

**GUIDES TO THE DEVELOPMENT OF  
STERILE PHARMACEUTICAL PREPARATION FACILITIES**

**PHARMACEUTICAL SERVICES DIVISION  
MINISTRY OF HEALTH  
MALAYSIA**

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## PREFACE



With rapid advancement in technology and aligning to transformation of the healthcare services, the Ministry of Health of Malaysia is constantly and proactively improving and expanding its services, to meet the demands and expectations of all stakeholders. Consequently, new policies, procedures and guidelines need to be established to ensure the quality of the services provided.

Over the years, clean room technology has evolved so much that it is important that the Ministry of Health establishes a guidance document to ensure that the development and maintenance of new and existing clean room facilities are done according to current international standards. Indeed, I am pleased that the Pharmaceutical Services Division, Ministry of Health Malaysia has taken the initiative to publish the 1st Edition of '*Guides to the Development of Sterile Pharmaceutical Preparation Facilities for Healthcare Establishments*'.

Standardization in the construction of clean rooms is important not only for improving public health across national boundaries, but also in controlling health care costs, as clean room suites often require significant resources to construct and maintain. This document certainly serves as a useful reference to ensure appropriate planning, development and upgrading of the sterile pharmaceutical preparation facilities in any healthcare establishment.

I would like to express my utmost appreciation to the Pharmaceutical Services Division, Ministry of Health Malaysia especially the drafting team, for their commitment and excellent efforts in formulating and publishing this document.

Thank you.

**TAN SRI DATO' SERI DR. HJ. MOHD. ISMAIL MERICAN**

Director General of Health, Malaysia

## FOREWORD



Realizing the crucial importance of quality, safety and efficacy of sterile pharmaceutical preparations such as eye drops, intravenous admixtures, parenteral nutrition and cytotoxic drug reconstitutions (CDR) in hospitals, there is an urgent need for better clean room facilities, both in new as well as existing hospitals. To assist those in the planning and development of such facilities, the Pharmaceutical Services Division, Ministry of Health Malaysia has established the

*'Guides to the Development of Sterile Pharmaceutical Preparation Facilities for Healthcare Establishments'.*

This document addresses several important aspects including policies, design, layout and specifications, management and quality control as well as storage, distribution and ancillary areas. It also provides recommendations for the layout of CDR and non-CDR preparation facilities and also lay down the specific requirements during the construction process of such facilities.

In accordance with current international standards and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guides for Good Preparation Practice (GPP), Malaysia being a member of PIC/S is committed towards implementing such guidelines, both in private and public settings. To ensure quality, safety and efficacy of products and also protect personnel, the document is intended to promote awareness amongst healthcare planners and developers of the stringent regulatory requirements for such facilities. It is my fervent hope that relevant stakeholders involved will find this guide useful and applicable.

Finally, I would like to honor and thank each and every one of you that have played important role and made remarkable contributions towards the success of the publication of this guideline.

Thank you.

**EISAH BINTI A. RAHMAN**

Senior Director of Pharmaceutical Services  
Ministry of Health Malaysia

## PRELUDE



First of all, I would like to convey my gratitude to Quality & Standard Section for their hard work to come up with the first edition of '*Guides to the Development of Sterile Pharmaceutical Preparation Facilities for Healthcare Establishments*'. 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 these guidelines. This will ensure uniformity and conformity in all the sterile preparation facilities developed henceforth.

The primary objective of these guidelines is to assist those involved in planning, developing and upgrading of CDR and non-CDR preparation facilities. It also aims to benefit pharmacists and other personnel who are engaged in managing these facilities. The recommendations made in these guidelines take into consideration the Pharmaceutical Services Division policies, working environment and the fulfillments of customers' needs in accordance with the current international standards such as Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guides for Good Preparation Practice (GPP).

I believe that the contents of these guidelines will be able to serve as a standard reference for all hospital pharmacists, healthcare planners and developers with regards to the design, space, layout requirements and equipments for the development of a sterile preparation facility. As for the existing facilities, I strongly suggest to all pharmacists to look into the possibility of upgrading their respective facilities based on the recommendations made in these guidelines.

Finally, I would like to congratulate and thank all parties that have contributed to the successful publication of this book.

Thank you

### **HASNAH BINTI ISMAIL**

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## STERILE PREPARATION FACILITIES

Preparation of sterile pharmaceutical products in hospitals involves the activities such as preparation of Eye Drops, Intravenous Admixtures, Parenteral Nutritions and Cytotoxic Drug Reconstitutions. For the purpose of these guidelines, the sterile preparation facilities are classified into Cytotoxic Drug Reconstitution (CDR) and Non-Cytotoxic Drug Reconstitution (Non-CDR).

