities of each personnel will depend on the duties and the requirement of the activities in the organisation. The responsibilities shall be put into the job function or description clearly.

b. New personnel shall be trained in all necessary areas according to the organisation. Training of new personnel shall be documented. Provisional Registered Pharmacist (PRP) and trainee dispenser shall be trained and supervised by pharmacist at all times.

3.1.3 TRAINING & CONTINUED EDUCATION

a. 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.

b. New personnel shall be adequately trained by pharmacist and assessed for competency. All training shall be documented.

c. Training for all personnel shall be provided on a continuous basis. All training shall be recorded.

d. Required training for new personnel are as in Checklist: Training Module of Personnel in Aseptic Unit (Appendix 1).

3.1.4 PERSONAL HYGIENE

a. Hand Washing

Before donning sterile gown, hand washing is done by practising the 7-step technique with appropriate disinfectant and clean water.
7-Step Technique:
  i. Scrub palm to palm
  ii. Right palm over left dorsum and left palm over right dorsum
  iii. Palm to palm fingers interlaced
  iv. Back of fingers to opposing palms with fingers interlocked
  v. Rotational rubbing of right thumb clasped in left palm and vice versa
  vi. Rotational rubbing, backwards and forwards with clasped fingers of right hand in left palm and vice versa
  vii. Rotational rubbing of right wrist and vice versa. Rinse and dry thoroughly

HAND WASHING TECHNIQUES

1. 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
b. Personnel Protective Equipment

Sterile garments shall be worn at all times when preparing IV admixture and eye preparation.

- Sterile Jumpsuit
  The fabric used shall be low-linting and have low electrostatic generating properties, sterilization compatible (gamma ray), lightweight, easy to wear, have minimum seams, loose fitting, close front, hooded and long sleeves with knit or elastic cuffs. Jumpsuits must be changed immediately when damaged or contaminated.

- Head Cover
  Head covering (e.g., bouffant cap) shall fit snugly around the head to contain hair and reduce contamination. It shall be made of disposable, low-linting material.

- Sterile Footwear
  Footwear or booties shall be made of low permeability fabric and long enough to cover ankle cuffs. The soles shall be made from a non-slip material.

- Sterile Gloves
  Choices of gloves shall be non-linting, long enough to cover wrist cuffs of the garment and powder free. Double gloving is recommended.

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

c. Gowning

  i. Remove make-up, jewellery and watch before gowning
  ii. Put on a “bouffant“ head cap, making sure that all hair is contained
  iii. Put on a face mask and make sure that no facial hair is exposed
  iv. Wash hands according to the ‘Seven - Step Hand Washing Technique’. Dry hands with electrical hand dryer
  v. Wear sterile powder-free gloves before gowning
  vi. Wear the hood on top of head cover (if the hood is a separate piece)
  vii. Wear jumpsuit; make sure that the jumpsuit does not touch the ground. Zip all the way to the top
  viii. Take a set of booties and place it over your feet
  ix. Wear gloves according to the gloving procedure (please refer to 4.2.7)
  x. Use the full-length mirror in the gowning room to ensure that all clean room apparel is worn correctly and properly fitted

d. Gloving

  i. Put on the right glove
  ii. Do not uncover the folded sleeve
  iii. Put on the left glove by inserting fingers of the right hand under the folded sleeve
  iv. Uncover the folded sleeve of the left glove with the fingers without touching the arm
  v. Fold back the folded sleeve on the right glove in the same way
3.1.5 PROCEDURES FOR ENTRY INTO THE CLEAN ROOM

a. Before entering the Clean Room:
   i. Remove accessories and make-up before entry
   ii. Wash hands and dry them with hand towel

b. Inside the Changing Room:
   i. Wear shoe cover and cross-over
   ii. Wear head cover and mask
   iii. Wash hands with appropriate disinfectants using proper hand washing techniques
   iv. Dry hands under electrical hand-dryer
   v. Enter the gowning room without touching the door handle

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

GLOVING TECHNIQUES

1. Pick up one glove with thumb and forefinger
2. Pull glove on hand
3. Slip partially gloved hand under cuff of second glove
4. Pull second glove over other hand and pull glove up to gowned wrist
5. Slip fingers of completely gloved hand under cuff of first hand, pull glove to gowned wrist
6. Gloving procedure completed
d. Entry into Grade B Clean Room:
   i. Follow steps as explained in a and b
   ii. Put on sterile non-powdered gloves
   iii. Enter gowned room without touching the door handle
   iv. Wear sterile garments (hood, jumpsuit and boots), minimizing contact with outer layer of the garments
   v. 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
   vi. Wear double sterile gloves according to gloving techniques with ends fastened over the sleeve cuffs

e. During Aseptic Compounding:
   i. Check periodically to ensure that garments are in good condition and the seams are sealed
   ii. Gloves shall be regularly disinfected during compounding operations

3.1.6 HEALTH REQUIREMENTS

Health assessment shall be carried out at least once a year to prevent possible product contamination to occur

3.1.6.1 Types of Health Assessment

i. Pre-placement Medical Examinations:
   • History (potential risk factors, occupational history)
   • HIV test, Hepatitis B, Tuberculosis
   • X-ray
   • Visual examination
   • Base line examination that includes Full Blood Count with white cell differential and biochemistry (Renal Profile, Liver Function Test and Electrolytes), physical observation (skin-related problem and neurological disorder, e.g., hand tremors)

ii. Periodic Medical Examinations:
   • HIV test, Hepatitis B, Tuberculosis
   • X-ray
   • Visual examination
   • Full Blood Count with white cell differential and biochemistry (Renal Profile, Liver Function Test and Electrolytes)

3.1.7 QUALIFICATION AND VALIDATION

a. All permanent personnel directly involved in the preparation of IV admixture and eye preparation shall be trained and qualified in aseptic technique

b. All permanent personnel directly involved in the preparation of IV admixture and eye preparation shall satisfy the following requirements:
   • Fulfill health requirements for recruitment as reviewed by physician
   • Undergone basic aseptic training
   • Assessed by Responsible Person
   • Performed and passed processing validation
   • Credentialing by Responsible Person
   • Revalidation shall be performed at least once a year
c. Every personnel involved in aseptic technique dispensing shall undergo validation test prior to working in the sterile unit. 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 PREMISE & EQUIPMENT

3.2.1 PRINCIPLES

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

3.2.2 GENERAL REQUIREMENTS

a. Premises and equipment shall be appropriately maintained and upgraded, ensuring that they are suitable for the intended activities and to minimize the risk of errors. There shall be appropriate workflow and segregation of activities.

b. 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.

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

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

e. Production, storage and quality control areas shall be accessible to authorized personnel only.

f. 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.

