1st EDITION

MAY 2010

GUIDES TO THE DEVELOPMENT OF RADIOPHARMACEUTICAL PREPARATION FACILITIES FOR HEALTHCARE ESTABLISHMENTS

PHARMACEUTICAL SERVICES DIVISION
MINISTRY OF HEALTH,
MALAYSIA

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PREFACE

First and foremost, I would like to congratulate the Pharmaceutical Services Division, Ministry of Health Malaysia for its proactive efforts in producing this document. In tandem with current developments in healthcare, nuclear pharmacy has indeed become a new chapter in the healthcare services in Malaysia.

In keeping abreast with latest developments, there is a crucial need for us to continuously and progressively look into areas that require improvements and expansion, besides fulfilling the expectations of the stakeholders. Through various programmes and quality initiatives, emphasis on human capital development particularly developing specialized skills and technical competency, is given due attention. Subsequently, new policies, procedures and guidelines must be well established to ensure quality, safety, effectiveness and efficiency of the services and products provided to the public.

Hence, it is pertinent that the Ministry of Health establishes a comprehensive guidance document to ensure that the physical development of the Radiopharmaceutical Preparation Facilities complies with current international standards. The publication of the '*Guides to the Development of Radiopharmaceutical Preparation Facilities for Healthcare Establishments*', 1st Edition provides an important reference for those involved in the planning, development and upgrading of the radiopharmaceutical preparation facilities in any healthcare establishment.

Finally, I would like to extend my heartfelt appreciation to the Pharmaceutical Services Division and members of the Nuclear Pharmacy Development Working Group for their tireless efforts and commitment in preparing and publishing the 1st Edition of this important guideline.

Thank you.

TAN SRI DATO' SERI DR. HJ. MOHD. ISMAIL MERICAN
Director General of Health
Ministry of Health Malaysia

FOREWORD

As we strive forward to provide the best pharmacy practices, the need for a comprehensive '*Guides to the Development of Radiopharmaceutical Preparation Facilities for Healthcare Establishments*' becomes crucial. Driven by the progressive development of radiopharmaceutical preparation facilities in the Nuclear Medicine Department, Ministry of Health, it is important that we document the specifications and requirements necessary to assist those involved in the planning and development of radiopharmaceutical preparation facilities in new and existing hospitals throughout the country.

The contents of these guidelines comprehensively cover key aspects incorporating background information, general policy, operational and development principles which address requirements for radiation protection and safety, quality assurance, personnel and equipment, layout, design and equipment needed for the construction of these facilities. The requirements of Good Manufacturing Practice (GMP) especially for clean rooms have also been updated to keep abreast with current international standards and technology.

As a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) since 1st January 2002, Malaysia adopts the PIC/S Guidelines for GMP. Hence, the need for us to benchmark against stringent requirements to ensure quality, safety and efficacy of radiopharmaceutical preparations produced as well as safeguard and protect personnel, patients and environment.

It is my sincere hope that these guidelines 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 these guidelines a great success.

Thank you.

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

PREFACE

First of all, I would like to convey my gratitude to the Nuclear Pharmacy Development Working Group for their hard work to come up with the first edition of '*Guides to the Development of Radiopharmaceutical Preparation Facilities for Healthcare Establishments'.* The publication of these guidelines are aimed to assist those involved in the planning and development of radiopharmaceutical preparation facilities in new and existing hospitals throughout the country.

These guidelines provide a wide range of requirements and specifications for establishing radiopharmaceutical preparation facilities under the nuclear medicine department not only in new hospitals but also in existing facilities as it can serve as a reference for upgrading existing radiopharmaceutical preparation facilities.

The contents of these guidelines cover the basic requirements such as space, layout and equipments needed for the construction of these facilities. The requirement of Good Manufacturing Practice (GMP) especially for clean room, also have been updated to keep abreast with the international standards practiced by Pharmaceutical Inspection Co-operation Scheme (PIC/S), an international organization of which Malaysia is a member since 1st January 2002.

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

Thank you

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BACKGROUND

Nuclear pharmacy practice has rapidly evolved in line with the development of nuclear medicine throughout this country. Radiopharmaceutical is not only confined to conventional practice solely for diagnostic purpose but it is also being used widely for therapeutic and prevention purposes. Extensive functional studies have also been carried out in cardiology, nephrology and neurology disciplines as well as infection and inflammation. This scenario has brought pharmacists to become involved in standardizing the requirements for developing of radiopharmaceutical preparation facilities.

Generally, radiopharmaceuticals differ from other pharmaceuticals due to their relatively short half-lives, production methods, quality control procedures, radiation risks and dosing regiments. Preparation of good quality and safe radiopharmaceutical products requires appropriate facility that is physically designed and environmentally controlled to minimize the risk of contamination and radiation. A thorough selection of equipment for preparation and quality control activities should be done appropriately to ensure quality, safety and efficacy of the product. Any default in the structure of the preparation facility may not only compromise the quality of products but also the safety of personnel, patient and environment. Hence, it is critically important to ensure that the facilities are built according to acceptable standards and guidelines.

SCOPE & HOW TO USE THESE GUIDELINES

These guidelines are to be used as a reference for planning and development of a new and upgrading of radiopharmaceutical preparation facilities, both in public and private healthcare establishments. Hospital administrators, nuclear pharmacists, developers and contractors may find these guidelines useful and applicable to be referred to. However, some adjustments could be made to tailor with the development of new technology and available resources. In order to comply with all the requirements, general policy must be used together with individual annexes.

GENERAL POLICY OF RADIOPHARMACEUTICAL PREPARATION FACILITIES

GENERAL POLICY OF RADIOPHARMACEUTICAL PREPARATION FACILITIES

PRINCIPLES

Radiopharmaceuticals are classified as medicinal products thus shall be prepared in accordance to Good Manufacturing Practice (GMP) or Good Preparation Practice (GPP) including their preparation facilities in hospital and other healthcare establishments. Normally, to facilitate administration activities, Radiopharmaceutical Preparation Facility (or formerly known as a Hot Laboratory) is built within or in close proximity to the hospital Nuclear Medicine Department.

Commonly used radiopharmaceuticals in healthcare establishments are as follow:

- Kit-based radiopharmaceuticals
- Positron Emission Tomography (PET) radiopharmaceuticals
- Radiolabeled blood preparations
- Radioiodine
- Ready-for-use radiopharmaceutical products

GENERAL OPERATIONAL & DEVELOPMENT PRINCIPLES

1.0 RADIATION PROTECTION & SAFETY

1.1 In working with radiopharmaceuticals, account has to be taken not only of the national laws on the preparation of drugs but also of the national requirements for occupational health and safety, Malaysian Atomic Energy Licensing Act 1984, Radiation Protection (Basic Safety Standard) Regulations 1988 and other relevant international regulations. Input from the Radiation Health and Safety Section of Engineering Services Division of the Ministry of Health shall be sought for

1.2 Radiopharmaceutical Preparation Facilities shall be in or near the Hospital Nuclear Medicine Department to minimize the travel of radioactive materials. These facilities may comprise of preparation areas for sterile and non-sterile radiopharmaceuticals

1.3 Radiopharmaceutical Preparation Facilities shall be specially designed to take into consideration aspects of radiation protection in accordance to As Low As Reasonably Achievable (ALARA) in addition to cleanliness and sterility. These facilities shall be designed and built by qualified contractors

1.4 The presence of high levels of radioactivity shall be used as a factor in considering its proximity to, gamma cameras, patient waiting areas, offices and working area above and below the Radiopharmaceutical Preparation Facilities

1.5 Appropriate measures shall be taken to avoid the spread of radioactivity from the controlled areas and to protect the controlled areas from particulate and bacterial contaminations

1.6 If design permit, centralized radioiodine preparation facility is preferable as this will minimize space consumption as well as better management of personnel and radiation control

1.7 The risk management level shall be in accordance to the types of radiation emitted and the half-lives of the radioisotopes. Particular attention shall be paid to the prevention of radioactive contamination and waste disposal

1.8 Water shower shall not be installed within the production area as it may spread radioactive contaminants to other parts of the body and the environment

1.9 Contaminated and used vials and syringes shall be disposed off safely and appropriately. Lead shielded waste containers for used syringes shall be located as close as possible to the location of use

1.10 Consumable items that have been used for dealing with radioactive must be kept in lead shielded containers/area

1.11 Radiation trefoil symbol should be displayed at the entrance and within radiopharmaceutical preparation facilities

1.12 Radioactive detector with alarm system shall be made available in the appropriate area. The detector shall be maintained regularly

1.13 Workstation in which radioactive materials emit gamma or high-energy beta radiation shall be shielded with appropriate materials suitable for the radiation protection. There must be sufficient space behind the shield for the use of remote handling tongs

1.14 Emergency/Decontamination kits and eye wash facility shall be provided at the appropriate areas for use in emergency

1.15 Radioactive waste shall be handled by hospital support service / concession company (if available) trained in radiation safety with the supervision of Radiation Protection Officer

2.0 QUALITY ASSURANCE

2.1 Preparation of radiopharmaceuticals shall be carried out by Nuclear Pharmacist or by other qualified personnel under immediate supervision of Nuclear Pharmacist in the Radiopharmaceutical Preparation Facility using the WHO Guidelines on Good Manufacturing Practices for Pharmaceuticals Products; Annex 3, and PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments

2.2 Generally, sharing of preparation facility between sterile and non-sterile products shall not be allowed. However, low usage sterile radiopharmaceutical products (e.g. ^{90}Yttrium-Ibritumomab for radioimmunotherapy) might be prepared in the non-sterile preparation facility (radioiodine) under the following conditions;