## POLICIES

- a. All sterile pharmaceutical preparations shall be produced in a qualified clean room facilities designed and built in accordance to Good Preparation Practice (GPP) requirements
- b. CDR preparation facility shall be made available in each state hospital and hospital with specialist
- c. Parenteral Nutrition preparation facility shall be made available in hospital with ICU, NICU and surgical department while IV Admixture shall be made available in all hospitals
- d. Clean rooms shall be designed and built by experienced clean room contractors. The proposed layout plan, grades and control parameters shall be submitted to the Pharmacy Practice and Development Division of Ministry of Health for approval prior to the development of the facilities
- e. The calibration of equipment including the monitoring devices used in clean rooms shall be conducted by an accredited agent
- f. Upon commissioning by the contractor, clean rooms and their major equipment (laminar airflow cabinet and cytotoxic drug safety cabinet/isolator) shall be tested by an independent third party agent for confirmation of compliance to standards. The testing agent shall be accredited by appropriate accreditation bodies such as National Associations of Testing Authorities (NATA - Australia) or National Environmental and Balancing Bureau (NEBB - USA)

- g. Prior to use, clean room facilities shall be inspected and qualified by auditors from the Pharmacy Practice and Development Division, Ministry of Health Malaysia. Approval letter for use will be issued by the Pharmacy Practice and Development Division
- h. Clean rooms, unidirectional airflow cabinet and cytotoxic drug safety cabinet/isolators shall be maintained regularly according to approved planned preventive maintenance procedures. The maintenance shall include thorough cleaning and testing by the accredited testing agent. Microbial monitoring shall be done regularly depending on the usage of the facilities and outcome of the test results
- i. Quality control testing on sterile preparation shall be carried out in-house and/or outsourced. If a product is prepared for a single patient, end product testing is not needed
- j. Qualified clean room facilities shall be inspected routinely by auditors from the Pharmacy Practice and Development Division, Ministry of Health Malaysia, at least every 2 years

## **DESIGN, LAYOUT AND SPECIFICATIONS**

- a. This area is for sterile preparation activities that may consist of either CDR Facility, Non-CDR Facility or both
- b. Premises and utilities for CDR Facility shall be separated from Non-CDR Facility (for eye drops, IV admixtures and parenteral nutritions)
- c. The building design shall take into account the flow of the materials, products and personnel. Personnel, equipment and work-in-process shall not be moved through areas in which other operations are running. This requires that areas used for processing shall have separate access from corridors and a one-way flow is preferable. A recommended total built-up area of 1,200 sq feet shall be made available for a complete set of clean room facility

- d. Dedicated air handling system shall be required for sterile preparation facilities and shall be fitted with alarms so that the working personnel are warned of any failure of the systems. The system shall be able to maintain 24 hours pressure differentials without cooling whenever the facilities are not in use
- e. Adequate lighting shall be provided in all clean rooms. Normally, a range of 500 - 600 lux ensures personnel comfort and ability to perform work efficiently and effectively. Lights fixtures shall be flush-mounted in the ceiling and sealed to prevent air leaks. It is preferable that they can be maintained and serviced from above. Electrical outlets shall be flushed-mounted, watertight, have no crevices and shall be cleanable
- f. The choice of construction materials is one of the most important considerations in the facility design. When choosing the materials for floors, ceilings and walls, the following specifications for the premises shall be considered:
  - i. Ceilings, walls, floors, fixtures, shelves, counters and cabinets shall be resistant to sanitizing agents and crevices free to avoid accumulation of dirt
  - ii. Construction materials used shall be able to resist chipping, shedding, flaking, oxidizing, or other deterioration
  - iii. Junctions of walls, floor and ceiling shall be curved (coved) to facilitate cleaning
  - iv. There shall not be horizontal fixed pipes or conduits over exposed components, in-process materials, drug products, and drug product contact surfaces
  - v. All service fittings shall be flushed with surrounding surfaces
  - vi. Airtight ceilings and walls, close fitting doors and sealed light fittings shall be in place as these have an impact on the HVAC system (heating, ventilation and air-conditioning)