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

3.2.3 CLEANING PROCEDURE FOR CLEAN ROOM & EQUIPMENT

3.2.3.1 Responsibilities

a. The Responsible Person is responsible for all matters regarding cleaning of the clean room.

b. The Responsible Person could delegate the cleaning duties to any pharmacy personnel and/or any hospital personnel, provided the delegated personnel are trained.
c. The Responsible Person shall provide training to the cleaning personnel to enable the personnel to perform cleaning duties

d. The Responsible Person shall supervise the cleaning procedures done by the delegated personnel

3.2.3.2 Equipment/Materials

- Dedicated sterile low shedding mops (autoclavable)
- Dedicated bucket system (if required)
- Sterile low lint wipes
- Sterile disinfectant
- Sterile water
- Personal Protective Equipment (PPE)

3.2.3.3 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 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

3.2.3.4 Cleaning Procedures

a. Frequency of Cleaning

- Qualified Clean Room

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Equipment/Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before and after production</td>
<td>Biohazard Safety Cabinet (BSC)/Isolator</td>
</tr>
<tr>
<td>After production or daily</td>
<td>Stainless steel bench and trolley in preparation room</td>
</tr>
<tr>
<td></td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td>Weekly</td>
<td>Stainless steel bench and trolley</td>
</tr>
<tr>
<td></td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td></td>
<td>Walls and sinks</td>
</tr>
<tr>
<td></td>
<td>Gowning cabinet, changing room cabinet</td>
</tr>
<tr>
<td></td>
<td>Biohazard Safety Cabinet (BSC)/Isolator</td>
</tr>
<tr>
<td>Monthly</td>
<td>Stainless steel bench and trolley</td>
</tr>
<tr>
<td></td>
<td>Floor, window and door knobs</td>
</tr>
<tr>
<td></td>
<td>Pass box and clinical waste bins</td>
</tr>
<tr>
<td></td>
<td>Walls and sinks</td>
</tr>
<tr>
<td></td>
<td>Gowning cabinet, changing room cabinet</td>
</tr>
<tr>
<td></td>
<td>Ceilings</td>
</tr>
<tr>
<td></td>
<td>Biohazard Safety Cabinet (BSC)/Isolator</td>
</tr>
</tbody>
</table>
b. Procedures

- **Biohazard Safety Cabinet (BSC)**
  i. Wear PPE before entering the clean room
  ii. The cabinet shall be cleaned at the start and the end of each work session
  iii. Wipe all internal surfaces with sterile alcohol 70% before the start of each work session
  iv. The top surface of the cabinet shall be cleaned first, followed by the left and right side and lastly, the working bench
  v. 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 using overlapping strokes
  vi. All soiled wipes shall be thrown into the clinical waste bag
  vii. After the completion of aseptic preparation, clean the cabinet according to the above procedure using sterile alcohol 70%

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Equipment/Area</th>
</tr>
</thead>
</table>
| Before and after production | Biohazard Safety Cabinet (BSC)/Isolator  
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  
Biohazard Safety Cabinet (BSC)/Isolator  
Stainless steel bench and trolley |
| Monthly           | Floor, window and door knobs  
Pass box and clinical waste bins  
Walls and sinks  
Gowning cabinet, changing room cabinet  
Ceilings  
Biohazard Safety Cabinet (BSC)/Isolator |

- Non-Qualified Clean Room
  - Facility with daily production

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Equipment/Area</th>
</tr>
</thead>
</table>
| Before and after production | Biohazard Safety Cabinet (BSC)/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  
Biohazard Safety Cabinet (BSC)/Isolator |
| 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  
Biohazard Safety Cabinet (BSC)/Isolator  
Stainless steel bench and trolley |
| Monthly           | Floor, window and door knobs  
Pass box and clinical waste bins  
Walls and sinks  
Gowning cabinet, changing room cabinet  
Ceilings  
Biohazard Safety Cabinet (BSC)/Isolator |
• **Isolator**
  i. Wear PPE before entering the preparation room
  ii. The isolator shall be cleaned at the start and the end of each work session
  iii. Clean the external surfaces of the transfer chambers and front visor
  iv. Wipe all internal surfaces with sterile alcohol 70% before the start of each work session
  v. Clean the inner surfaces of both transfer chambers
  vi. Clean the back of the isolator, followed by the left and right side, the front visor, glove sleeves and lastly, the working bench. Use overlapping strokes to wipe
  vii. Discard all used wipes into the waste bin placed in the transfer chamber
  viii. After the completion of sterile preparation, clean the isolator according to the above procedure using sterilized water, followed by sterile alcohol 70%

• **Stainless steel bench, trolley in preparation room, door knobs and clinical waste bins**
  i. Wipe all equipment with low lint wipes and sterile alcohol 70%
  ii. Ensure that all hard-to-reach areas are covered during cleaning

• **Window**
  i. Clean from top to bottom with low lint wipes and sterile alcohol 70%
  ii. Ensure that all hard-to-reach areas are cleaned

• **Pass box**
  i. Clean the inner surface of the pass box before transferring materials and equipment into the pass box for the first time on that day.
  ii. 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%

• **Floors**
  i. Wipe (mop) the floor using appropriate disinfectant
  ii. Use overlapping strokes from the cleanest area to the dirtiest

• **Walls**
  i. Clean walls using low lint wipes or extendable mop with appropriate disinfectant (sterile alcohol 70%)
  ii. 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
  iii. Ensure that all hard-to-reach areas are cleaned

• **Ceilings**
  i. Clean ceilings using low lint wipes or extendable mop with appropriate disinfectant (sterile alcohol 70%) from the cleanest area to the dirtiest
  ii. Avoid contact with HEPA filters while cleaning
  iii. Ensure that all hard-to-reach areas are cleaned
3.2.3.5 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)

c. Disinfectants used shall be rotated every 6 months to prevent resistance

d. Disinfectants shall be diluted in the clean room and the expiry date must be labelled clearly

3.2.3.6 Storage of Cleaning Materials

a. All cleaning materials shall be stored in the utility room (for facility with utility room) or component preparation room (for facility without utility room)

3.2.3.7 Management of Used Cleaning Materials

a. All waste shall be disposed daily after each production

b. Reusable cleaning materials shall be rinsed and sterilized before next use

3.2.3.8 Cleaning Procedure under Special Circumstances

a. In the event of out of specification or serious problems such as Air Handling Unit (AHU) breakdown, high count of microbiological reading, or major renovation of clean room that jeopardizes the cleanliness of the room, thorough cleaning shall be done before any aseptic activity

b. Monitoring of clean room control parameters shall be done to ensure effectiveness of the thorough cleaning. Should the monitored control parameters exceed the permitted limit, another round of thorough cleaning shall be done followed by monitoring until the results are within specified limit

c. Minor renovation and/or maintenance activity that does not require shutting down the AHU unit shall be followed by a round of thorough cleaning before commencement of aseptic activity

d. Refer to Maintenance Procedure for Clean Room & Equipment for further details

3.2.3.9 Documentation

a. All cleaning done shall be recorded. The Responsible Person shall verify all the documentations

b. All records shall be maintained according to Hospital Documentation Procedure

c. List of Forms:
   Cleaning Forms (Appendix 2)
3.2.4 MAINTENANCE PROCEDURE FOR CLEAN ROOM & EQUIPMENTS

This procedure is applicable in the maintenance activity of both qualified and non-qualified IV Admixture clean rooms. However, for non-qualified clean room, this procedure shall be applied wherever possible.