- Sterile product preparation shall be done in the negative pressure laminar air flow isolator
- All requirements for sterile preparation procedures shall be complied with
- Procedural control shall be in place to ensure complete segregation of preparation activities of both products

3.0 PERSONNEL

3.1 Personnel required to work in radiation, controlled and clean-room areas shall be selected with care, to ensure that they can be relied on to observe the appropriate codes of practice. They shall be free from any diseases or conditions that could compromise the integrity of the product

3.2 Personnel dealing with radioactive materials are required to follow the requirements of Radiation Protection (Basic Safety Standards) Regulation 1988. These include medical checkup and personnel dose monitoring. Personnel shall be qualified in handling radioactive material

3.3 Personnel working in radiopharmaceutical preparation clean room shall be qualified according to approved personnel qualification procedures. Apart from GMP / GPP, they shall also be trained with the principles of national and international radiation safety guidelines and policy

3.4 All personnel shall be trained and assessed continuously and appropriately according to their job functions. There shall be sufficient personnel for efficient and effective operations of the preparation facilities

3.5 Pharmacist shall be in charge of the Radiopharmaceutical Preparation Facility. All procurement, preparation, quality control and dispensing activities shall be carried out by trained pharmacists

4.0 PREMISES AND EQUIPMENT

PRODUCTION

4.1 Radiopharmaceutical products shall be stored, processed, packaged and controlled in dedicated and self-contained facilities

4.2 Normally, direct access to preparation areas from common corridor shall be avoided

4.3 The bioburden of all materials that been brought into production areas shall be minimized. Appropriate facility for cleaning down the materials shall be made available

4.4 All preparation activities shall be done according to approved procedures and recorded in the appropriate batch preparation record. Upon completion of the preparation process, all finished products including radiopharmaceuticals shall be labeled and tested accordingly prior to release

4.5 Preparation areas including clean rooms shall be maintained regularly according to approved plan preventive maintenance procedures

4.6 Housekeeping utensils (e.g. mop) shall not be shared between production and non-production areas

4.7 Separate air conditioning system shall be used for radioactive and non-radioactive areas

4.8 Re-circulation of air extracted from area where radioactive products are handled shall be avoided. Air from operations involving radioactivity shall be exhausted through appropriate filters that are regularly checked for performance

4.9 Air outlets shall be designed to minimize environmental contamination by radioactive particles and gases and appropriate measures shall be taken to protect the controlled areas from particulate and microbial contamination

4.10 The preparation of sterile radiopharmaceuticals shall be carried out in a positive pressure clean room with a negative pressure airlock. The negative pressure airlock shall be efficient to ensure containment. Entrance and exit of the room shall be via a containment airlock or a sink airlock (or negative sink)

4.11 Air handling systems for clean room shall be fitted with alarms so that the working personnel are warned of any failure of the systems especially air pressure differential

4.12 Air pressure gauges shall be installed at appropriate location normally right outside each clean room

4.13 A control panel for monitoring of clean room temperature and humidity shall be located immediately outside the preparation area

4.14 The Radiopharmaceutical Preparation Facilities shall be made lockable and the access shall be restricted to authorized personnel only

4.15 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. Normally, the minimum size of preparation area is double the size of equipment

4.16 Drain for radioactive effluent shall be built to facilitate maintenance, cleaning, minimizing the risk of contamination to other building areas and connected directly to the delay tank

4.17 Material used for buildings and rooms shall be appropriately selected to facilitate cleaning and sanitation process. Aspects of radiation protection shall be taken into consideration

4.18 If design permit, viewing glass shall be made available at suitable location (e.g.: preparation room, away from radioactive source) for supervision purposes

4.19 All major equipments (hot cells, radiopharmaceutical laminar flow safety cabinets, negative pressure isolators, dose calibrators etc.) shall be qualified and routinely calibrated

4.20 Floor, benches and other work surfaces shall be sufficiently strong to bear with the weight of the shielding

4.21 Hot cell used for processing and filling of sterile radioactive substances/products shall be of Grade A air quality. The background shall be of Grade B clean room if a hot cell cabinet is used but Grade D background is acceptable for a hot cell isolator

4.22 Non-sterile radiopharmaceutical products shall be prepared in a negative pressure controlled area to protect the external environment from radioactive contamination. For protection of personnel, work stations such as a radiopharmaceutical laminar flow safety cabinet or a negative pressure isolator shall be used

QUALITY CONTROL

4.23 Due to short half-lives, prepared radiopharmaceuticals can be released and administered to patients immediately without going through the full test. However, there shall be a written procedure detailing all preparation steps and quality control data shall be considered before released

4.24 Quality Control (QC) laboratory shall not be built inside the radiopharmaceutical preparation room. All preparation activities can share the same QC laboratory except blood radiolabeling activity

4.25 Apart from radioiodine and ready-for-use radiopharmaceuticals, quality control activities shall be carried out in separate designated quality control room

STORAGE

4.26 Space of storage areas shall be sufficient to allow orderly storage of various categories of materials and products. Non-radioactive materials shall be stored in accordance to Good Storage Practice Guidelines (GSP)

4.27 Each radiopharmaceutical preparation facility shall have dedicated store for radioactive materials, non-radioactive materials and radioactive waste. However these rooms can be shared between all the activities carried out within the Nuclear Medicine Department

4.28 Appropriate transportation aids (e.g. trolley) shall be used to carry heavy radioactive sources, Technetium-99m generators, phantoms and others

4.29 A separate designated storage area for radioactive and non-radioactive materials shall be provided to minimize radiation exposure. Requirement for radiation protection shall be complied with

ANNEX 1:
KIT-BASED RADIOPHARMACEUTICALS

ANNEX 1

KIT-BASED RADIOPHARMACEUTICALS

A kit-based radiopharmaceutical is a ready-made non-radioactive product (cold kit) that has been labeled with radioactive such as Tc-99m.

PRINCIPLES

1. Personnel shall be appropriately trained and qualified to work in nuclear pharmacy with respect to preparation, quality control, regulatory requirement and radiation protection

2. Personnel required to work in sterile preparation area shall undergo proper training and must be competent in aseptic technique, Good Preparation Practice (GPP), Good Radiopharmacy Practice (GRP) and basic microbiology

3. All sterile kit-based radiopharmaceutical preparations shall be produced in qualified clean room facilities designed and built in accordance to GPP requirement

4. Dedicated air conditioning system shall be used for preparation areas. Air from operations involving radioactivity should be exhausted through appropriate filters that are regularly checked for performance

5. Clean rooms shall be designed and built by qualified clean room contractors. The proposed layout plan, grades and control parameters shall be submitted to Pharmacy Practice and Development Division of Ministry of Health for approval prior to the development of the facilities

6. Upon commissioning by the contractor, clean rooms and their major equipment shall be tested by an independent third party agent for conformation of compliance to standards. The testing agent shall be certified by appropriate certification bodies such as National Associations of Testing Authorities (NATA) or National Environmental and Balancing Bureau (NEBB)

7. Prior to use, clean room facilities shall be inspected and qualified by auditors from the Pharmacy Practice and Development Division of Ministry of Health Malaysia and subsequently approval letter for use shall be issued

8. Conformation on radiation safety aspect shall be given by the Radiation Health and Safety Section of Engineering Services Division of the Ministry of Health prior to use

9. Qualified clean room facilities will be inspected routinely by auditors from the Pharmacy Practice and Development Division of Ministry of Health

10. Calibration of equipment including monitoring devices used shall be conducted by an accredited agents

11. Clean rooms and all equipment shall be maintained regularly according to approved planned preventive maintenance procedures. The maintenance shall include thorough cleaning and testing by the certified testing agent. Microbial monitoring shall be done regularly depending on the usage of the facilities and outcome of the test results

12. Elution from generators, preparing including radiolabeling and dispensing of radiopharmaceuticals shall be done in a Grade A workstation

13. Access to the control area shall be via a gowning area and be restricted to authorized personnel only

14. Kit-based radiopharmaceutical preparation room can be shared with the preparation of radiopharmaceuticals for radioimmunotherapy

LAYOUT, DESIGN AND SPECIFICATIONS

15. Premises and utilities for each radiopharmaceutical preparation facility shall be separated from each other to avoid mix-up or cross contamination between products. However, certain rooms such as stores, radioactive waste room and quality control room can be shared between different facilities

16. 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. Normally, the minimum size of preparation area is double the size of equipment to be installed in the room

17. The entry, flow and exit patient and staff shall be separated from the entry, flow and exit of radioactive material

18. Ideally, this facility shall have dedicated rooms for :

    i. Preparation Room
    ii. Component Room
    iii. Changing Room
    iv. Quality Control Room
    v. Gowning Room
    vi. Negative Airlock
    vii. Radioactive Store
    viii. Non-Radioactive Store
    ix. Radioactive Waste Room

    However, in case of space constraints gowning room may serve as a negative airlock provided there are radiation detector / monitoring devices available in the room

19. Except in personnel change room, sinks and drains shall not be installed in any preparation area

20. 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

21. Adequate lighting shall be provided in all clean rooms. Normally, a range of 500 - 600 lux ensures personnel comfort and ability to perform 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

22. 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)

FACILITY REQUIREMENTS

23. For existing facilities, a certified agent shall be appointed to test the performance of the facilities on a regular basis

24. Kit-based radiopharmaceutical preparations and radiolabeled blood preparations shall be performed in separate workstation to prevent cross-contamination

25. All surfaces (walls, floor, tables and furniture) shall be made out of materials easy to clean, disinfect and decontaminate in case of a radioactive spillage

26. 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

27. 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

28. Bare wood, ledges and other unsealed surfaces shall be avoided in clean rooms

29. 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 of the latter

30. Sink for hand washing can be fitted in the first or earlier part of the changing room. The preparation room shall not contain any sink or floor drains