## **CYTOTOXIC DRUG RECONSTITUTION (CDR)**

### **A. Facility Requirements**

- i. A totally separate clean room area (premises and utilities) shall be provided for Cytotoxic Drug Reconstitution (CDR) activities that require containment for the protection of the environment. Entrance and exit of the CDR room shall be via a containment airlock or a sink airlock (or negative sink)
- ii. A CDR facility shall have personnel changing rooms (for changing and gowning), a component room, a CDR room and an area for storage, receiving and distribution activities
- iii. Apart from cleanliness, design of the facility shall consider and fulfill the requirement of containment. This can be achieved by having a negative airlock adjacent to the CDR room. Depending on the layout design, this airlock can also be suitably located to contain the whole facility
- iv. Although a one-way flow of processes is recommended, the requirement for containment shall not be compromised
- v. Air handling unit (AHU) and its room shall be dedicated. The air handling system for CDR room and airlock shall not be re-circulated and shall be fitted with an emergency push button for use during spillage
- vi. Flooring shall be a continuous, non-cracking material that is mechanically and chemically robust. Preferably, floors shall be overlaid with wide sheet vinyl flooring with heat-welded seams and coving to the sidewall
- vii. Walls and ceilings shall be free from cracks, built with a smooth, non-shedding, cleanable finish that is impervious to water, cleaning and sanitizing solution. To avoid condensation problem, sandwich panel wall system (e.g. Polyurethane panel) shall be used

- viii. Bare wood, ledges and other unsealed surfaces shall be avoided in clean rooms. Glass window is required for CDR room and it shall be of flushed double glazed type
- ix. There shall be two parts of personnel changing room. The second or final part of the personnel changing room leading into the CDR room shall be of the same grade of the latter
- x. Sink for hand washing can be fitted in the first or earlier part of the changing room. The CDR room shall not contain any sink or floor drains
- xi. Taps shall be elbow, foot or beam-operated. Surface of materials, including bench tops, shall have minimum joints and seams; be non-shedding and easy to clean
- xii. All doors for clean rooms shall be fitted with inter-locking systems so that only one door can be opened at a time to ensure the pressure cascade is not compromised. All airlock doors shall be provided with self-closers
- xiii. Doors and windows shall have a hard, smooth, impervious finish and close tightly and also fit flush with surrounding walls. The size of all doors shall be sufficient for the equipment to be brought into
- xiv. A cytotoxic drug safety cabinet or isolator (CDR cabinet/isolator) shall be used to ensure maximum personnel protection. The cabinet and isolator used shall be of a Grade A air quality for the protection of product
- xv. A CDR Isolator shall be used by hospital with less than 10 CDR preparations per day
- xvi. Appropriate measuring devices shall be installed for CDR cabinet or isolator such as :
  - Pressure gauges for monitoring the pressure across the HEPA filters
  - Down flow sensor for velocity

- A limit window sash sensor shall be available to ensure negativity within CDR cabinet
- xvii. The CDR room shall be of Grade B if a cytotoxic drug safety cabinet is used. If an isolator (negative isolator) is used, the room shall be of at least Grade D air quality
- xviii. Since the CDR room shall not have a workbench, equipment installed (either cabinet or isolator) shall come with its own stands. There shall be sufficient space underneath the cabinet for allowing cleaning process
- xix. Component room shall be of Grade C or D air quality and shall be entered by personnel via a personnel changing room of a similar grade
- xx. Utility cabinet, stainless steel sink with an appropriate depth and backsplash to avoid splashing and work bench shall be fitted in the component room
- xxi. Buffer/staging room or a hatch shall be used for transferring materials (e.g. components, cleaning materials and equipment). If a one way flow facility is not possible, the buffer/staging room or hatch can be used for transferring materials and products out as well
- xxii. Adequate numbers of plug points shall be made available
- xxiii. Plug points connected to essential power supply shall be made available for pharmaceutical refrigerators. In case of power failure, Uninterrupted Power Supply (UPS) shall be provided for Cytotoxic Drugs Reconstitution (CDR) cabinet/ isolator and HVAC system
- xxiv. For existing facilities, an accredited agent shall be appointed to test the performance of the facilities on a regular basis
- xxv. Heating, Ventilation and Air-conditioning (HVAC) System

