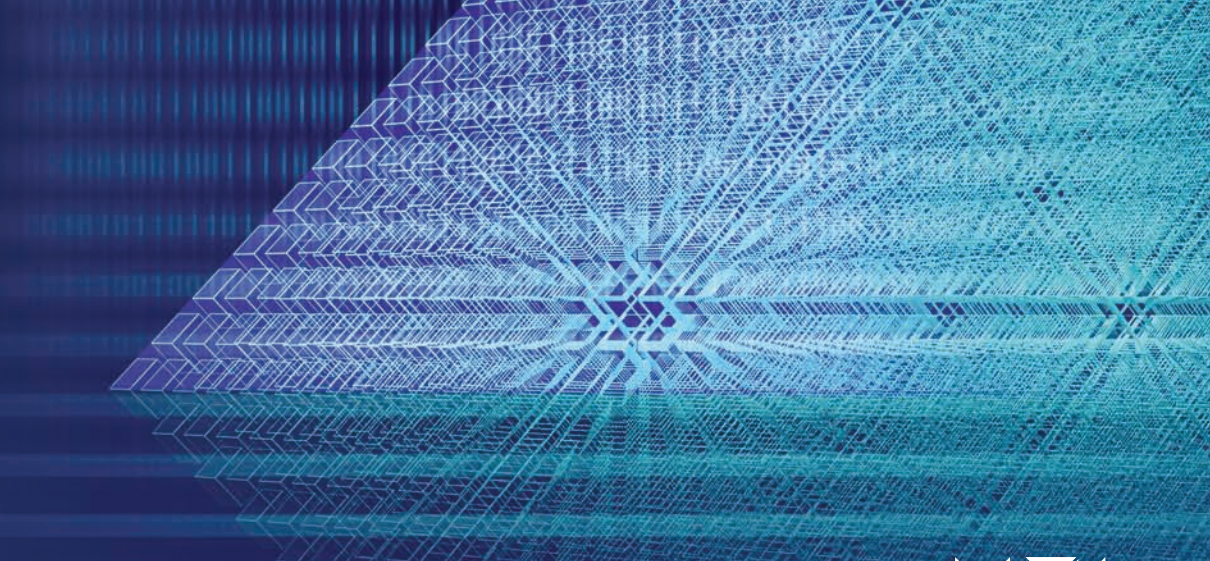

TECHNICAL REPORTS SERIES NO. 471

Cyclotron Produced Radionuclides: Guidelines for Setting Up a Facility

IAEA
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CYCLOTRON PRODUCED RADIONUCLIDES: GUIDELINES FOR SETTING UP A FACILITY

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The Agency's Statute was approved on 23 October 1956 by the Conference on the Statute of the IAEA held at United Nations Headquarters, New York; it entered into force on 29 July 1957. The Headquarters of the Agency are situated in Vienna. Its principal objective is "to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world".

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INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 2009

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PO Box 100
1400 Vienna, Austria
fax: +43 1 2600 29302
tel.: +43 1 2600 22417
email: sales.publications@iaea.org
http://www.iaea.org/books

Printed by the IAEA in Austria
July 2009
STI/DOC/010/471

IAEA Library Cataloguing in Publication Data

Cyclotron produced radionuclides : guidelines for setting up a facility. — Vienna : International Atomic Energy Agency, 2009.
p. ; 24 cm. — (Technical reports series, ISSN 0074–1914 ; no. 471)
STI/DOC/010/471
ISBN 978–92–0–103109–9
Includes bibliographical references.

1. Radioisotopes in medical diagnosis. 2. Radioisotopes — Therapeutic use. 3. Cyclotrons. I. International Atomic Energy Agency. II. Series: Technical reports series (International tomic Energy Agency) ; 471.

IAEAL 05–00596

FOREWORD

Cyclotrons are currently used for the preparation of a wide variety of radionuclides that find application in single photon emission computed tomography (SPECT) as well as in positron emission tomography (PET). Consequently, radiopharmaceutical production using cyclotron produced radioisotopes is one of the areas that is in high demand in Member States.

The selection of a cyclotron to be purchased depends on the scope of the work to be performed in each facility. For example, the widely used PET radionuclides can be prepared in large quantities in a cyclotron with energy ranging from 9 to 19 MeV, whereas higher energy machines (~30 MeV) are needed for preparation of the commonly used SPECT radionuclides. Hence, judicious planning and execution is needed when establishing a cyclotron based radionuclide and radiopharmaceutical production facility. The scope of the facility must be defined, including identification of the most optimum cyclotron needed and construction of a laboratory which will be able to use the cyclotron to the best advantage. The laboratory design will have to take into account good manufacturing practices (GMP) for radiopharmaceutical production as well as radiation protection practices.

This report gives guidelines for the design and implementation of a radionuclide and radiopharmaceutical production facility using cyclotrons. Based on the scope of the work to be performed, five different categories of cyclotron facilities are defined, and essential requirements for each category are discussed. Reference material is included on the layout of the building and the design of the laboratory, as well as some basic principles to follow GMP and radiation protection practices. Administrators interested in establishing new cyclotron facilities, managers who are in the process of setting up new facilities in their countries, radiopharmaceutical scientists, production technologists as well as regulators interested in the field are expected to benefit from this publication.