31. 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

32. 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

33. 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

34. Preparation room shall be of Grade B if a radiopharmaceutical laminar flow safety cabinet is used. If an isolator (negative pressure isolator) is used, the room shall be of at least Grade D air quality

35. Utility cabinet, work bench and stainless steel sink with an appropriate depth to avoid splashing shall be fitted in the component room

36. Material airlock (e.g. trolley height pass box) with interlocked doors shall be used for transferring in materials (e.g. components, cleaning materials and equipment). If a one way flow of facility is not possible, the material airlock can be used for transferring materials and products out as well

37. Adequate numbers of plug points shall be made available. 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 radiopharmaceutical laminar flow safety cabinet / hot-cell and HVAC system

38. Quality control room shall be built equipped with sufficient equipments and glassware including radiation shielding such as lead glass and lead bricks. There should be radioactive sign / label for radiation working area

39. Heating, Ventilation and Air-conditioning (HVAC) System

    i. 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)

    ii. Due consideration shall be given in planning the placement of room HEPA filters and cabinets to be installed so as to avoid airflow obstruction. Diffusers shall not be used

    iii. Pre-filters (primary and secondary) of AHU and HEPA filters shall be changeable from outside the clean room

    iv. 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

    v. Equipment installed shall not jeopardize the set room conditions including temperature, humidity, air pressure, noise level, etc.

    vi. Air pressure shall be made higher in the cleaner grade of clean rooms

    vii. Air return grilles shall be located at a low-level to sweep or purge the rooms

    viii. Re-circulation of air extracted from area where radioactive products are handled should be avoided. Air outlets should be designed to minimize environmental contamination by radioactive particles and gases and appropriate measures should be taken to protect the controlled areas from particulate and microbial contamination

ix. 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 ± 5%)
- Pressure differentials (10 – 15 Pascals)
- Material flow
- Personnel flow

40. Radiation protection system shall be implemented to monitor any radiation contamination within the facilities

41. Environmental monitoring system shall be in placed to monitor the kit based areas from particles and bacterial contaminations

42. Dose calibrator(s) shall be properly shielded from background activity influences

LIST OF EQUIPMENT REQUIRED

43. Preparation Room

i. Grade A Radiopharmaceutical Isolator OR Radiopharmaceutical Laminar Flow Safety Cabinet; lead-lined with sliding L-shape lead barrier, built-in dose calibrator, generator elution port and radioactive waste container
ii. Hot plate or water bath; lead shielded
iii. Lead vial container
iv. Lead syringe shield
v. Lead carrier
vi. Lead brick
vii. Radiation survey meter
viii. Surface contamination detector
ix. Handling aids (eg. tongs, forceps)
x. Trolley; two tiers, heavy duty (200kg load), stainless steel
xi. Lead syringe holder
xii. Work bench; phenolic top OR other suitable equivalent material
xiii. Intercom system
xiv. Sanitisable stool with wheels and adjustable height
xv. Radiation environment detector; wall mounted
xvi. Stop watch

44. Component Room

i. Rack/shelves; stainless steel (to keep sterile syringes, needles, filters, etc)
ii. Workbench; phenolic top with drawers, or stainless steel
iii. Trolley; two tiers, heavy duty (200kg load), stainless steel
iv. Sink; stainless steel
v. Intercom system

45. Personnel Gowning Room

i. Garment cabinet or five-tier lockers for sterile gloves, head caps, mask
ii. Six feet long mirror; wall mounted
iii. Cross over bench

46. Personnel Changing Room

i. Sink with elbow tap; stainless steel
ii. Cabinet (to hang street clothes)
iii. Liquid soap dispenser (foot-operated)
iv. Electrical hand dryer
v. Six feet long mirror; wall mounted
vi. Cross over bench
vii. Hand and foot contamination detector (to be placed in the common corridor within the preparation facility)

47. Change area

i. Shoe rack

48. Quality Control Laboratory

i. Forceps
ii. Tongs
iii. Gamma counter / Dose calibrator
iv. Bench top shield
v. Laboratory glasswares (e.g. beakers, test tubes, measuring cylinders, pipettes, burettes, conical flask etc.)
vi. Radio-Thin Layer Chromatography
vii. Sink with elbow tap; stainless steel
viii. Radiation detector / Survey meter
ix. Storage for sample / Chemical
x. Lead shielding / Lead glass / Lead bricks
xi. Radioactive waste container

49. Radioactive store

i. Radioactive cabinet
ii. Trolley; platform, heavy duty (200kg load)
iii. Forceps, tongs

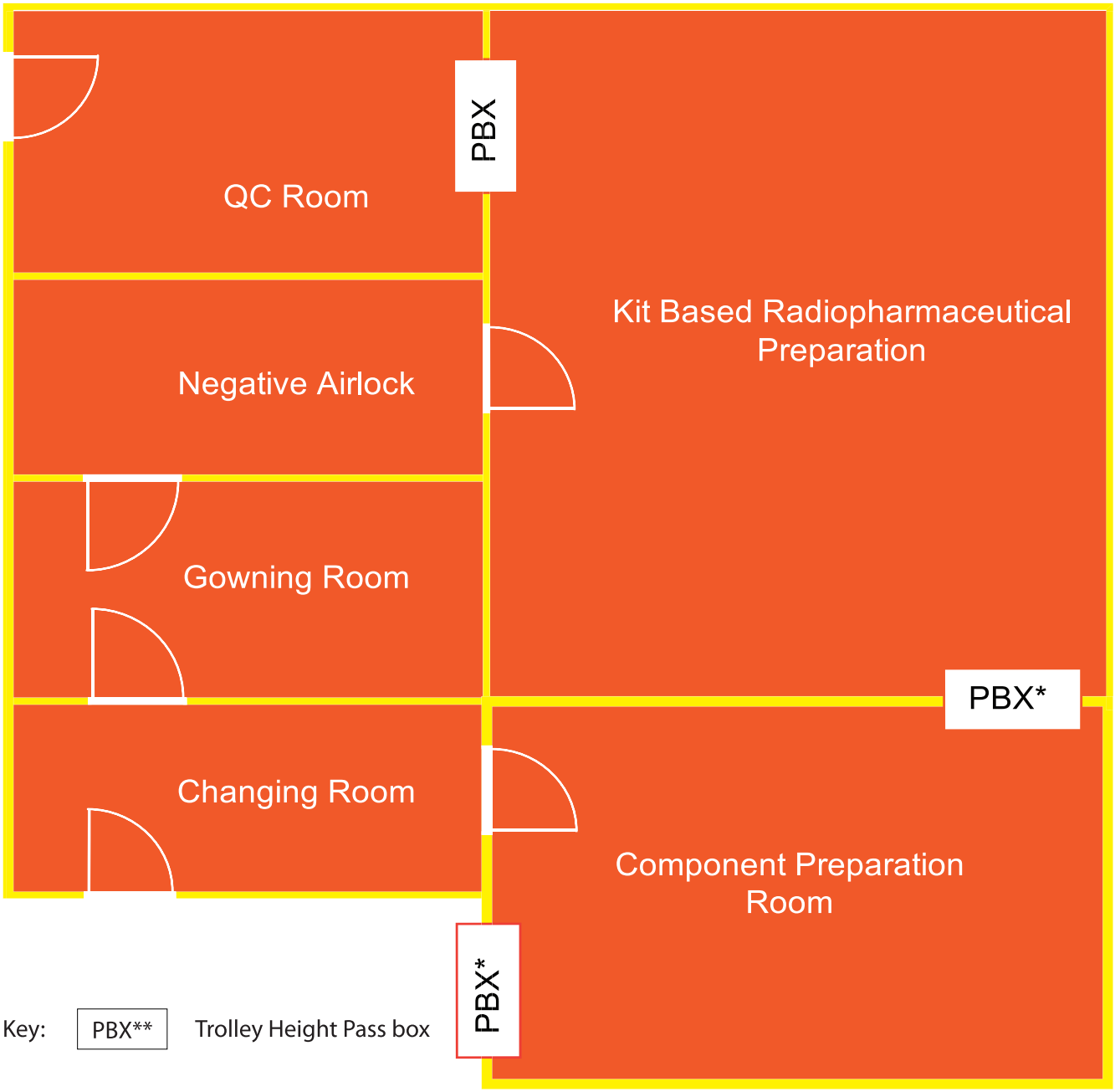
50. Non-radioactive store

i. Pharmaceutical refrigerator
ii. Rack / shelves
iii. Trolley; platform heavy duty (200kg load)
iv. Trolley; two tiers, heavy duty (200kg load)

51. Radioactive waste room

i. Drums, waste tank
ii. Survey meter
iii. Decontamination kit

EXAMPLE OF KIT-BASED RADIOPHARMACEUTICAL FACILITY LAYOUT PLAN



ANNEX 2 :
PET RADIOPHARMACEUTICAL

ANNEX 2

PET RADIOPHARMACEUTICAL

PET (Positron Emission Tomography) Radiopharmaceutical is a sterile cyclotron produced radiopharmaceutical such as F-18 FDG (Fluorodeoxyglucose), F-18 FDOPA and C-11 Methionine.

They are normally indicated for diagnosis of tumour, study of organ function such as heart and brain as well as for research and development.