3.2.4.1 Responsibilities

Pharmacist in-charge:
   a. Performing the environmental monitoring of the clean room and equipment during the preparation process
   b. Sending out settle plate and contact plate for testing
   c. Approving of environmental monitoring results by third party
   d. Analyzing, checking and verifying the monitoring and testing report
   e. Obtaining the accreditation status of third party (testing agent)

Hospital Support Services (HSS) and Third Party Testing Agent:
   a. Ensure that the third party testing agent have appropriate accreditation
   b. Execution of the test and data collection
   c. Submit the test report to person in-charge

3.2.4.2 Equipment/Materials

- Thermometer
- Hygrometer (for humidity)
- Pressure Gauge
- Settle Plates-TSA/SDA (90 mm)
- Contact Plate-TSA (55 mm)
- All relevant maintenance equipment used by Third Party Testing Agent and HSS

Note: All devices used in performing testing need to be calibrated

3.2.4.3 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:
   - PPM by HSS
   - PPM by Third Party Testing Agent
c. Physical Monitoring

For physical monitoring, the monitoring parameter and frequency are listed as below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Biohazard Safety Cabinet (BSC)/Isolator</th>
<th>Clean Room</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Temperature</td>
<td></td>
<td>a) Before preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Every day if no preparation</td>
</tr>
<tr>
<td>2. Humidity</td>
<td></td>
<td>a) Before preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Every day if no preparation</td>
</tr>
<tr>
<td>3. Air Pressure Differential</td>
<td></td>
<td>a) Before preparation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Every day if no preparation</td>
</tr>
<tr>
<td>4. Pressure Differential Across HEPA Filter</td>
<td>Before preparation</td>
<td></td>
</tr>
<tr>
<td>5. Isolator Glove Integrity</td>
<td></td>
<td>Once a week (if any)</td>
</tr>
</tbody>
</table>

- **Temperature and Humidity Monitoring**
  i. Record the temperature and humidity reading in the Temperature, Humidity and Air Pressure Differential Monitoring for Clean Room Form (Appendix 3)
  ii. Check, analyse and verify the records
  iii. For deviation from specification, please refer to 3.2.4.4 and also 1.3 under Chapter 1

- **Air Pressure Differential Monitoring**
  i. Record the air pressure differential reading in the Temperature, Humidity and Air Pressure Differential Monitoring for Clean Room Form (Appendix 3)
  ii. Check, analyse and verify the records
  iii. For deviation from specification, please refer to 3.2.4.4 and also 1.3 under Chapter 1
d. Microbiological Monitoring

For microbiological monitoring, the monitoring parameter and frequency are listed as below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Biohazard Safety Cabinet (BSC)/Isolator</th>
<th>Clean Room</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Settle plate (90mm diameter)</td>
<td>a) Every working session b) After major breakdown or After major maintenance</td>
<td>a) Once a week during preparation b) After major breakdown or After major maintenance</td>
</tr>
<tr>
<td>2. Surface sample test (Contact plate/ Swab test) (55 mm diameter)</td>
<td>a) Once a week</td>
<td>a) Once a month b) After major breakdown or After major maintenance</td>
</tr>
<tr>
<td>3. Personnel monitoring - glove finger dabs</td>
<td>a) At the end of each working session</td>
<td></td>
</tr>
<tr>
<td>4. Active air samples</td>
<td>a) Every 3 months b) After major breakdown or After major maintenance</td>
<td>a) Every 3 months b) After major breakdown or After major maintenance</td>
</tr>
</tbody>
</table>

Note: All the parameters mentioned above shall be monitored during in-operation.
Procedure for microbial monitoring is as follows:

<table>
<thead>
<tr>
<th>(A) Settle Plate Microbiological Environment (TSA and SDA)</th>
<th>(B) Contact Plate Microbial Surface (55mm diameter)</th>
<th>(C) Swab Test Microbial Surface</th>
<th>(D) Glove Finger Dabs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place the settle plates. Remove the cover of the settle plate and place next to it. Expose the agar for several hours. Do not leave the settle plate open for more than 4 hours</td>
<td>Press the contact plate agar onto the surface of the dedicated location</td>
<td>Swab the surface at the intended location</td>
<td>Operator need to press firmly on the respective settle plate</td>
</tr>
<tr>
<td>Record the time when the settle plates are opened and closed</td>
<td>Use IPA (isopropyl alcohol) to thoroughly wipe the stains of agar from the surface</td>
<td>Place the swab back into the tube</td>
<td>-</td>
</tr>
</tbody>
</table>

Replace the plates’ or tubes’ covers and seal them with laboratory parafilm

<table>
<thead>
<tr>
<th>Obtain plates or swab kit</th>
<th>Label plates or tubes</th>
</tr>
</thead>
</table>

Send the plates or tubes to the laboratory immediately

<table>
<thead>
<tr>
<th>Incubate as follows: TSA plates - 48hrs at 30 - 35˚C (for bacteria)</th>
<th>Incubate as follows: TSA plates - 48hrs at 30 - 35˚C (for bacteria)</th>
<th>For bacterial colony culture</th>
<th>Incubate as follows: TSA plates - 48hrs at 30 - 35˚C (for bacteria) SDA plates - 5 days at 20 - 25˚C (for yeasts and mould)</th>
</tr>
</thead>
</table>

Record, analyse, check and verify the records

For deviation from specification, please refer to 3.6.3.4 and also 1.3 in Chapter 1
e. PPM by Hospital Support Services (HSS) or Third Party Testing Agent
   i. Obtain the PPM schedule from HSS and make appropriate
      arrangement to facilitate maintenance activities. These would
      include:
      • Washing / changing of primary and secondary filter
      • Calibration of pressure gauges, thermometer and hygrometer
      • Testing by third party agent on clean room and major
        equipment

PPM by Third Party Testing Agent are listed as below:

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

Note: All the parameters mentioned above shall be monitored during at-rest.
ii. Ensure that all Third Party Testing Agents involved in maintenance adhere to proper hand washing and gowning procedures before entering the clean room (if required)

iii. Before testing is done, the following need to be checked:
   - Check the accreditation status of the Third Party Testing Agent
   - Check the equipment calibration status
   - Confirm and verify the list of testing parameters that need to be carried out by Third Party Testing Agent

iv. Obtain the testing report from the Third Party Testing Agent
v. Analyse, check and verify the testing report
vi. For deviation from specification, please refer to 3.2.4.4 and also 1.3 in Chapter 1

3.2.4.4 Action to be taken if there is deviation from specification

a. In the event of out of specification or serious problems such as Air Handling Unit (AHU) breakdown, high count of microbiological reading, or major renovation of clean room that jeopardizes the cleanliness of the room, the following actions shall be taken:
   i. Inform immediately HSS or Third Party Testing Agent for further action
   ii. Perform investigation immediately and take corrective action

3.2.4.5 Documentation

a. All records and reports shall be maintained according to Hospital Documentation Procedure
b. List of Forms and Specifications:
   - Temperature, Humidity and Air Pressure Differential Monitoring For Clean Room (Appendix 3)
   - Particle Count Limit, Microbial Limit & Temperature, Humidity and Air Pressure Differential Limit (Appendix 4)

3.3 PRODUCTION

3.3.1 PRINCIPLES

Production operations shall guarantee the required quality, and be performed and supervised by competent people

3.3.2 GENERAL REQUIREMENTS

a. Production shall be performed by trained personnel. Products and materials shall be protected from microbial and other contamination at all times through swabbing of materials prior to use and strict adherence to aseptic technique
b. Appropriate flow of materials, segregation and adequate line clearance shall be practised to prevent accidental cross-contamination or mix-up of preparations
c. Only sterile materials shall be taken into Grade A and B areas
3.3.3 PRE-PREPARATION

a. Before entering the clean room, pharmacist shall ensure that:
   - Worksheets and labels are done and counterchecked
   - Starting materials are gathered and counterchecked
   - Worksheets and labels are brought in plastic covers
   - Starting materials are sprayed and swabbed with alcohol 70% when put into pass box or air lock.