- Humidity, temperature, pressurization and air filtration or air cleanliness shall be controlled in order to protect the products, personnel and the environment. Appropriate devices for measuring and monitoring the parameters shall be installed or made available (e.g. pressure gauges, thermo-hygrometers, etc)
- Due consideration shall be given to the placement of ceiling mounted HEPA filters to avoid creating of air currents inside the cabinet underneath. Diffusers shall not be used
- Pre-filters (primary and secondary) of AHU and HEPA filters shall be changeable from outside the clean room
- Temperature (not more than 22°C) and humidity (55 ± 5%) need to be controlled primarily for the stability of products and the comfort of personnel
- Equipment installed shall not jeopardise the set room conditions including temperature, humidity, air pressure, noise level, etc
- Air pressure shall be made higher in the cleaner grade of clean rooms
- Air return grilles shall be located at a low-level to sweep or purge the rooms
- Air extracted from areas where cytotoxic drugs are reconstituted shall not be re-circulated; air outlets shall be designed to avoid possible environmental contamination from particles and vapors

xxvi. Environmental control is a critical factor in determining the successful operation of the manufacturing facility especially a clean room. Therefore, the design and construction which relates to a clean room shall include consideration of the following:

- Building finishes and structure
- Air filtration
- Air change rate or flushing rate
- Location of air terminals and directional airflow
- Room pressure
- Particulate loading (viable and non-viable)
- Temperature (not more than 22°C)
- Relative humidity ( $55 \pm 5\%$ )
- Pressure differentials (10 – 15 Pascals)
- Material flow
- Personnel flow

## **B. List of Equipment Required**

### **i. CDR Room**

- Cytotoxic Drugs Reconstitution (CDR) cabinets / isolator 4ft. or 6 ft. with stainless steel stand
- Trolley (stainless steel)
- Intercom system
- Non-wheeled stainless steel stool with adjustable height (for safety reasons)
- Roller mixer

### **ii. Component room**

- Rack/shelves for keeping of sterile bags, syringes, needles, filters, etc. (stainless steel)
- Phenolic bench top with stainless steel drawers
- Trolley (stainless steel)
- Sink (stainless steel)
- Intercom system



**iii. Personnel Gowning Room**

- Garment cabinet or five-tier lockers for sterile gloves, head caps, mask
- Wall mounted six foot long mirror
- Cross over bench

**iv. Personnel Changing Room**

- Sink with elbow tap (stainless steel)
- Cabinet (to hang street clothes)
- Wall mounted six foot long mirror
- Liquid soap dispenser (foot-operated)
- Electrical hand dryer
- Cross over bench

**v. Storage, Receiving and Distribution Room**

- Pharmaceutical refrigerator, twin doors connected to an essential power supply
- Trolleys (stainless steel)
- Computers and printers including "Uninterrupted Power Supply"
- Display for temperature, relative humidity and pressure for the clean rooms
- Tables and chairs
- Telephone
- Intercom System
- Filing cabinets
- Pneumatic tube terminal (optional)

## **PN / IV ADMIXTURE / EYE DROP (NON-CDR)**

### **A. Facility Requirement**

- i. Appropriate clean room facilities shall be provided for Non-Cytotoxic Drugs Reconstitution (Non-CDR) activities such as the preparation of Parenteral Nutrition Solutions, Intravenous Admixtures and Eye Drops
- ii. The facility shall have personnel changing rooms (for changing and gowning), a component room, a preparation room and an area for storage, receiving and distribution activities
- iii. Flooring shall be a continuous, non-cracking material that is mechanically and chemically robust. Preferably, floors shall be overlaid with wide sheet vinyl flooring with heat-welded seams and coving to the sidewall
- iv. Walls and ceilings shall be free from cracks, built with a smooth, non-shedding, cleanable finish that is impervious to water, cleaning and sanitizing solution. To avoid condensation problem, sandwich panel wall system (e.g. Polyurethane panel) shall be used
- v. Bare wood, ledges and other unsealed surfaces shall be avoided in clean rooms. Glass window is required for the preparation room and it shall be of flushed double glazed type
- vi. There shall be two parts of personnel changing room. The second or final part of the personnel changing room leading into the preparation room shall be of the same grade as the latter
- vii. A sink for hand wash can be fitted in the first or earlier part of the changing room. The preparation room shall not contain any sink or floor drains
- viii. Taps shall be elbow, foot or beam-operated. Surface of materials, including bench tops, shall have minimum joints and seams; be non-shedding and easy to clean