PRINCIPLES

1. Personnel shall be appropriately trained and qualified to work in PET radiopharmaceutical preparation facility with respect to preparation, quality control, regulatory requirement and radiation protection

2. Personnel required to work in sterile preparation area shall undergo proper training and must be competent in aseptic technique, Good Manufacturing Practice (GMP) and basic microbiology

3. All sterile PET radiopharmaceutical preparations shall be produced in qualified clean room facilities designed and built in accordance to Good Manufacturing Practice (GMP) requirement

4. Dedicated air conditioning system shall be used for preparation areas. Air from operations involving radioactivity should be exhausted through appropriate filters that are regularly checked for performance

5. Clean rooms shall be designed and built by qualified clean room contractors. The proposed layout plan, grades and control parameters shall be submitted to Pharmacy Practice and Development Division of Ministry of Health for approval prior to the development of the facilities

6. Upon commissioning by the contractor, clean rooms and their major equipment shall be tested by an independent third party agent for conformation of compliance to standards. The testing agent shall be certified by appropriate certification bodies such as National Associations of Testing Authorities (NATA) or National Environmental and Balancing Bureau (NEBB)

7. Prior to use, clean room facilities shall be inspected and qualified by auditors from the Pharmacy Practice and Development Division of Ministry of Health Malaysia and subsequently approval letter for use shall be issued

8. Conformation on radiation safety aspect shall be given by the Radiation Health and Safety Section of Engineering Services Division of the Ministry of Health prior to use

9. Qualified clean room facilities will be inspected routinely by auditors from the Pharmacy Practice and Development Division of Ministry of Health

10. Calibration of equipment including monitoring devices shall be conducted by an accredited agents

11. Clean rooms and all equipment shall be maintained regularly according to approved planned preventive maintenance procedures. The maintenance shall include thorough cleaning and testing by the certified testing agent. Microbial monitoring shall be done regularly depending on the usage of the facilities and outcome of the test results

12. Access to the clean rooms shall be via gowning/changing room and be restricted to authorized personnel only

LAYOUT, DESIGN AND SPECIFICATIONS

13. Premises and utilities for each radiopharmaceutical preparation facility shall be separated from each other to avoid mix-up or cross contamination between products. However, certain rooms such as stores, radioactive waste room and quality control room can be shared between different facilities

14. 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. Normally, the minimum size of preparation area is double the size of equipment to be installed in the room

15. The entry, flow and exit patient and staff shall be separated from the entry, flow and exit of radioactive material

16. Ideally, this facility shall have dedicated rooms for :

i. Radioisotope Preparation
- Cyclotron Vault
- Cyclotron Control Room
- Gas Room
- Equipment Room
- Service Room

ii. Radiopharmaceutical Preparation
- Production Room
- Component Room
- Utility Room
- Negative Airlock
- Gowning Room
- Changing Room

- Finish Product Room including Quarantine Area

iii. Quality Control Laboratory

iv. Store
- Starting Material Area
- Consumable Storage Area

However, in case of space constraints gowning room may serve as a negative airlock provided there are radiation detector / monitoring devices available in the room

17. Except in personnel change room, sinks and drains shall not be installed in any preparation area

18. 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

19. Adequate lighting shall be provided in all clean rooms. Normally, a range of 500 - 600 lux ensures personnel comfort and ability to perform 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

20. 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)

FACILITY REQUIREMENTS

21. For existing facilities, a certified agent shall be appointed to test the performance of the facilities on a regular basis

22. Hot cells are essential for PET radiopharmaceutical preparation thus the clean room environment shall be of at least Grade C

23. All critical processes such as filling shall be done in a Grade A hot cell

24. All surfaces (walls, floor, tables and furniture) shall be made out of materials easy to clean, disinfect and decontaminate in case of a radioactive spillage

25. 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

26. 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

27. Bare wood, ledges and other unsealed surfaces shall be avoided in clean rooms

28. 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 of the latter

29. Sink for hand washing can be fitted in the first or earlier part of the changing room. The preparation room shall not contain any sink or floor drains

30. 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

31. 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

32. 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

33. Component room shall be Grade C or D and shall be entered by personnel via a personnel change room of a similar grade

34. Appropriate cleaning facilities shall be made available in the component room whenever cleaning of utensils is carried out

35. Utility cabinet, work bench and stainless steel sink with an appropriate depth to avoid splashing shall be fitted in the component room

36. Material airlock (e.g. trolley height pass box) with interlocked doors shall be used for transferring in materials (e.g. components, cleaning materials and equipment). If a one way flow of facility is not possible, the material airlock can be used for transferring materials and products out as well

37. Dedicated quality control room shall be built equipped with sufficient equipments and glassware

38. Adequate numbers of plug points shall be made available. 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 hot cell and HVAC system

39. Heating, Ventilation and Air-conditioning (HVAC) System

i. 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)

ii. Due consideration shall be given in planning the placement of room HEPA filters and cabinets to be installed so as to avoid airflow obstruction. Diffusers shall not be used

iii. Pre-filters (primary and secondary) of AHU and HEPA filters shall be changeable from outside the clean room

iv. 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

v. Equipment installed shall not jeopardize the set room conditions including temperature, humidity, air pressure, noise level, etc.

vi. Air pressure shall be made higher in the cleaner grade of clean rooms

vii. Air return grilles shall be located at a low-level to sweep or purge the rooms

viii. Re-circulation of air extracted from area where radioactive products are handled should be avoided. Air outlets should be designed to minimize environmental contamination by radioactive particles and gases and appropriate measures should be taken to protect the controlled areas from particulate and microbial contamination

ix. 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 ± 5%)
- Pressure differentials (10 – 15 Pascals)
- Material flow
- Personnel flow

40. Radiation monitoring system shall be implemented to monitor any radiation contamination within the facilities

41. Environmental monitoring system shall be in placed to monitor the clean rooms from particles and bacterial contaminations

LIST OF EQUIPMENT REQUIRED

42. Radioisotope Preparation Area

i. Cyclotron room
- Cyclotron
- Detector
- CCTV monitoring system
- Gas detector

ii. Cyclotron Control room
- Computer
- Radiation monitoring system; computerised
- File cabinet

iii. Gas room
- Gas cylinder tank
- Gas cylinder tank holder

iv. Equipment room
- Server
- Cooling system
- Radiation detector

v. Service room
- Locker for maintenance tool
- Drain for delivery line

43. Radiopharmaceutical Preparation Area

i. Production room

- Grade A Hot cell ; for critical activity such as filling
- Lead shielded waste container; stainless steel
- Waste container; stainless steel
- Lead vial container for PET Radiopharmaceutical
- Radiation survey meter
- Installed area radiation monitor
- Handling aids (eg. tongs, forceps)
- Trolley: two-tier, heavy duty, stainless steel
- Work bench; phenolic top, or stainless steel
- Intercom system
- Sanitisable stool with wheels and adjustable height
- Unidirectional (Laminar) Air Flow Cabinet, if necessary

ii. Component room

- Rack/shelves for keeping of sterile syringes, needles, filters, etc.; stainless steel
- Workbench; phenolic top with drawers, or stainless steel
- Trolley; two-tier, stainless steel
- Sink; stainless steel
- Intercom system

iii. Airlock

iv. Personnel Gowning Room

- Garment cabinet or five-tier lockers for sterile gloves, head caps, mask
- Mirror; six feet long, wall mounted
- Cross over bench

v. Personnel Changing Room

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

i. Finish Product Room

- Survey meter

- Rack/shelves
- Lead transport box
- Trolley; platform, heavy duty (200kg load)

44. Quality Control Room

i. Handling aids (forceps, tongs, capper, decapper)
ii. Cabinet for solid chemical
iii. Cabinet for inflammable chemical
iv. Radiation survey meter
v. PET L-shield
vi. Laboratory glassware (e.g. beakers, test tubes, measuring cylinders, conical flask etc.)
vii. Chromatography devices
- Radio-High Performance Liquid Chromatography with suitable detector
- Radio-Thin Layer Chromatography
- Gas Chromatography

viii. pH meter
ix. Gamma spectrophotometer
x. Analytical balance
xi. Oven
xii. Pharmaceutical refrigerator connected to an essential power supply
xiii. Deep freezer connected to an essential power supply
xiv. Vacuum pump and filter apparatus
xv. Rack/shelves/cabinet/work bench
xvi. Bubble point test apparatus
xvii. Radioactive waste shielded container
xviii. Burettes
xix. Pipettes
xx. Water filter
xxi. Water deionizer
xxii. Stool with wheels and adjustable height
xxiii. Developing chamber