3.3.4 DURING PREPARATION

3.3.4.1 Cleaning of Cabinet / Isolator

i. The Biohazard Safety Cabinet/ Isolator shall be left running for a minimum of 20-30 minutes
ii. BSC Cabinet/ Isolator shall be cleaned prior to commencement of production, using sterile alcohol with caution to prevent spraying directly into the HEPA filter

3.3.4.2 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. For antibiotic preparations, a BSC Cabinet is recommended to be used and for other preparations, a horizontal LAF Cabinet is sufficient

c. For preparations using horizontal LAF Cabinet, 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 zig-zag arrangement to allow filtered air to pass through

d. Withdrawal of Solution from Ampoule
   - Cleaning and Preparation of Ampoule
     i. Make sure that the ampoule and contents of the ampoule are in good condition, i.e., intact, not expired, clear and no foreign particles
     ii. 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
     iii. With the ampoule in upright position, ensure that no more solution or bubble is trapped at the ampoule neck

   - Fixing Needle to Syringe
     i. Half unwrap the syringe pack and the needle pack
     ii. Hold both the needle and the syringe in one hand
     iii. Fix the syringe to needle with special precaution not to touch the critical sites
     iv. Put the syringe and needle aside to be used later
• Breaking the Ampoule
  i. Swab the neck of the ampoule with alcohol 70%
  ii. Snap the ampoule neck by pulling it slightly towards self and pull it upward
  iii. Discard the ampoule neck immediately into the sharps bin

• Withdrawing Solution from Ampoule
  i. Insert the needle into the ampoule cautiously, avoiding contact between the needle and the ampoule neck. Position the needle in the shoulder area of the ampoule so that the bevel tip is facing downwards
  ii. Hold the ampoule in one hand and syringe in the other. Pull the plunger back with the thumb and index finger to withdraw the required volume of drug solution into the syringe using the 'non touch' technique
  iii. Remove air from the syringe and measure the volume of the contents withdrawn

e. Adding Diluent to a Vial Containing Powder
  i. Place the vial on the bench. Swab the rubber bung with alcohol 70%
  ii. 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
  iii. Push the needle down and at the same time, pierce the needle through the rubber bung
  iv. Push the plunger down slowly until the entire diluent is transferred into the vial
  v. Pull the plunger to its initial position. This will ensure that there is no pressure difference within and outside the vial
  vi. Pull the needle slowly out of the rubber and discard the needle into the sharps bin
  vii. Let the vial stand and swirl for a few minutes in order to dissolve the powder

f. Withdrawing Drug Solution from a Vial
  i. Swab the rubber bung with alcohol 70%
  ii. Pull in the required volume of air into the syringe
  iii. Place the vial upright in a vertical position and hold firmly
  iv. 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
  v. Push the needle down and at the same time, pierce the needle through the rubber bung
  vi. Invert the whole set with the vial on top of the syringe
  vii. 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 the syringe
  viii. Place the vial on the working cabinet bench top and pull out the needle from the vial
  ix. Remove air bubbles and adjust to the required volume

g. Procedure of Drug Reconstitution in IV drips.
  i. Remove caps of drip bottles and swab the rubber bungs with sterile alcohol 70%
  ii. A needle with 0.2 µm filter is fix at the injection port of IV drip bottle
  iii. Draw out the volume of drug required from vial or ampoule
  iv. Inject the drug into the drips bottle through the filter
v. Remove syringe, filter and needle at the injection port
vi. Swab the rubber bungs with alcohol and seal
vii. Label the drip bottle

i. Procedure for Intravenous Admixture
i. Remove caps of drip bottles and swab the rubber bungs with alcohol 70%
ii. Insert a mini spike filter 0.45 µm into injection port of the drips
iii. Break the ampoule required and withdraw the solution from ampoule by using syringe attached to glass filter (5 µm meter)
iv. Transfer the solution to a sterile ‘gallipot’/ syringe
v. Repeat procedures (iii) - (v) until all the solution has been taken out
vi. By using a new syringe (30 ml), withdraw all the solution from the ‘gallipot’/syringe
vii. Transfer the volume required into another new syringe by using a fluid connector with 0.2 µm filter
viii. Attach the syringe already filled with analgesic solution to mini spike of the drips and top up volume in the syringe to meet the total volume of the product
ix. Mix the solution until homogenous and make sure that no air bubble is trapped in the syringe
x. Close the syringe with stopper
xi. Label the syringe
xii. Repeat procedures from (viii) - (xii)

j. Procedure for Eye Drop Preparation
i. Remove caps of drip bottles and swab the rubber bungs with alcohol 70%
ii. Insert a mini spike filter 0.45 micron meter into injection port of the drips
iii. Remove cap of antibiotic vial and swab the rubber bung with alcohol 70%
iv. Draw out the volume of solution required with syringe through mini spike from drips
v. Inject the volume withdrawn from drip into antibiotic vial and dissolve it
vi. Let the vial stand and swirl for a few minutes to dissolve the powder
vii. Draw out the antibiotic solution from the antibiotic vial itself by using a syringe
viii. Attach the syringe filled with antibiotic solution to filter 0.2 micron meter
ix. Transfer the antibiotic solution into each of the eye drop bottles
x. Close the eye drop bottles with inserts and caps tightly
xi. Label the eye drop bottles

3.3.5 POST-ADMIXING PROCEDURE

3.3.5.1 Cleaning
i. Remove all broken ampoules, needles and syringes from working bench and floor, and dispose them into a sharps bin
ii. Spread water for injection liberally on the bench and wipe with wipers until dry
iii. Start swabbing the BSC as detailed in the cleaning procedure
3.3.5.2 Packaging & Labeling of IV Admixture & Eye Preparation

a. The packaging material used for IV admixture and eye preparation shall allow an antimicrobial treatment and sufficient protection against external influences and possible contamination.

b. Labels shall include:
   - Product name
   - Final volume
   - Content and amount
   - Batch number (if required)
   - Date of preparation
   - Expiry date

3.3.5.3 Disposal of IV Admixture & Eye Preparation Waste

a. Materials that have been used in the preparation and administration of IV admixture & eye preparation may present a source of injury to personnel not involved in the preparation and administration if the disposal is not properly handled.

b. Containers used for disposal of IV admixture & eye preparation 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.