- ix. All doors for clean rooms shall be fitted with inter-locking system so that only one door can be opened at a time to ensure the pressure cascade is not compromised. All airlock doors shall be provided with self-closers
- x. Doors and windows shall have a hard, smooth, impervious finish and close tightly and also fit flush with surrounding walls. The size of all doors shall be sufficient for the equipment to be brought into
- xi. A positive pressure unidirectional airflow cabinet or isolator shall be used for Parenteral Nutrition and Eye Drop. For IV Admixture preparations, a negative pressure unidirectional cabinet or isolator shall be used to ensure maximum personnel protection
- xii. The cabinet and isolator used shall be of a Grade A air quality for the protection of product. There shall be sufficient space underneath the cabinet for allowing cleaning process
- xiii. The preparation room shall be of Grade B if a unidirectional airflow cabinet is used. If an isolator (positive isolator) is used, the room shall be of at least Grade D air quality
- xiv. Since the preparation room shall not have a work bench, equipment installed (either cabinet or isolator) shall come with its own stands
- xv. Component room shall be of Grade C or D air quality and shall be entered by personnel via a personnel changing room of a similar grade
- xvi. Utility cabinet, stainless steel sink with an appropriate depth and backsplash to avoid splashing and work bench shall be fitted in the component room
- xvii. Buffer/staging room or a hatch shall be used for transferring materials (e.g. components, cleaning materials and equipment). If a one way flow of facility is not possible, the buffer/staging room or hatch can be used for transferring materials and products out as well

- xviii. Adequate numbers of plug points shall be made available
- xix. Plug points connected to essential power supply shall be made available for pharmaceutical refrigerators. In case of power failure, Uninterrupted Power Supply (UPS) shall be provided for the unidirectional airflow cabinet/ isolator and HVAC system
- xx. For existing facilities, an accredited agent shall be appointed to test the performance of the facilities on a regular basis
- xxi. Heating, Ventilation and Air-conditioning (HVAC) System
- Humidity, temperature, pressurization and air filtration or air cleanliness shall be controlled in order to protect the products, personnel and the environments. Appropriate devices for measuring and monitoring the parameters shall be installed or made available. (E.g. pressure gauges, thermo-hygrometers, etc.)
  - Due consideration shall be given to the placement of ceiling mounted HEPA filters to avoid creating of air currents inside the cabinet underneath. Diffusers shall not be used
  - Pre-filters (primary and secondary) of AHU and HEPA filters shall be changeable from outside the clean room
  - Temperature (not more than 22°C) and humidity ( $55 \pm 5\%$ ) need to be controlled primarily for the stability of products and the comfort of personnel. Equipment installed shall not jeopardise the set temperature of the room
  - The air pressure shall be made higher in the cleaner grade of clean rooms. The air return grilles shall be at the low-level to sweep or purge the rooms
- xxii. Environmental control is a critical factor in determining the successful operation of the manufacturing facility especially

a clean room. Therefore, the design and construction, which related to a clean room shall include consideration for:

- Building finishes and structure
- Air filtration
- Air change rate or flushing rate
- Location of air terminals and directional airflow
- Room pressure
- Particulate loading (viable and non-viable)
- Temperature (not more than 22°C )
- Relative humidity (55 ± 5%)
- Pressure differentials (10 – 15 Pascals)
- Material flow
- Personnel flow

## **B. List of Equipment Required**

List of equipment for Non-CDR facilities (Intravenous Admixture [IV Ad], Parenteral Nutrition [PN] and Eye Drops)

### **i. Preparation Room**

- Positive Pressure Unidirectional (horizontal) Airflow cabinets / isolator 4 or 6 ft. with stainless steel stand for Parenteral Nutrition and Eye Drop
- Negative Pressure Unidirectional cabinets / isolator 4 or 6 ft. with stainless steel stand for IV Admixture preparations
- Trolley (stainless steel)
- Intercom system
- Stainless steel stool with wheels and adjustable height

### **ii. Component Room**

- Rack/shelves for keeping of sterile bags, syringes, needles, filters, etc. (stainless steel)
- Phenolic bench top with stainless steel drawers
- Plug points

- Trolley (stainless steel)
- Sink (stainless steel)
- Intercom system

### **iii. Personnel Gowning Room**

- Garment cabinet or five-tier lockers for sterile gloves, head caps, mask
- Wall mounted six foot long mirror
- Cross over bench

### **iv. Personnel Changing Room**

- Sink with elbow tap (stainless steel)
- Wall mounted six foot long mirror
- Cabinet (to hang street clothes)
- Plug points
- Liquid soap dispenser (foot-operated)
- Electrical hand dryer
- Cross over bench

### **v. Storage, Receiving and Distribution Room**

- Pharmaceutical refrigerator, twin doors connected to an essential power supply
- Trolleys (stainless steel)
- Computers and printers including "Uninterrupted Power Supply"
- Display for temperature, relative humidity and pressure for the clean rooms
- Table/chairs
- Telephone
- Intercom System
- Filing cabinets
- Pneumatic tube terminal (optional)
- Plug points