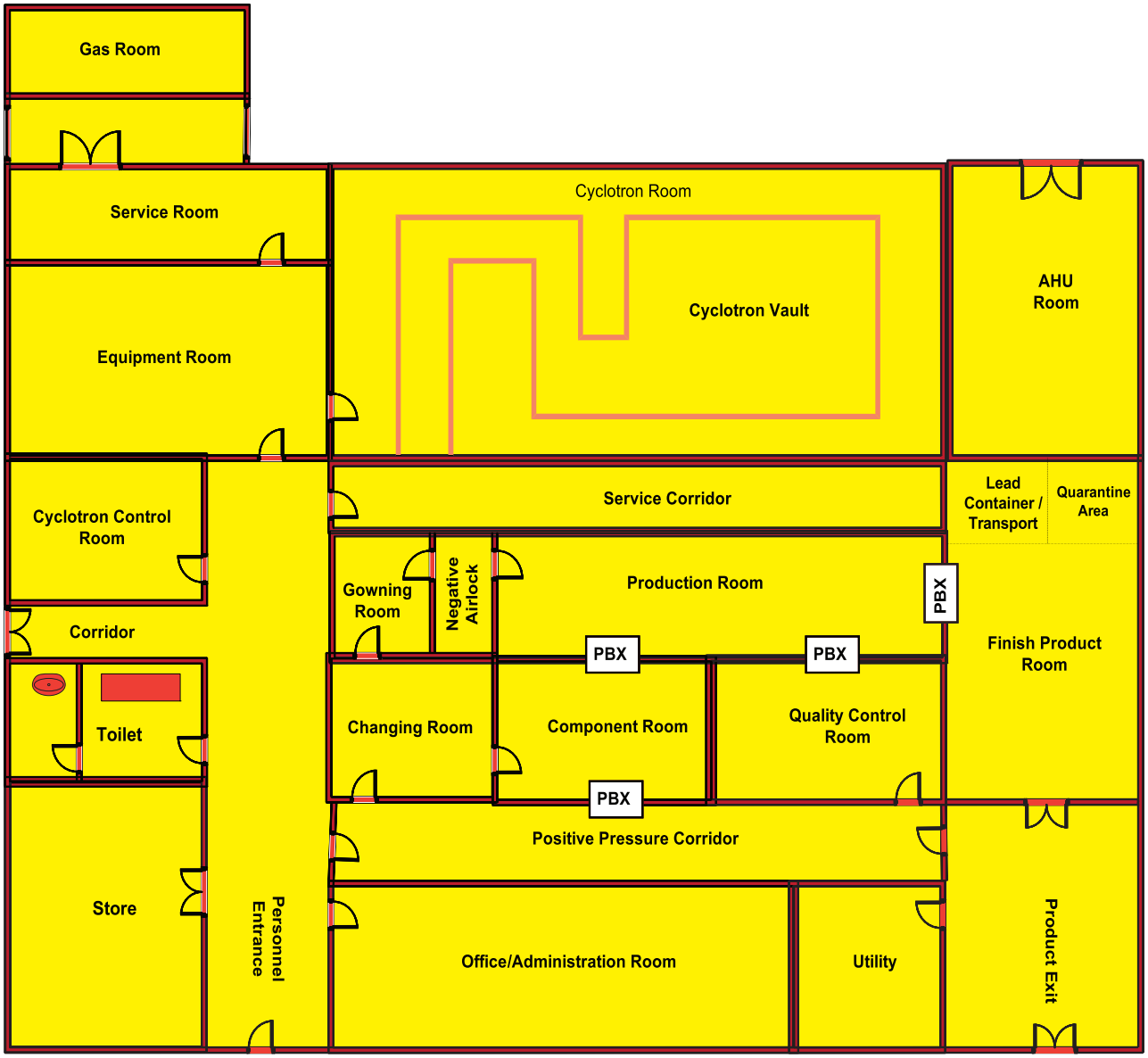
45. Store

i. Rack/shelves
ii. Trolley: platform, heavy duty (200kg load)
iii. Trolley; two-tier, heavy duty (200kg load)
iv. Chemical decontamination kit

46. Miscellaneous Room

i. Administration Office
ii. Staff Rest room
iii. Toilet
iv. Locker room
v. Utility room/Housekeeping

EXAMPLE OF PET RADIOPHARMACEUTICAL FACILITY LAYOUT PLAN



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*Note: Maize structure for cyclotron room is not required if the cyclotron vault is shielded

ANNEX 3:
RADIOLABELED BLOOD PREPARATION: IN-VITRO

ANNEX 3

RADIOLABELED BLOOD PREPARATION: IN-VITRO

In-vitro blood radiolabeling is a process of labeling the blood component such as platelet, red blood cells and white blood cells with radiotracers prior to administration to patients.

PRINCIPLES

1. Personnel shall be appropriately trained and qualified to work in nuclear pharmacy with respect to preparation, quality control, regulatory requirement and radiation protection

2. Personnel required to work in sterile preparation area shall undergo proper training and must be competent in aseptic technique, Good Preparation Practice (GPP), Good Radiopharmacy Practice (GRP) and basic microbiology

3. Qualified personnel is required for safe operations such as aseptic cell manipulation, radiolabeling of autologous blood cell, transfer of sterile solutions, handling of biological material and operator protection methods from biohazard materials

4. All in-vitro blood radiolabeling preparations shall be produced in qualified clean area facilities designed and built in accordance to Good Preparation Practice (GPP) requirement

5. Dedicated air conditioning system shall be used for preparation areas. Air from operations involving radioactivity should be exhausted through appropriate filters that are regularly checked for performance

6. Clean rooms shall be designed and built by qualified clean area contractors. The proposed layout plan, grades and control parameters shall be submitted to Pharmacy Practice and Development Division of Ministry of Health for approval prior to the development of the facilities

7. Upon commissioning by the contractor, clean rooms and their major equipment shall be tested by an independent third party agent for conformation of compliance to standards. The testing agent shall be certified by appropriate certification bodies such as National Associations of Testing Authorities (NATA) or National Environmental and Balancing Bureau (NEBB)

8. Prior to use, clean room facilities shall be inspected and qualified by auditors from the Pharmacy Practice and Development Division of Ministry of Health Malaysia and subsequently approval letter for use shall be issued

9. Conformation on radiation safety aspect shall be given by the Radiation Health and Safety Section of Engineering Services Division of the Ministry of Health prior to use the facility

10. Qualified clean room facilities will be inspected routinely by auditors from the Pharmacy Practice and Development Division of Ministry of Health

11. Appropriate cleaning procedure shall be in place for isolators (Grade A negative pressure) or Radiopharmaceutical Laminar Flow Safety Cabinet and centrifuge buckets to ensure there is no mix-up contamination

12. Calibration of equipments including monitoring devices shall be conducted by an accredited agents

13. Clean rooms and all equipment shall be maintained regularly according to approved planned preventive maintenance procedures. The maintenance shall include thorough cleaning and testing by the certified testing agent. Microbial monitoring shall be done regularly depending on the usage of the facilities and outcome of the test results

14. Only one blood radiolabeling procedure shall be performed at one time

15. Necessary procedure shall be in place to avoid needle stick injuries

16. Access to the control area shall be via a gowning area and be restricted to authorized personnel only

17. The protection of operators towards biological and radiation hazard is of paramount important

18. Staff health program shall be well planned and executed including vaccination

19. Biological waste shall be disposed in accordance to hospital policy and radioactive waste shall be dealt with applied local rules

LAYOUT, DESIGN AND SPECIFICATIONS

20. Premises and utilities for each radiopharmaceutical preparation facility shall be separated from each other to avoid mix-up or cross contamination between products. However, certain rooms such as stores, radioactive waste room and quality control room can be shared between different facilities

21. 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. Normally, the minimum size of preparation area is double the size of equipment to be installed in the room

22. The entry, flow and exit patient and staff shall be separated from the entry, flow and exit of radioactive material

23. Ideally, this facility shall have dedicated rooms for :

i. Blood Radiolabeling Room
ii. Component Room
iii. Changing Room
iv. Quality Control Room
v. Gowning Room
vi. Negative Airlock
vii. Radioactive Store
viii. Non-Radioactive Store
ix. Radioactive Waste Room

However, in case of space constraints gowning room may serve as a negative airlock provided there are radiation detector / monitoring devices available in the room

24. Except in personnel change room, sinks and drains shall not be installed in any radiopharmaceutical preparation area and gowning

25. 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

26. Adequate lighting shall be provided in all clean rooms. Normally, a range of 500 - 600 lux ensures personnel comfort and ability to perform 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

27. 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)

FACILITY REQUIREMENTS

28. For existing facilities, a certified agent shall be appointed to test the performance of the facilities on a regular basis

29. Radiolabeled blood preparations and kit-based radiopharmaceutical preparations shall be performed in a separate workstation to prevent cross-contamination

30. All surfaces (walls, floor, tables and furniture) shall be made out of materials easy to clean, disinfect and decontaminate in case of a radioactive spillage. Normally, sink is not required in blood radiolabeling room

31. 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

32. 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

33. Bare wood, ledges and other unsealed surfaces shall be avoided in clean rooms

34. 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 of the latter

35. Sink for hand washing can be fitted in the first or earlier part of the changing room. The preparation room shall not contain any sink or floor drains

36. 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

37. 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

38. 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

39. Blood radiolabeling room and gowning room shall be of Grade B if a radiopharmaceutical laminar flow safety cabinet is used

40. Blood radiolabeling room and gowning room shall be of Grade D if a negative pressure isolator is used

41. Radiopharmaceutical laminar flow safety cabinet or a total containment workstation (negative pressure isolator) shall be used as a workstation

42. Utility cabinet, work bench and stainless steel sink with an appropriate depth to avoid splashing shall be fitted in the component room

43. Material airlock with interlocked doors shall be used for transferring in materials (e.g. components, cleaning materials and equipment). If a one way flow of facility is not possible, the material airlock can be used for transferring materials and products out as well

44. Quality control room shall be built equipped with sufficient equipments and glassware

45. Adequate numbers of plug points shall be made available. 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 radiopharmaceutical laminar flow safety cabinet / isolator and HVAC system

46. Heating, Ventilation and Air-conditioning (HVAC) System

i. 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)

ii. Due consideration shall be given in planning the placement of room HEPA filters and cabinets to be installed so as to avoid airflow obstruction. Diffusers shall not be used

iii. Pre-filters (primary and secondary) of AHU and HEPA filters shall be changeable from outside the clean room

iv. 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

v. Equipment installed shall not jeopardize the set room conditions including temperature, humidity, air pressure, noise level, etc.

vi. Air pressure shall be made higher in the cleaner grade of clean rooms

vii. Air return grilles shall be located at a low-level to sweep or purge the rooms

viii. Re-circulation of air extracted from area where radioactive products are handled should be avoided. Air outlets should be designed to minimize environmental contamination by radioactive particles and gases and appropriate measures should be taken to protect the controlled areas from particulate and microbial contamination

ix. 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 ± 5%)
- Pressure differentials (10 – 15 Pascals)
- Material flow
- Personnel flow

47. Radiation protection system shall be implemented to monitor any radiation contamination within the facilities

48. Environmental monitoring system shall be in placed to monitor the blood radiolabeling areas from particles and bacterial contaminations