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

3.3.5.4 Storage

a. All IV admixture and eye preparation shall be stored in refrigerator (2-8°C)

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 unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas shall be assigned for their temporary storage until the decision on their future use has been taken.
3.3.5.5 Dispensing
   a. Countercheck to ensure that all labels are complete with the patient’s particulars

   b. To ensure that IV admixture and eye preparation are transported in a manner that does not adversely affect their quality, IV admixture and eye preparation 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

3.3.5.6 Rejected and returned Materials and Products
   - Rejected products
     a. Rejected materials and products shall be marked as such and stored in separate areas
   - Returned products
     a. Dispensed products that was returned and had left the control of the preparation establishment shall be destroyed

   b. Where any doubt arises over the quality of the product, it shall not be considered suitable for re-issue or re-use. Any action taken shall be appropriately recorded

   c. For deviation from specification of final product, please refer to Chapter 1

3.4 QUALITY CONTROL

3.4.1 PRINCIPLES

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

3.4.2 GENERAL REQUIREMENTS

   a. Testing equipment shall be suitable for its intended use

   b. 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

3.4.3 SAMPLING

   a. Samples taken for analysis shall be representative of the material being tested

   b. Samples shall be taken from the final container of the preparation prior to sealing of infusion port
3.4.4 TESTING OF FINISHED PRODUCTS

a. 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.

b. No quality control testing is necessary for extemporaneously prepared products.

c. 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.

3.4.5 PRODUCT RELEASE

a. The Responsible Person is ultimately responsible for the quality of the products prepared and released. The actual release can be delegated to another appropriately competent person (i.e., Releasing Officer).

b. Product release shall include verification that the products comply with the valid specifications and that they have been prepared in accordance with valid procedures and the principles of Good Preparation Practice.
CHAPTER 4

WORK CONTRACTED OUT

4.1 PRINCIPLES

a. 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. Such services, which often are contracted out to another department or organisation, may include:
   - maintenance of the air handling system, water systems or other utility systems
   - maintenance of key equipment such as isolators, laminar air flow cabinets, sterilisers, 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

b. 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

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

4.2 GENERAL REQUIREMENTS

a. 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

b. 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

4.3 CONTRACT GIVER

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

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

c. 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
4.4 CONTRACT ACCEPTOR
   a. Any work shall be performed in accordance with the contract
   b. Any service or results not complying with the required specification shall be notified to the Responsible Person of the contract giver
   c. 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

4.5 SHARING OF FACILITIES
   a. 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 party, to prevent conflicts and misunderstandings
   b. The mutual agreement shall be in the form of a written technical agreement, authorized and signed by the Responsible Person of both parties

4.6 PREPARING FOR OTHER USERS
   a. It is the responsibility of the service provider to establish the rules and regulations pertaining to the acquisition of the services by the users
   b. The users shall specify the level of services required and shall comply with requirements from the service provider
   c. The mutual agreement shall be in the form of a written technical agreement, authorized and signed by the Responsible Person of both parties
CHAPTER 5

COMPLAINTS & PRODUCT RECALLS

5.1 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.

5.2 QUALITY PROBLEMS

a. 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.

b. 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.

5.3 RECALLS

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

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

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

d. 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.

5.4 DISPOSAL OF RETURNED/RECALLED PRODUCTS

a. 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.

b. 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 6

SELF AUDITS

6.1 PRINCIPLES

a. The quality assurance system, including personnel matters, premises, equipment, documentation, production, quality control, 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 Good Preparation Practice.

b. 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.

c. Self audits shall be conducted in an independent and detailed way by designated competent people.
CHAPTER 7

SAFETY

7.1 PRINCIPLES

a. Fire safety and needle-prick injury procedures as stipulated in this manual are applicable to all aseptic services

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

c. The management of extravasated cytotoxic drugs also needs to be focused on. The degree of damage caused by extravasation is in relation to the amount of drug extravasated and the speed at which it is recognised

7.2 FIRE SAFETY

a. In the event of fire occurring outside the clean room, the following procedure could be adopted:
   i. Received notification of fire
   ii. Remain calm
   iii. Stop all current activities
   iv. Press the emergency button (for CDR clean rooms)
   v. Degown (if possible)
   vi. Leave the clean room
   vii. Run to the nearest emergency exit, according to hospital Fire & Safety policy

b. If the fire occurs in the clean room:
   i. Remain calm
   ii. Stop all current activities
   iii. Press the emergency button (for CDR clean rooms)
   iv. Leave the clean room immediately
   v. Shout “Fire” three times
   vi. Degown (if possible)
   vii. Run to the nearest emergency exit, according to hospital Fire & Safety policy

7.3 NEEDLE PRICK INJURY

Needle-prick injury is defined as the accidental puncture of the skin by a needle during a medical intervention

a. 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

7.4 CYTOTOXIC SPILL MANAGEMENT

7.4.1 Materials
- Content of Spill Kit (Appendix 5)
- Flow Chart on the Management of Spill (Appendix 6)
- Spillage Reporting Form (Appendix 7)
- Incident Reporting Form (Appendix 9)

7.4.2 Procedure
a. Within the cabinet
   i. Ensure that the cabinet remains operating
   ii. For liquid spill, use absorbent pads and dispose them into the sharp bin
   iii. For powder spill, use gauze (wet with water) and dispose them into the sharps bin
   iv. Any broken glass fragments shall be disposed in sharps bin
   v. Wipe the entire area using gauze wetted with alkaline solution (Decon 90) for several times
   vi. Wipe several times with sterile water
   vii. Swab with alcohol 70%
   viii. Discard all contaminated items into the cytotoxic waste bin
   ix. Fill the spillage reporting form and send it to the pharmacist in-charge.
       This form is to replenish the used spill kit
   Note: If chemo preparation mat is used, then skip steps ii) - v). Wrap up mat together with spilled contents and discard into the cytotoxic waste bin

b. Outside the cabinet, in the clean room
   Once spill occur,
   i. Halt all ventilations in the area by pushing the emergency button
   ii. Open a spill kit available in the unit:
   iii. Contain the spill area with absorbent pads/gauze
       a. Absorb liquid spill with gauze / absorbent pads
       b. Absorb powder spill with wet gauze
   iv. Any broken glass fragments shall be scooped using brush and dustpan and disposed in sharp bin. Discard used brush and dustpan in cytotoxic waste bag
   v. Wipe the entire area using lint-free wipes wetted with strong alkaline solution (e.g., Decon 90) several times
   vi. Wipe several times with sterile water until clean followed by alcohol 70%
   vii. Discard contaminated items (e.g., lint-free wipes, first layer of glove) in the cytotoxic waste bag
   viii. Tie the cytotoxic waste bag and put into a second bag
   ix. Degown and dispose of garment according to procedure
   x. Wash hands thoroughly with soap and water
   xi. Fill the spillage reporting form and send it to the pharmacist in-charge
   xii. Ensure that the spill kit is replenished and maintained
c. Outside the clean room
   Once spill occur,
   Open a spill kit available in the unit
   i. Place a caution sign at the incident area
   ii. Wear the respirator mask first and other appropriate PPE provided in
       the spill kit
   iii. Contain the spill area with absorbent pads / gauze
       c. Absorb liquid spill with gauze / absorbent pads
       d. Absorb powder spill with wet gauze
   iv. Any broken glass fragments shall be scooped using brush and dustpan
       and disposed in sharp bin. Discard used brush and dustpan in cytotoxic
       waste bag
   v. Wipe the entire area using gauze wetted with strong alkaline solution
       (e.g., Decon 90) several times
   vi. Wipe several times with water until clean
   vii. Discard contaminated items (e.g., gauze, first layer of glove) in the
       cytotoxic waste bag
   viii. Tie the cytotoxic waste bag and put into a second bag
   ix.  Put the respirator, gown, shoe cover and glove into the cytotoxic waste
        bag
   x.  Tie the cytotoxic bag and put into a non-disposable cytotoxic bin
   xi. Wash hands thoroughly with soap and water
   xii. Fill the spillage reporting form and send it to the pharmacist in-charge
   xiii. Ensure that the spill kit is replenished and maintained