## MANAGEMENT AND DOCUMENT CONTROL AREAS

The management and document control area consists of an administration office for preparation planning, documentation and quality control activities. Thus, appropriate facilities for an office shall be provided. An open office space for personnel with computer terminals shall be made available according to norms and working space for sufficient number of personnel. Within this office area there shall be rooms for:

### 1. Pharmacist In-Charge's Room

Room shall be provided for Pharmacist in-charge of the Production Pharmacy Unit. Pharmacist in-charge of non-sterile preparation facilities, Pharmacist in-charge of CDR facilities and Pharmacist in-charge of TPN facilities. Their rooms shall be strategically located to allow supervision and administrative works. Each room shall be equipped with:

- a. Computer and printer including "Uninterrupted Power Supply"
- b. Table and chairs
- c. Telephone
- d. Filing cabinets
- e. Pneumatic tube terminal (optional, except for Pharmacist in-charge of CDR facilities)

### 2. Meeting / Discussion

This room shall be equipped with chairs, tables, whiteboard and LCD projectors.

### 3. Documentation and Storage of Records

Adequate space is required to store 2 years documents such as batch records, preparation procedures and distribution records. This room shall be equipped with metal filing cabinets, telephone, fax, tables, chairs and computer.

## **STORAGE, RECEIVING AND DISTRIBUTION AREAS**

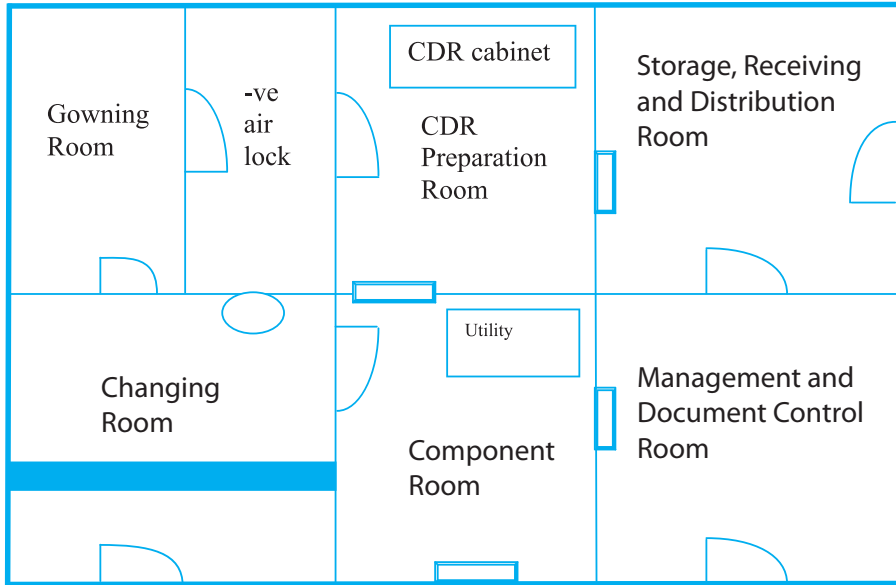
- a. This section shall have sufficient reception, receiving and distribution areas. The areas shall be designed to protect materials and products from the weather and equipped to allow containers of incoming materials to be cleaned where necessary before storage
- b. Sufficient storage area including shelves (or racking system) shall be provided for storage of products and materials including disposables
- c. Storage areas shall be designed to ensure good storage conditions e.g. clean, dry and maintained. If special storage conditions are required (e.g. temperature and humidity) these shall be provided, checked and monitored regularly using appropriate devices

## **ANCILLARY AREAS**




- a. Rest and refreshment rooms shall be separated from preparation and control areas. This room shall be equipped accordingly
- b. Facilities for changing and storing clothes and for washing and toilet purposes shall be easily accessible and appropriate for the number of users. Toilets shall not directly communicate with preparation or storage areas
- c. The qiblat direction of Muslim Male and Female Prayer Rooms shall not be facing any nearby toilet
- d. Utility room shall be equipped for storing of housekeeping equipment and shall be well ventilated to facilitate drying processes of mops and towels