49. The dose calibrator(s) shall be properly shielded from background activity influences

LIST OF EQUIPMENT REQUIRED

50. Blood Radiolabeling Room

i. Blood Radiolabeling Isolator OR Radiopharmaceutical Laminar Flow Safety Cabinet; lead lined, with sliding L-shape lead barrier, built-in dose calibrator and waste container
ii. Lead vial container
iii. Lead syringe shield
iv. Lead brick
v. Radiation survey meter
vi. Contamination surface detector; portable
vii. Radiation environment monitor
viii. Tongs
ix. Forceps
x. Trolley; two tiers, stainless steel
xi. Lead syringe holder
xii. Intercom system
xiii. Stool with wheels and adjustable height; stainless steel
xiv. Stopwatch
xv. Plug point

xvi. Rotator
xvii. Tray; stainless steel
xviii. Centrifuge

51. Component Room

i. Rack/shelves for keeping of sterile syringes, needles, filters, etc.; stainless steel
ii. Workbench; phenolic top with drawers, or stainless steel
iii. Trolley; two tiers, stainless steel
iv. Sink; stainless steel
v. Intercom system

52. Personnel Gowning Room

i. Garment cabinet or five-tier lockers for sterile gloves, head caps, mask
ii. Six feet long mirror; wall mounted
iii. Cross over bench

53. Personnel Changing Room

i. Sink with elbow tap; stainless steel
ii. Cabinet (to hang street clothes)
iii. Liquid soap dispenser (foot-operated)
iv. Electrical hand dryer
v. Six feet long mirror; wall mounted
vi. Cross over bench
vii. Hand and foot contamination detector (outside the room)

54. Quality Control Laboratory

i. Forceps
ii. Tongs
iii. Gamma counter
iv. Bench top shield
v. Laboratory glasswares (e.g. beakers, test tubes, measuring cylinders, pippetes, burretes, connical flask etc.)
vi. Waste container: lead lined
vii. Sink with elbow tap; stainless steel

55. Radioactive Material Store

i. Radioactive cabinet
ii. Trolley; platform, heavy duty (200kg load)
iii. Forceps, tongs

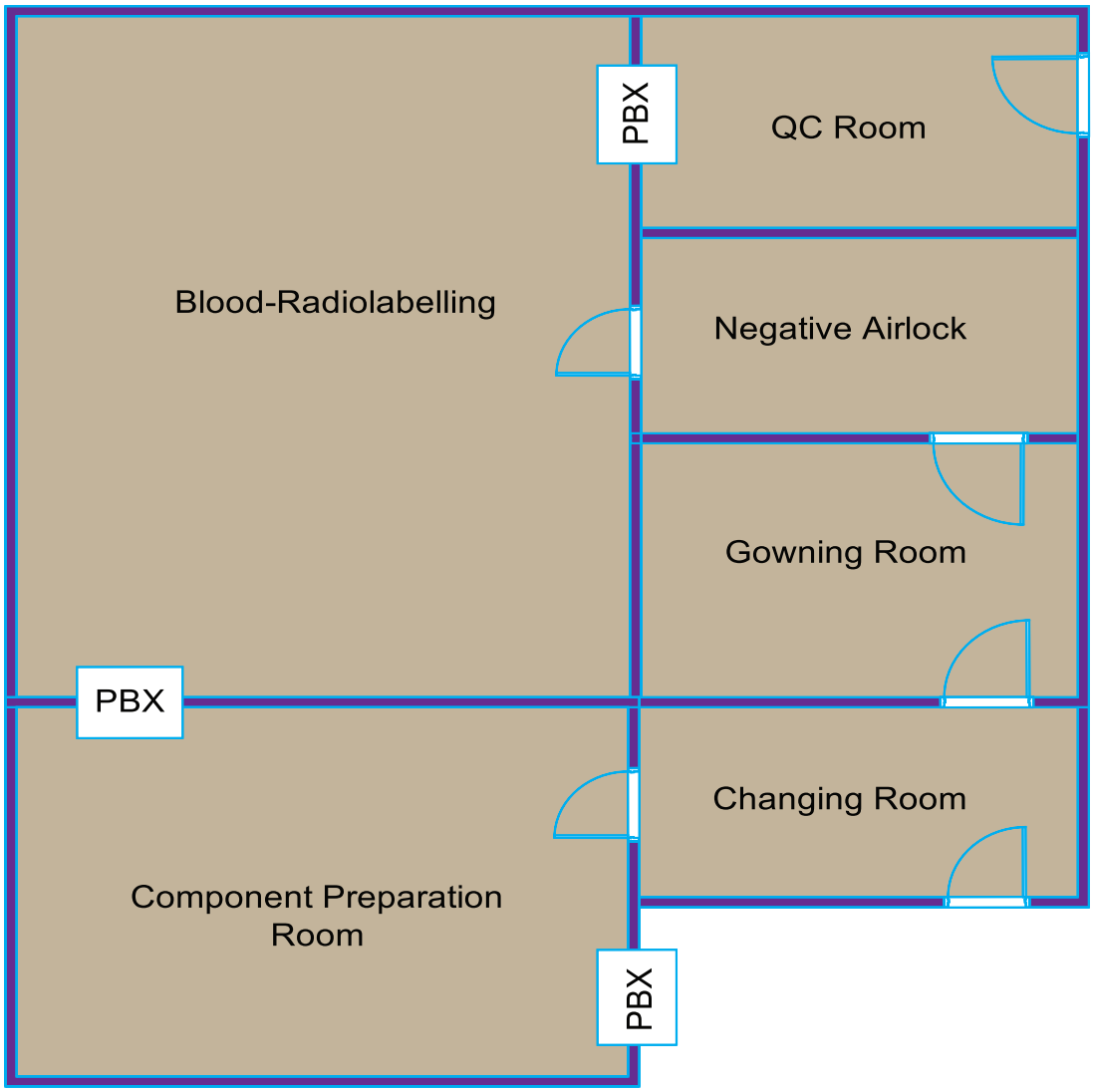
56. Non-radioactive Material Store

i. Pharmaceutical refrigerator
ii. Rack/shelves
iii. Trolley; platform heavy duty (200kg load)
iv. Trolley; two tiers, heavy duty (200kg load)

57. Radioactive Waste Room

i. Drums, waste tank
ii. Survey meter
iii. Decontamination kit

EXAMPLE OF RADIOLABELED BLOOD PREPARATION FACILITY LAYOUT PLAN



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ANNEX 4 :
NON-STERILE RADIOPHARMACEUTICAL - RADIOIODINE

ANNEX 4

NON-STERILE RADIOPHARMACEUTICAL - RADIOIODINE

Radioiodine liquid is a non-sterile radiopharmaceutical that can be prepared by dilution process and administered to patient orally.

PRINCIPLES

1. Preparation facility for oral radioiodine is only required if liquid dosage forms or combination of liquid and capsules dosage forms are being used. Preparation facility is not needed for radioiodine capsule. However dispensing room shall be made available in Nuclear Medicine Department

2. If design permitted, at least two rooms are required for dispensing of radioiodine to outpatient to ensure there is always a room available if spillage (e.g.; patient vomiting) occurred in the other room

3. Centralized radioiodine preparation area shall be considered whenever possible to optimize used of radioactive source and other resources

4. Dedicated air conditioning system shall be used for preparation areas. Air from operations involving radioactivity should be exhausted through appropriate filters that are regularly checked for performance

5. Generally, radioiodine preparation facility shall not be used for the preparation of sterile products. However, low usage sterile radiopharmaceutical products (e.g. ^{90}Yttrium-Ibritumomab for radioimmunotherapy) might be prepared in the radioiodine preparation room with the following conditions;

    - Sterile product preparation shall be done in the negative pressure laminar air flow isolator
    - All requirements for sterile preparation procedures shall be complied with
    - Procedural control shall be in-place to ensure complete segregation of preparation activities of both product

LAYOUT, DESIGN AND SPECIFICATIONS

6. The preparation of non-sterile radiopharmaceuticals shall be carried out in a negative pressure control area with a positive pressure airlock

7. 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. Normally, the minimum size of preparation area is double the size of equipment to be installed in the room

8. The entry, flow and exit patient and staff shall be separated from the entry, flow and exit of radioactive material

9. Ideally, this facility shall have dedicated rooms for:

- Radioiodine Preparation Room
- Personnel Changing Room / Positive Airlock
- Dispensing Room
- Radioactive Waste Room / Area

10. Adequate lighting shall be provided in preparation area. Normally, a range of 500 - 600 lux ensures personnel comfort and ability to perform efficiently and effectively. Lights fixtures shall be flush-mounted in the ceiling and sealed to prevent air leaks. Electrical outlets shall be flushed-mounted, watertight, have no crevices and shall be cleanable

11. 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)

FACILITY REQUIREMENTS

12. Re-circulation of air extracted from area where radioactive products are handled should be avoided. Air outlets should be designed to minimize environmental contamination by radioactive particles and gases and appropriate measures should be taken to protect the controlled areas from particulate and microbial contamination

13. Exhausted air shall be filtered by an appropriate filter in order to prevent contamination. The effectiveness of the filter should be regularly monitored and the filter replaced when necessary. For Radioiodine, absorber units such as activated carbon or silver zeolite shall be installed in the exhaust system

14. A material airlock (e.g. trolley height pass box) with interlocked doors shall be used for transferring in materials (e.g. components, cleaning materials and equipment). If a one way flow of facility is not possible, the material airlock can be used for transferring materials and products out as well

15. Staff and personnel shall be trained and qualified in all aspects related to radioiodine preparation

16. Dedicated room shall be provided for the dispensing of radioiodine preparation

17. Radioiodine liquid shall be prepared in a controlled and unclassified area minimum of ISO Class 9

18. Preparation and storage of unit of dose radioiodine solutions shall be done in a radioiodine fume hood equipped with absorbent (activated carbon / silver zeolite). Therefore, an appropriate size of radioiodine fume hood shall be provided