   Note: In cases of large spills (more than 5 ml), extra precautions shall be taken:
   · Isolate the area to prevent further contamination
   · Halt all ventilations in the area (e.g., fan, air-conditioning)

e. Contamination of Personnel
   In the event that staff becomes contaminated with a cytotoxic agent, the
   following procedure shall be followed:
   i. All overtly contaminated protective clothing shall be removed and
      placed in the cytotoxic waste container
   ii. All contaminated clothing shall be removed and if heavily contaminated,
      shall be discarded into the cytotoxic waste container. Clothing with
      minimal amount of contamination shall be laundered separately and
      rinsed well
   iii. An emergency shower shall be used if appropriate. If this is not
      available, then the contaminated area of skin shall be washed with soap
      and rinsed with large amounts of water
   iv. Affected eyes shall be thoroughly irrigated with water or sodium
      chloride 0.9% for at least 15 minutes
   v. For needle prick injury, blood shall be squeezed from the injured finger
   vi. Medical advice shall be obtained soon after
   vii. Incident Reporting Form shall be filled and sent to the quality assurance
      unit for further management

7.5 EXTRAVASATION

7.5.1 Procedure

   i. Stop injection/infusion immediately, but do not remove the cannula
   ii. Aspirate slowly 3 to 5ml of blood through the cannula by using a new
       syringe to remove as much of the cytotoxic drug as possible
iii. Remove the cannula. Avoid applying pressure to the extravasated site
iv. Administer appropriate antidote (if available) for the specific cytotoxic
drug that extravasated - refer to the Guidelines on the Management of
Extravasation (Appendix 8)
v. Apply warm or cold compresses (15-20 minutes per compression, four
times a day for 2 to 3 days) as appropriate for the specific drug used
vi. Apply steroid cream (Hydrocortisone 1% cream or betamethasone
1:10 or similar) twice a day until the erythema subsides
vii. Elevate the arm
viii. Notify the responsible physician of the occurrence and discuss the need
for further intervention
ix. Inform and instruct the patient and relatives appropriately
x. Regular control (aftercare). Refer to the Guidelines on the Management
of Extravasation (Appendix 8)
Appendices

Appendix 1

CHECKLIST: TRAINING MODULE OF PERSONNEL IN ASEPTIC UNIT

Name:

<table>
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<th>No.</th>
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<th>Assessed by</th>
<th>Date</th>
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<td>Basic microbiology</td>
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<td>2.</td>
<td>Principles of clean room</td>
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<td>3.</td>
<td>Aseptic technique</td>
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<td>Gloving</td>
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<td>7.</td>
<td>Gowning and/or de-gowning</td>
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<td>Spill management (if required)</td>
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## Appendix 2

### CLEANING FORM

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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Expiry Date:</td>
<td></td>
</tr>
<tr>
<td>(c) Ceiling (Monthly)</td>
<td>Cleaner:</td>
<td>Checked by:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix 3

### FORM FOR MONITORING OF CLEAN ROOM TEMPERATURE, HUMIDITY AND AIR PRESSURE DIFFERENTIAL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Limit</th>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>20 ± 2°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RH (%)</td>
<td>55 ± 5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparation Room to -ve Airlock / Gowning Room</td>
<td>10 - 15 Pa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gowning to Change Room</td>
<td>10 - 15 Pa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compartment to Change Room</td>
<td>10 - 15 Pa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change Room to Outside</td>
<td>10 - 15 Pa</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Done by: __________________________  Reviewed By: ________________________  Date: ____________

Verified By: ______________________  Date: ____________

Periodically Comments: __________________________
Appendix 4

LIMITS FOR CLEAN ROOM CONTROL PARAMETERS

a) Particle Count Limit

<table>
<thead>
<tr>
<th>Grade</th>
<th>At Rest</th>
<th>In Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 0.5µm</td>
<td>&gt; 0.5µm</td>
</tr>
<tr>
<td>A</td>
<td>3,520</td>
<td>20</td>
</tr>
<tr>
<td>B</td>
<td>3,520</td>
<td>20</td>
</tr>
<tr>
<td>C</td>
<td>352,000</td>
<td>2,900</td>
</tr>
<tr>
<td>D</td>
<td>3,520,000</td>
<td>29,000</td>
</tr>
</tbody>
</table>

b) Microbial Limit

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommended limits for microbial contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Air sample (cfu/m³)</td>
</tr>
<tr>
<td>A</td>
<td>&lt;1</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
</tr>
<tr>
<td>C</td>
<td>100</td>
</tr>
<tr>
<td>D</td>
<td>200</td>
</tr>
</tbody>
</table>

c) Temperature, Humidity and Air Pressure Differential Limit:

- Non-CDR [Parenteral Nutrition (PN), IV Admixture & Eye Drops]:

<table>
<thead>
<tr>
<th>Room</th>
<th>Temperature (°C)</th>
<th>RH (%)</th>
<th>Adjacent Room</th>
<th>Differential Pressure (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation</td>
<td>20 ± 2</td>
<td>55 ± 5</td>
<td>Gowning</td>
<td>+ (10 – 15)</td>
</tr>
<tr>
<td>Comp. Preparation</td>
<td>20 ± 2</td>
<td>55 ± 5</td>
<td>Changing</td>
<td>+ (10 – 15)</td>
</tr>
<tr>
<td>Gowning</td>
<td>20 ± 2</td>
<td>55 ± 5</td>
<td>Changing</td>
<td>+ (10 – 15)</td>
</tr>
<tr>
<td>Changing</td>
<td>20 ± 2</td>
<td>55 ± 5</td>
<td>Outside</td>
<td>+ (10 – 15)</td>
</tr>
</tbody>
</table>

- CDR:

<table>
<thead>
<tr>
<th>Room</th>
<th>Temperature (°C)</th>
<th>RH (%)</th>
<th>Adjacent Room</th>
<th>Differential Pressure (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR Preparation</td>
<td>20 ± 2</td>
<td>55 ± 5</td>
<td>-ve Airlock</td>
<td>+ (10 – 15)</td>
</tr>
<tr>
<td>-ve Airlock</td>
<td>20 ± 2</td>
<td>55 ± 5</td>
<td>Gowning</td>
<td>- (10 – 15)</td>
</tr>
<tr>
<td>Comp. Preparation</td>
<td>20 ± 2</td>
<td>55 ± 5</td>
<td>Changing</td>
<td>+ (10 – 15)</td>
</tr>
<tr>
<td>Gowning</td>
<td>20 ± 2</td>
<td>55 ± 5</td>
<td>Changing</td>
<td>+ (10 – 15)</td>
</tr>
<tr>
<td>Changing</td>
<td>20 ± 2</td>
<td>55 ± 5</td>
<td>Outside</td>
<td>+ (10 – 15)</td>
</tr>
</tbody>
</table>
## Appendix 5

### CONTENT OF SPILL KIT

<table>
<thead>
<tr>
<th>No.</th>
<th>Content of Spill Kit</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Disposable Gown</td>
<td>1 piece</td>
</tr>
<tr>
<td>2.</td>
<td>Surgical Glove</td>
<td>1 pair</td>
</tr>
<tr>
<td>3.</td>
<td>Chemo Glove</td>
<td>1 pair</td>
</tr>
<tr>
<td>4.</td>
<td>Shoe Cover</td>
<td>1 pair</td>
</tr>
<tr>
<td>5.</td>
<td>Respirator Mask N95</td>
<td>1 piece</td>
</tr>
<tr>
<td>6.</td>
<td>Sharp Container</td>
<td>1 bin</td>
</tr>
<tr>
<td>7.</td>
<td>Brush and Dustpan</td>
<td>1 set</td>
</tr>
<tr>
<td>8.</td>
<td>Cytotoxic Waste Bag</td>
<td>2 piece</td>
</tr>
<tr>
<td>9.</td>
<td>Gauze and Absorbent Pads</td>
<td>10 pieces each</td>
</tr>
<tr>
<td>10.</td>
<td>Decon 90</td>
<td>120ml</td>
</tr>
<tr>
<td>11.</td>
<td>Water</td>
<td>500ml</td>
</tr>
<tr>
<td>12.</td>
<td>Spill Handling Procedure</td>
<td>1</td>
</tr>
<tr>
<td>13.</td>
<td>Spill Reporting Form</td>
<td>1</td>
</tr>
<tr>
<td>14.</td>
<td>Caution Sign</td>
<td>1 piece</td>
</tr>
</tbody>
</table>
Appendix 6

FLOW CHART ON THE MANAGEMENT OF CYTOTOXIC SPILL

1. Spill Kit
2. Place a caution sign at the incident area
3. Place a caution sign at the incident area
4. Absorb liquid spill with gauze / absorbent pads
5. Absorb powder spill with wet gauze
6. Any broken glass fragments should be picked up using a brush and dustpan and placed in sharp bin
7. Wipe the entire area with alkaline solution (Decon 90 - 3 times) and rewipe with water (3 times)
8. Swab with alcohol 70% (only in clean room and cytotoxic drug safety cabinet)
9. Discard contaminated items (e.g. gauze, first layer of glove) into cytotoxic waste bag
10. Tie the cytotoxic waste bag and put into a second bag
11. Remove and discard respirator mask, gown, shoe cover and second layer of glove into the cytotoxic waste bag
12. Tie the cytotoxic waste bag and place inside a non disposable cytotoxic waste bin
13. Wash hands thoroughly with soap and water
14. Fill in the spillage reporting form and submit to the pharmacist in charge
15. Ensure that the spill kit is replenished and maintained
Appendix 7

**SPILLAGE REPORTING FORM**

Return to Pharmacy on day of incident

<table>
<thead>
<tr>
<th>Drug involved</th>
<th>Ward/Clinic/area</th>
</tr>
</thead>
</table>

**What form was drug supplied in?**

- liquid - vial/ampoule
- dry powder - vial/ampoule
- syringe
- plastic bag

<table>
<thead>
<tr>
<th>Drug involved</th>
<th>Ward/Clinic/area</th>
</tr>
</thead>
<tbody>
<tr>
<td>vol/amp of drug supplied</td>
<td>vol/amp of drug supplied</td>
</tr>
</tbody>
</table>

**Date:**

**Time of incident:**

**Cause of spill**

- Container supplied leaking
- Container dropped
- Container faulty
- Container pierced
- IV line disconnected
- Pump problem
- Other (describe) ............................

<table>
<thead>
<tr>
<th>Cause of spill</th>
<th>Location of incident</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient area</td>
</tr>
<tr>
<td></td>
<td>Corridor</td>
</tr>
<tr>
<td></td>
<td>Nursing staff/area</td>
</tr>
<tr>
<td></td>
<td>Pharmacy area</td>
</tr>
<tr>
<td></td>
<td>Other ..................</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Description of incident - what happened? To whom? Any precipitating cause?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**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 8

### Guidelines on the Management of Extravasation

<table>
<thead>
<tr>
<th>Cytotoxic Drugs</th>
<th>Types of Damage</th>
<th>Pharmacological Antidote</th>
<th>Non-pharmacological antidotes</th>
<th>Methods of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Vesicant at a concentration ≥ 0.5mg/ml</td>
<td>Inj. Sodium Thiosulphate</td>
<td>None</td>
<td>Administer as above. Use 2ml 10% Na thiosulphate solution for each 100mg cisplatin</td>
</tr>
<tr>
<td>Doxorubicin, Daunorubicin, Mitomycin, Epirubicin, Idarubicin</td>
<td>Vesicant</td>
<td>Topical Solution Dimethyl Sulfoxide (DMSO)</td>
<td>Cold compresses</td>
<td>Apply cold pad with circulating ice water, ice pack, or cryogel pack for 15-20 minutes at least 4 times daily for first 24-48 hours. Some research studies suggest benefit of 99% dimethyl sulfoxide (DMSO) 1-2 ml applied to the site every 6 hour. Allow air dry and continue for a minimum of 7 days</td>
</tr>
<tr>
<td>Vincristine, vinblastine, vinorelbine</td>
<td>Vesicant</td>
<td>SC Hyaluronidase</td>
<td>Warm compresses</td>
<td>Apply heat for 15-20 minutes at least 4 times daily for first 24-48 hours. In clinical practice, 1500 IU of hyaluronidase reconstituted with 2 ml WFI or 0.9% N/S. Administer (0.2-0.4ml) SC or intradermal injections around the circumference of the extravasation</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Irritant</td>
<td>None</td>
<td>Warm compresses</td>
<td>Treatment necessary only if large amount of concentrated solution extravasates</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Irritant</td>
<td>None</td>
<td>Cold compresses</td>
<td>Apply ice pack for 15-20 minutes at least 4 times daily for first 24 hours</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Irritant</td>
<td>None</td>
<td>Warm compresses</td>
<td>Apply warm pack for 15-20 minutes at least 4 times daily for 24-48 hours after extravasation</td>
</tr>
<tr>
<td>Mechlorethamine HCl (nitrogen mustard)</td>
<td>Irritant</td>
<td>Inj Sodium Thiosulphate</td>
<td>None</td>
<td>Prepare 1/6 M solution: If 10% Na thiosulphate solution. Through existing IV line, inject 4ml with 6ml water for injection (WFI) or if 25% Na thiosulphate, mix 1.6ml of Na thiosulphate with 8.4ml WFI. Inject SC if needle is removed. Use 2ml antidote for every 1mg drug extravasated</td>
</tr>
</tbody>
</table>
### Appendix 9

## INCIDENT REPORTING FORM

<table>
<thead>
<tr>
<th>Patient’s Name:</th>
<th>MRN:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: Sex: Room No.:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Episode No.: Date:</th>
</tr>
</thead>
</table>

**Hospital Incident Report:**

Note: A hospital incident is any happening that is not consistent with the routine operation of the hospital and is reported by the staff. The Hospital Incident Report is generated immediately or before the end of a shift and forwarded to the unit head/ward supervisor.