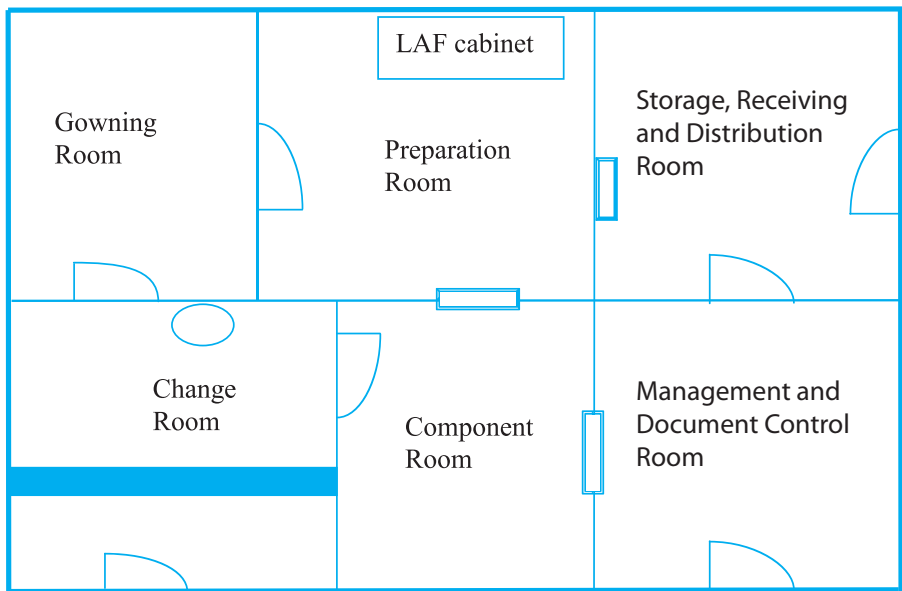
## APPENDIX 1: EXAMPLE OF LAYOUT PLAN FOR CYTOTOXIC DRUG RECONSTITUTION (CDR) PREPARATION FACILITIES






### Legend:

-  Crossover bench
-  Pass box
-  Sink

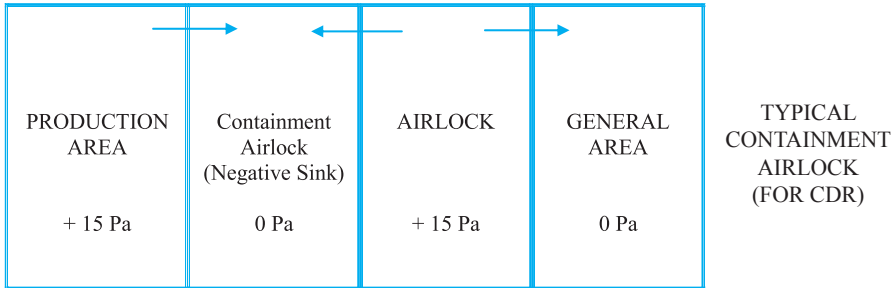
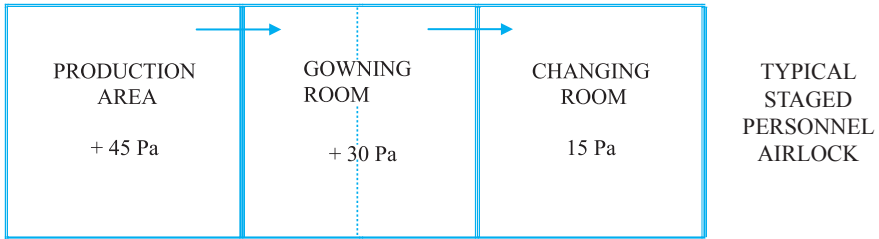
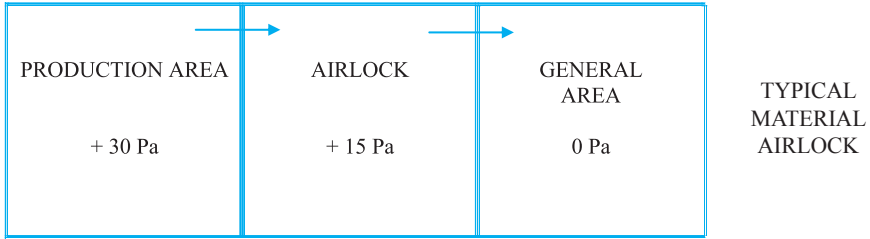
## APPENDIX 2: EXAMPLE OF LAYOUT PLAN FOR PN / IV ADMIXTURE / EYE DROP (NON-CDR) PREPARATION FACILITIES