19. Separate toilet shall be provided for the use of patients. A sign-requesting patient to flush the toilet well and wash their hands shall be displayed to ensure adequate dilution of excreted radioactive material and minimize contamination

20. There shall be a lead barrier between dispenser and the patient in the radioiodine dispensing room

21. Dispensing of radioiodine for inpatient shall be done in the radioiodine ward

22. Dispensing of radioiodine for outpatient shall be done in the dedicated dispensing room

23. It is recommended to provide dedicated route so that the post ingested radioiodine patient will not come in contact with other personnel and patients. This is to avoid unnecessary radiation exposure to personnel working in the area

LIST OF EQUIPMENT REQUIRED

24. Personnel Changing Room

    i. Sink with elbow tap; stainless steel
    ii. Six foot long mirror; wall mounted
    iii. Cabinet (to hang personal/street clothes)
    iv. Liquid soap dispenser (foot-operated)
    v. Electric hand dryer
    vi. Personnel Protective Equipment (e.g.; lead apron, lead thyroid shield, lead glove, goggles, half mask respirator)

25. Preparation Room

i. Radioiodine/Radioisotope Fume Hood ; lead lined with disposable activated carbon filter and sliding L-shaped lead barrier
ii. Pipettes (1-200 ul, 200-1000 ul, 1-5 ml)
iii. Lead lined waste container
iv. Contamination monitor
v. Dose calibrator with vial/syringe dipper & printer
vi. Radiation survey meter
vii. Lead bricks, interlocking
viii. Stool with wheels and adjustable height
ix. Workbench; stainless steel or phenolic top
x. Radioactive decontamination kits

26. Dispensing to outpatient; room shall have:

i. Lead lined mobile barrier
ii. Chair
iii. Dispensing table
iv. Lead-lined waste container
v. Radioactive decontamination kits

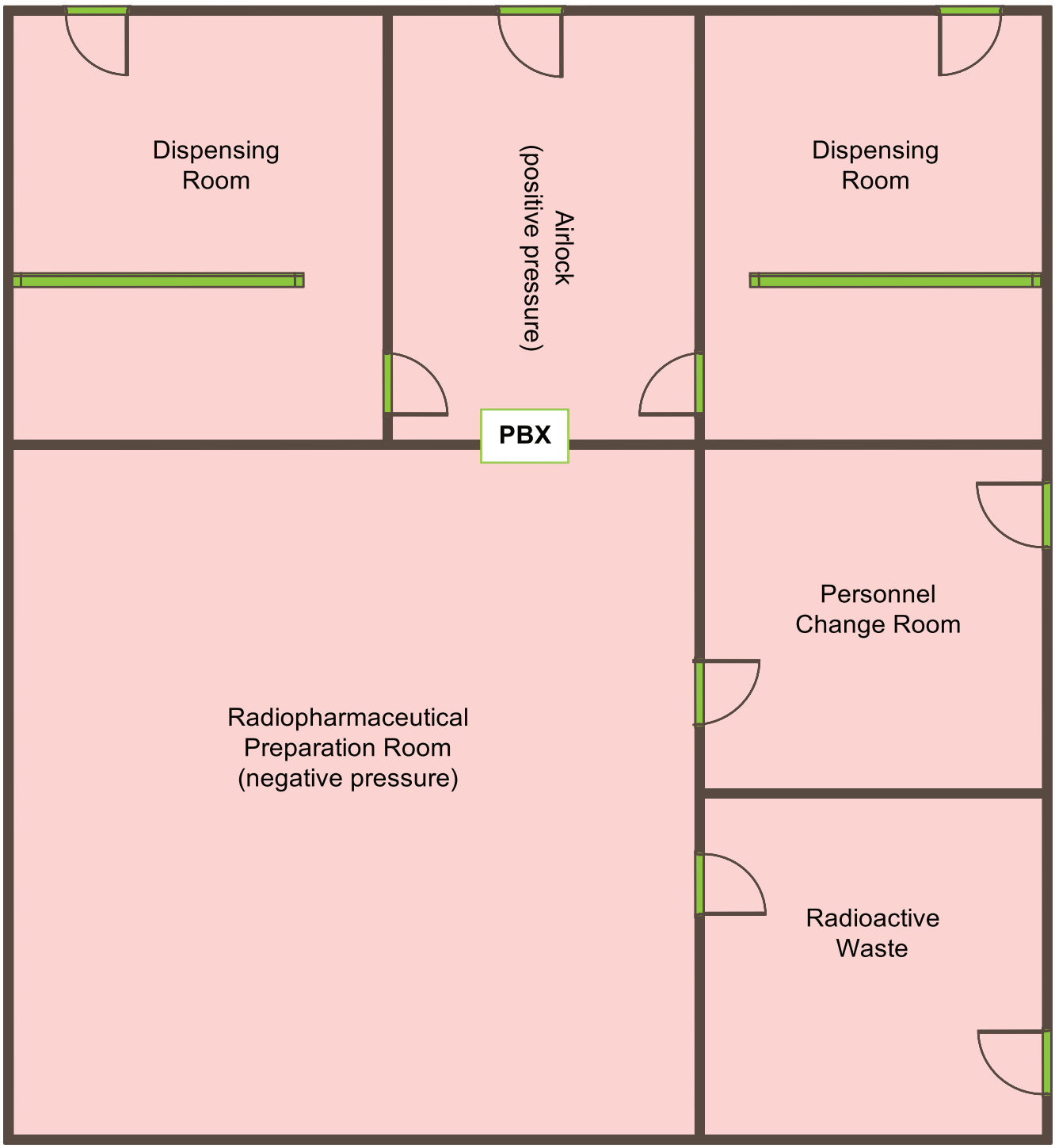
27. Dispensing to inpatient

i. Motorized trolley for radioiodine transfer

28. Radioactive Waste Room

i. Storage container radioactive waste
ii. Lead shielded drums for gloves, syringe, vials
iii. Radioactive decontamination kits

EXAMPLE OF RADIOIODINE FACILITY LAYOUT PLAN



Key: Lead Barrier; mobile

PBX Trolley Height Pass box

ANNEX 5 :
MISCELLANEOUS

ANNEX 5

MISCELLANEOUS

This annex addresses facility requirement for products that are not discussed in the earlier annexes of these guidelines.

i) Ready-for-use radiopharmaceutical usually supplied as sterile (e.g. Gallium-67 Citrate, Iodine-131 MIBG, F-18 FDG) and non-sterile (e.g.Iodine -131 capsule)

ii) Radiopharmaceutical for Radioimmunotherapy (e.g.Yttrium-90 Ibritumomab usually supplied as separate vials of Yttrium-90 Chloride Solution and Ibritumomab Tiuxetan Solution)

FACILITY REQUIREMENTS

1. Ready-for-use radiopharmaceutical

   i) Sterile products

   Unclassified, controlled dispensing room for dosing/dilution shall be made available equipped with appropriate equipment. A dedicated room shall be provided for injection of radiopharmaceutical

   ii) Non-sterile products

   An unclassified room shall be made available for dispensing (opening of container and checking of activity) and administering of radioiodine capsule

   iii) Sterile and Non-sterile products

   Unclassified, controlled dispensing room shall be made available with appropriate equipment for both activities:

   - Dosing and dilution of radiopharmaceutical injection
   - Opening of container and checking the activity of radioiodine capsule

   A dedicated room shall be provided for injection of radiopharmaceutical and radioiodine capsule. Both products can be administered in the same room

2. Radiopharmaceutical for Radioimmunotherapy

   Preparation of radiopharmaceuticals for radioimmunotherapy can be shared with preparation of kit-based radiopharmaceutical preparations room

LIST OF EQUIPMENT REQUIRED

3. Dispensing Room – Sterile (e.g. Gallium-67 Citrate, Iodine-131 MIBG, F-18 FDG)

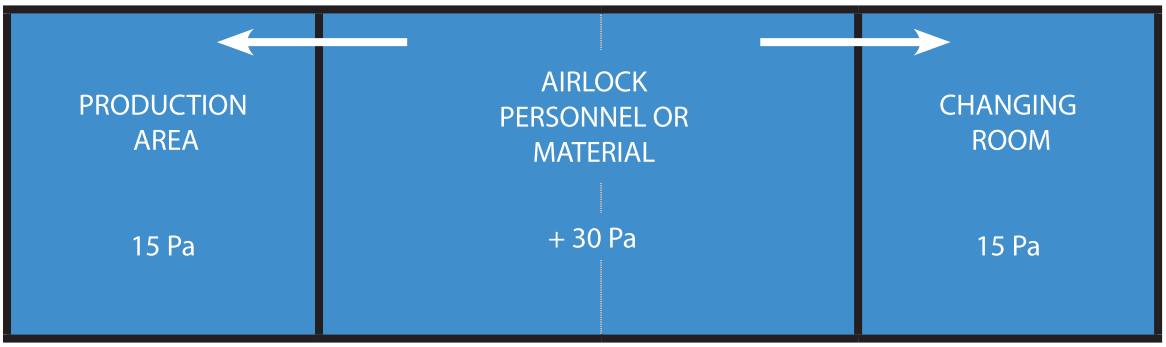
   i. Grade A Radiopharmaceutical Laminar Flow Safety Cabinet; lead lined with sliding L-shape lead barrier, built-in dose calibrator and waste container
   ii. Lead vial container
   iii. Lead syringe shield
   iv. Lead carrier
   v. Lead syringe holder
   vi. Radiation survey meter
   vii. Surface contamination detector
   viii. Handling aids (eg. Tongs, forceps)
   ix. Radioactive decontamination kits