### SECTION A: To completed by person involved

<table>
<thead>
<tr>
<th>Name of person</th>
<th>Department</th>
</tr>
</thead>
</table>

#### GENERAL

**Type of Incident**
- [ ] Patient related
- [ ] Staff related
- [ ] Non-patient related e.g. visitor
- [ ] Medical staff related
- [ ] Security related
- [ ] Others (specify) __________________

**Incident happened at**
- [ ] Ward (specify) __________________
- [ ] In Bathroom
- [ ] MDC Clinic
- [ ] Hospital Ground
- [ ] Operating Room
- [ ] Others (specify) __________________

#### A. CLINICAL REPORT

**1.1 For Use In All Locations**

- [ ] Medication Error
- [ ] Adverse drug/blood reaction
- [ ] Transfusion error
- [ ] Adverse outcome of procedure
- [ ] Discharge against medical advice (AOR discharge)
- [ ] Equipment related incident
- [ ] Fall or accident
- [ ] Radiology/laboratory error
- [ ] Needle stick injury

**1.2 For Use In Operation Rooms**

- [ ] Cardiac/respiratory arrest
- [ ] Wrong procedure performed
- [ ] Wrong patient operated upon
- [ ] Unplanned return to the OT within 24 hrs of surgery
- [ ] Prolonged stay in recovery room for more than 2 hrs
- [ ] Operative consent error
- [ ] Incorrect instrument or swab count
- [ ] Elective surgery cancelled in OT
- [ ] Preoperative orders not carried out
- [ ] Reintubation

**1.3 For Use In ICU/CCU/NICU**

- [ ] Accident extubation
- [ ] Dislodgement of catheter
- [ ] Readmission to ICU within 24 hours of discharge to ward
- [ ] Unexpected death
- [ ] Complication during stay in ICU
- [ ] Unplanned ICU admission post-operatively

**1.4 For Use In Labour Room**

- [ ] Death of foetus weighing > 800 g or 28 weeks of gestation
- [ ] Poor Apgar score (equal to or less than 5, 6 and 7 at 1, 5 and 10)
- [ ] Injury to neonate during delivery
- [ ] Mother transferred to ICU/CCU post-delivery
- [ ] Unplanned post-delivery procedure

**1.5 For Use In Anaesthetic Procedures**

- [ ] Laryngo/bronchospasm
- [ ] Failed intubation
- [ ] Aspiration of gastric content
- [ ] Myocardial ischaemia
- [ ] Injury to teeth

#### B. NON-CLINICAL INCIDENTS

**2.1 Safety Related**

- [ ] Trapped in elevator
- [ ] Electric shock
- [ ] Hit by object
- [ ] Assault
- [ ] Others (specify) __________________
INCIDENT REPORTING FORM

2.2 Security Related

- Theft
- Damaged Article
- Fire
- Unauthorized Personnel
- Missing Person
- Patient Absconding
- Others (specify) ________________

2.3 Miscellaneous

- Food/Beverage (specify) ________________
- Engineering (specify)
- Billing (specify)
- Housekeeping (specify) ________________
- Others (specify) ________________

SECTION B: Continuation

Narrative description of incident

________________________________________________________________________

Name of staff: ____________________________ Signature of staff: ____________________________

Name(s) witnesses (if any):

________________________________________________________________________

Immediate observation (where applicable)

Reminder:

- Is observation taken
- Is information documented in chart
- Is patient stable
- Is doctor notified
- Is injury visible

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is observation taken</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is information documented in chart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is patient stable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is doctor notified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is injury visible</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical assessment by Medical Officer (where applicable)

________________________________________________________________________

Name of Doctor: ____________________________ Signature: ____________________________

Date: ____________________________

Time: ____________________________
INCIDENT REPORTING FORM

SECTION C: To completed by Ward Supervisor/Unit Head immediately or before and of shift

COLLECTIVE ACTION

Is this incident preventable? □ Yes □ No
Has this incident resolved with no repercussions? □ Yes □ No

If answer is No, please specify

Is it a potential medico legal case? □ Yes □ No
Complaint public/media? □ Yes □ No
Has counseling been given to staff involved in the incident? □ Yes □ No

What immediate action has been taken to rectify the incident?

____________________________________________________________________

SECTION D: To be completed by CNO / Operations & Administration Manager within 48 hours

PREVENTIVE ACTION

Does the nature of the incident warrant a formal discussion at any level? □ Yes □ No
As counseling been effectively carried out to prevent future incident? □ Yes □ No
Is follow up still necessary? □ Yes □ No

Remarks

____________________________________________________________________

Name: ___________________________ Date: ___________________________
Signature ___________________ Time: ___________________________

SECTION E: Reviewed by CEO

Case Resolved □ Yes □ No

Remarks

____________________________________________________________________

Signature ___________________ Date: ___________________________
1. Aseptic technique
Aseptic technique refers to carrying out a procedure under controlled conditions in a manner that will minimize the chance of contamination.

2. 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 minimize the introduction, generation and retention of particles inside the room and to control other relevant parameters (e.g., temperature, humidity) as necessary.

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

4. Disinfectant
A chemical that destroys vegetative forms of harmful microorganisms from surfaces.

5. 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.

6. HEPA (High Efficiency Particulate Air) Filter
A dedicated filter that can remove at least 99.97% of airborne particles of 0.3 microns in diameter.

7. Isolator
A containment device that utilizes barrier technology for the enclosure of a controlled work space.

8. 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).

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

10. Preparation
All operation of purchasing materials and products, production, quality control, release, storage, delivery of product and related controls.

11. 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.

12. 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.

13. Quality Control
Any test that has been performed to examine the quality of final product.

14. Responsible Person
The pharmacist responsible for all aspects of the services within an aseptic preparation unit. These duties include the approval of all system of work and documentation used in the unit.

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

3. Handwashing. Steriline
5. Pharmaceutical Inspection Co-operation Scheme. 2009. PIC/S Guide To Good Manufacturing Practice For Medicinal Products. PE 009-08
16. Extravasation Policy of Clatterbridge Centre for Oncology NHS Trust. www.nwopg.nhs.uk
18. Office of Occupational Medicine, Occupational Safety and Health Administration. 1986. Guidelines for Cytotoxic Drugs
24. On line Medical Dictionary. 2005. cancerweb.ncl.ac.uk/omd
PHARMACEUTICAL SERVICES DIVISION
MINISTRY OF HEALTH, MALAYSIA