### Legend:

-  Crossover bench
-  Pass box
-  Sink

### APPENDIX 3: AIR LOCKS FOR PERSONEL AND MATERIALS IN CLEAN ROOMS



**Legend:**



### APPENDIX 4: EXAMPLES OF TYPES OF CONSTRUCTION MATERIAL FOR CLEAN ROOMS

INTERIOR SURFACE	TYPES OF MATERIALS	COMMENTS
<b>FLOOR</b>	Epoxy, polyurethane resin or heavy duty homogenous vinyl sheets	<ul style="list-style-type: none"> <li>- monolithic, non-porous topping with non-skid surface</li> <li>- retards bacterial growth</li> <li>- abrasive</li> </ul>
<b>WALL</b>	Polyurethane panels	<ul style="list-style-type: none"> <li>- non shedding</li> <li>- generally maintenance free</li> <li>- moderately durable</li> <li>- difficult to repair in case of damage by impact</li> <li>- crevices at joints need to be sealed e.g. with flexible silicone rubber material</li> </ul>
<b>CEILING</b>	Polyurethane panels	<ul style="list-style-type: none"> <li>- designed for heavy loads</li> <li>- space above ceiling can be used for ducts, services pipes and testing of HEPA filters</li> </ul>

## APPENDIX 5: RECOMMENDED FILTRATION LEVELS FOR DIFFERENT CLEAN ROOM GRADES

CLEAN ROOM CLASSIFICATION		RECOMMENDED FILTRATION
PIC/S	ISO 14644-1 CLASS	
Pharmaceutical (Unclassified Control Area)	ISO Class 9	Production facility with HVAC provision but not subject to particulate or bacterial control. Pharmaceutical condition : G4 filters
Grade D	ISO Class 8	Production facility operating on 100% outside air: G4 and F8 filters
Grade D	ISO Class 8	Production facility operating on re-circulated plus ambient air where potential for product cross-contamination exists : G4, F8 and H13 filters
Grade C	ISO Class 7	Facility operating on re-circulated air or 100% ambient air : G4, F8 and H13 filters (HEPA filters to be terminally located)
Grade B	ISO Class 6	Facility operating on re-circulated air or 100% ambient air : G4, F9 and H14 filters (HEPA filters to be terminally located)
Grade A	ISO Class 5	Facility operating on re-circulated air or 100% ambient air : G4, F9 and H14 filters (HEPA filters to be terminally located)

The filter classifications referred above relate to the EN1822 and EN779 test standards which are the latest filter test standards, recommended for international use. (EN 779 relates to filter classes G1 to F9 and EN 1822 relates to filter classes H10 to U16.

## APPENDIX 6: CLEAN ROOM CLASSIFICATIONS

xCLEAN ROOM GRADE & TYPE OF FILTER	AIR FILTER EFFICIENCY (%)	AIR CHANGE RATE (CHANGES PER HOUR)	MAXIMUM PARTICLE COUNT (> 0.5UM)		MAX. NO. OF VIABLE MICROBES PER CUBIC METER	ACTIVITIES/PURPOSE
			STATE	PER METERS <sup>3</sup>		
A (ISO 5)  HEPA filter	99.997	>120 Vertical air flow: 0.3 m/sec + 20% Horizontal air flow: 0.45 m/sec + 20%	at rest	3,520	<1	Laminar flow area for aseptic manipulation of sterile products. Space where sterile product is exposed.
			in operation	3,520		
B (ISO 6)  HEPA filter	99.997	>40	at rest	3,520	10	Clean room for sterile products. Background Environment for Grade A
			in operation	352,000		
C (ISO 7)  HEPA filter	99.995	>25	at rest	352,000	100	Clean room for preparation of sterile products. (less critical steps)
			in operation	3,520,000		
D (ISO 8)  Secondary filter	95	>20 (WHO)	at rest	3,520,000	200	Clean room for manufacturing of sterile products - less critical steps. Also being used for non-sterile manufacturing
			in operation	Not Defined		

**Note:**

- > Air change rates are the key to cleaning a room effectively shall it get contaminated. Hence, the higher the air change rate, the better quality the room. High rates shall be selected where the air quality is continually challenged – e.g. by dusty environment.

## REFERENCES

1. PIC/S Guide To Good Practices For The Preparation Of Medicinal Products In Healthcare Establishments. PE 010-3. Geneva, Pharmaceutical Inspection Co-Operation Scheme, 1<sup>st</sup> October 08.
2. PIC/S Guide To Good Manufacturing Practice For Medicinal Products. PE 009-09. Geneva, Pharmaceutical Inspection Co-Operation Scheme, 1<sup>st</sup> September 2009.
3. Supplementary Guidelines On Good Manufacturing Practices For Heating, Ventilation And Air Conditioning (HVAC) Systems For Non-Sterile Dosage Forms. Geneva, World Health Organization, 15<sup>th</sup> October 2005.