4. Dispensing Room - Non Sterile (e.g. Iodine-131 Capsule)

   i. Radioiodine/Radioisotope Fume Hood ; lead lined with disposable activated carbon filter and movable L-shaped lead barrier
   ii. Dose calibrator
   iii. Radiation survey meter
   iv. Surface contamination detector
   v. Handling aids (eg. Tongs, forceps)
   vi. Radioactive decontamination kits
   vii. Work bench
   viii. Radiation environment detector; wall mounted
   ix. Clock; wall
   x. Trolley; two tiers, heavy duty (200kg load)

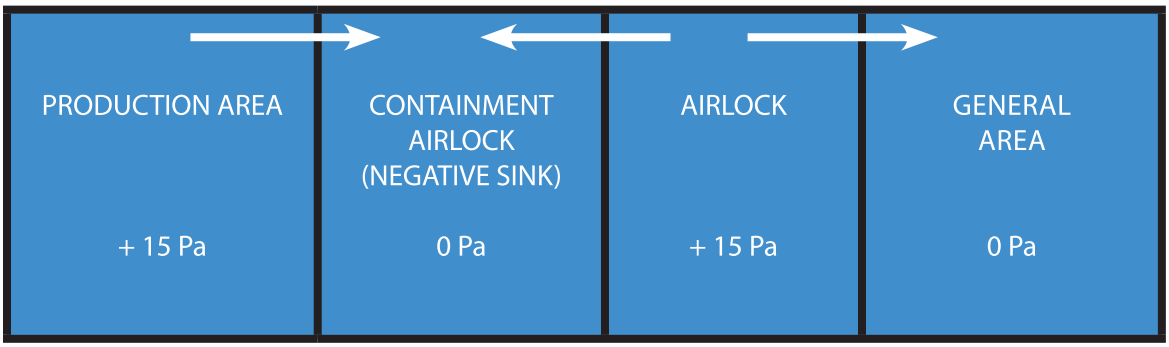
APPENDIX 1 : AIR LOCKS FOR PERSONNEL AND MATERIALS IN CLEAN ROOMS

NON- STERILE RADIOPHARMACEUTICAL PREPARATION



TYPICAL CONTAINMENT AIRLOCK

STERILE RADIOPHARMACEUTICAL PRODUCTION/PREPARATION



TYPICAL CONTAINMENT AIRLOCK

LEGEND:

AIR FLOW

Pa PASCALS

APPENDIX 2 : EXAMPLES OF TYPE OF CONSTRUCTION MATERIAL

INTERIOR SURFACE	TYPES OF MATERIALS	COMMENTS	SUITABLE FOR
FLOOR	a. Solid concrete	- dust accumulating - non resistant to chemical spills	Store areas only
	b. Solid concrete with the following alternative finishes:		
	- Vinyl tiles	- limited chemical resistance - requires welded joints in order to damp proof, abrasive - for moderately light usage	Non-production areas - offices, corridors and laboratories
	- Epoxy, polyurethane or heavy duty vinyl sheets	- monolithic, non-porous topping with non-skid surface - retards bacterial growth, abrasive	Production areas, including clean rooms
	- Cement tiles	- economical and easy to repair - requires grouting - joints are difficult to clean - non-resistant to chemical spills - abrasive	Offices and pantry
WALL	a. Bricks or block, structural wall of high density, smoothly plastered, made water-proof by painting with acrylic or high polymer enamel polyurethane or epoxy	- Easily crack of improperly processed - generate dust during demolishing for repair or renovation	Non-sterile production area

INTERIOR SURFACE	TYPES OF MATERIALS	COMMENTS	SUITABLE FOR
	b. Polyurethane panels	- non shedding - generally maintenance free - moderately durable - difficult to repair in case of damage by impact - crevices at joints need to be sealed e.g. with flexible silicone rubber material	Clean rooms
CEILING	a. Polyurethane panels	- designed for heavy loads - space above ceiling can be used for ducts and servicing activities	Clean rooms
	b. Suspended	- requires supporting steel work - not suitable for heavy loadings - shall be sealed to prevent contamination from the space above them e.g. with silicone rubber - not suitable for sterile processing rooms which a monolithic surface is required.	Non-sterile production area

APPENDIX 3 : CLEAN ROOM CLASSIFICATIONS

CLEAN 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 METER^3		
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		Laminar flow area for aseptic manipulation of sterile products. Space where sterile product is exposed.
			in operation	3,520	<1	
B (ISO 5) HEPA filter	99.997	>40	at rest	3,520		Clean room for sterile products. Background Environment for Grade A
			in operation	352,000	10	
C (ISO 7) HEPA filter	99.995	>25	at rest	352,000		Clean room for preparation of sterile products. (less critical steps)
			in operation	3,520,000	100	
D (ISO 8) Secondary filter	95	>20 (WHO)	at rest	3,520,000		Clean room for manufacturing of sterile products - less critical steps. Also being used for non-sterile manufacturing
			in operation	Not Defined	200	

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

APPENDIX 4 : SUMMARY OF THE ENVIRONMENTAL FACILITIES REQUIRED FOR RADIOPHARMACEUTICAL PRODUCTION

PRODUCT TYPE	WORKSTATION REQUIREMENTS	PRODUCTION ENVIRONMENT
Oral	Hygienic conditions conforming to BS EN 12469 class 1 for protection for volatile radionuclides	Controlled Area / Grade D
Generator storage and elution	Laminar flow cabinet GMP grade A and BS EN 12469 class II	Cleanroom grade B
	Isolator GMP grade A and BS EN 12469 class III	Cleanroom grade D
Parenteral prepared by closed system transfer procedures	Laminar flow cabinet GMP grade A and BS EN 12469 class II	Cleanroom grade B
	Isolator GMP grade A and BS EN 12469 class III	Cleanroom grade D
Parenteral prepared by open system transfer procedures	Laminar flow cabinet GMP grade A and BS EN 12469 class II	Cleanroom grade B
Long-lived radiopharmaceuticals prepared by closed or open system transfer procedures	Isolator GMP grade A and BS EN 12469 class III	Cleanroom grade D
Blood component labeling prepared by open system transfer procedures	Laminar flow cabinet GMP grade A and BS EN 12469 class II	Cleanroom grade B
Blood component labeling prepared by closed system transfer procedures	Isolator GMP grade A and BS EN 12469 class III	Cleanroom grade D
PET Radiophrmaceutical	Non-isolator GMP grade A hotcell	Cleanroom grade C
	Isolator GMP grade A hotcell	Cleanroom grade D

APPENDIX 5: RECOMMENDED FILTRATION LEVELS FOR DIFFERENT CLEAN ROOM GRADES

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

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

GLOSSARY

Airlock
An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or materials.

Commissioning
A well planned, documented and managed engineering approach to the start-up and turnover of facilities, systems and equipment, to comply with specified parameters and meet acceptance criteria and further results is a safe and functional operation. Commissioning takes place at the conclusion of project construction but prior to validation.

Centralized Radioiodine Preparation Facility
One off centre for radioiodine preparation activity for in-patient and outpatient.

Clean area/room
An area/room with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area and in which other relevant parameters (e.g. temperature, humidity and pressure) are controlled as necessary.

Containment
A process or device to contain product, dust or contaminant in one zone, preventing them from escaping to another zone.

Cross-contamination
Contamination of a material or product with another material or product.

Control area/room
An area/room constructed and operated in such a manner that some attempt is made to control the introduction of potential contamination (an air supply approximating to grade D may be appropriate).

Cyclotron
A particle (deuteron or proton) accelerator that produce high energy charged particles which bombard the target material to allow nuclear reaction to take place.

Dose Calibrator
Device measuring the radioactivity in Becquerels (Bq) or Curies (Ci), of a radioactive sample.

Generator
A radioactive parent (long-lived radionuclide) and daughter (short-lived) contained in an ion exchange column or dissolved in a suitable solvent in a liquid-liquid extraction system where the radioactive daughter is separated from its parent by elution from the ion exchange column, or a solvent extraction procedure. For example Tc-99m is separated from Mo-99 from Tc-99m/Mo-99 generator.

Hot Cell
Shielded workstations for manufacture and handling of radioactive materials. Hot cells are not necessarily designed as an isolator.

Isolator, Grade A
A containment device which utilises barrier technology to provide an enclosed, controlled workspace.

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

Nuclear Pharmacist
Pharmacist that meets the training and qualified to practice as nuclear pharmacist.

Preparation
All operations of purchasing materials and products, production, quality control, release, storage, delivery of medicinal products and the related controls

Note: The simple provisioning of medicinal products according to authorized instructions and without necessitating pharmaceutical technical knowledge where medicinal products are made ready for immediate application (e.g.: dissolution of a powder for immediate application according to the instructions in the package leaflet of an authorized product), is normally not normally considered as preparation.

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

Quality Control
Part of Good Manufacturing Practice which concerned with sampling, specifications and testing, and with organization, documentation and release procedures which ensures that the necessary and relevant test are actually carried out and that materials are not released for use, nor product released for sale or supply, until their quality has been judged to be satisfactory e.g. radiochemical purity and radionuclidic purity.

Quarantine
The status of starting or packaging materials, of material and substances, of intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or rejection.

Radioimmunotherapy
Immunotherapy using antibodies labeled with radioisotopes.

Radiopharmaceuticals
Any drugs which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

Ready-for-use Radiopharmaceuticals

Radiopharmaceutical product that procured directly from supplier which not require any further preparation.

Reagent Kit

A sterile and pyrogen-free reaction vial containing non-radioactive chemicals that are required to produce a specific radiopharmaceutical after reaction with a radioactive component.

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