This publication was prepared by a group of consultants with extensive experience in the field. The IAEA thanks them, as well as the reviewers of the draft, for their valuable contributions. D. Schlyer of the Brookhaven National Laboratory, USA, was the Chair of the consultants group and the IAEA is thankful to him for coordinating the preparation of this book and for editing the final manuscript. The IAEA officers responsible for this publication were M.R.A. Pillai and M. Haji-Saeid of the Division of Physical and Chemical Sciences.

EDITORIAL NOTE

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CONTENTS

1. INTRODUCTION

1.1. BACKGROUND

Radionuclides, and the radiopharmaceuticals derived from them, are an established tool for key investigations in numerous disciplines of the life sciences and for diagnosis and treatment of many life threatening diseases. A large number of Member States are in the process of setting up new cyclotron facilities for the production of radiopharmaceuticals for positron emission tomography (PET) and single photon emission computed tomography (SPECT). Some of these cyclotrons are also planned to be multidisciplinary facilities not only for isotope and radiopharmaceutical production, but also for other purposes such as materials research and analytical techniques using charged particles. The types of facilities needed depend on the type of radionuclides to be produced, their quantity, as well as the type of their application. This report is intended to help those Member States in the process of setting up a cyclotron facility for the production of radionuclides and radiopharmaceuticals, as well as for other applications.

1.2. OBJECTIVE

The decision to install a new radioisotope production facility is generally based on national and institutional policies on science, technology and healthcare. Establishing a cyclotron facility for producing radionuclides and/or manufacturing radiopharmaceuticals is a complex process and requires careful planning in order to be successful. In addition to the technological complexity requiring a highly skilled staff, it is also costly to build and to operate. The aspiration to build such a facility is the first step. The next step is the commitment of the government or funding agency to the project and the development of the scope of the facility in relation to the national interests for healthcare or research.

This publication provides guidance once the political/economic decisions to build a facility have been made, although it may be useful in the decision making process as well. What must follow these higher level decisions is a critical evaluation of the project and the recognition that many interrelated factors must be considered during planning and implementation. Lack of attention to these factors can lead to poor decisions with costly ramifications. Conversely, a judicious assessment should result in the successful fulfilment of the goals of the project.

Thus, the primary objective of this book is to help Member States in making the decision on which type of cyclotron installation is most appropriate for them and to highlight the critical design issues, which must be considered for establishing a successful centre.

1.3. SCOPE

This publication provides technical guidelines for planning new radionuclide manufacturing facilities; however, it does not address governmental policies or financial implications. It covers the most important design and technical aspects, including, but not limited to, feasibility study and strategic planning, facility requirements and design, staffing, radiation protection, good manufacturing practices (GMP), and quality management. Each topic is discussed in terms of the experience of experts in designing, installing and managing a variety of radioisotope facilities around the world. The design issues related to large scale multipurpose accelerator installations are beyond the scope of this book.

1.4. STRUCTURE

This publication is divided into ten sections and nine appendices. Section 2 provides a categorization of cyclotron centres suitable for radionuclide and radiopharmaceutical production and addresses project planning and defining the appropriate scope of the new facility. This includes the formation of a task force for planning, potential applications, a cost–benefit analysis, and a business plan.

Section 3 discusses various aspects of cyclotron facility design and construction, particularly addressing the installation of cyclotrons and related utilities. Section 4 is devoted to the design of laboratory spaces, workflow patterns and environmental conditions necessary to achieve the pharmaceutical quality in products. Section 5 catalogues the equipment necessary to carry out routine operations. This chapter also discusses personnel requirements for efficient operation. Qualified staff with appropriate training is essential for manufacturing radiopharmaceuticals that conform consistently to the required specifications. Section 6 gives some examples of cyclotron facilities whose primary goal is radionuclide and radiopharmaceutical production and discusses the design principles of those facilities.

Radiopharmaceuticals, being pharmaceutical products, must be regulated in terms of production and use. Section 7, on quality management systems and

Section 8, on good manufacturing practices (GMP), discuss in detail the essential elements related to the requirements of radiopharmaceutical manufacture including various types of controls, process monitoring and documentation for manufacturing radiopharmaceuticals of acceptable quality. Adherence to the requirements specified in these chapters forms the backbone of a manufacturing system that must be planned and implemented in compliance with the local regulatory bodies where appropriate. In the absence of specific regulations in a Member State, the discussion provided in this book may be employed as guidelines in conjunction with other regulations such as those from the World Health Organization, the European Union and the United States Food and Drug Administration.

Section 9, on radiation protection, describes arrangements for the safety of personnel and the general public following the safety guidance of the IAEA in radionuclide production facilities. Section 10 gives a brief summary of this publication.

Finally, Appendix 1 provides an extensive list of key issues related to facility consideration, Appendix 2 gives some examples of radiological work permits and associated forms, Appendix 3 tabulates an extensive checklist for establishing a sound quality management system, while Appendices 4–9 provide several examples of standard operating procedures and batch records related to radiopharmaceutical production.

2. PROJECT PLANNING

2.1. INTRODUCTION

Creating a cyclotron facility is a multidisciplinary project. Careful project planning is essential for the construction of a cyclotron based radiopharmaceutical production facility. Therefore, the formation of a task force comprising experts in all related fields and including the potential users from hospitals, universities and perhaps industry should be the first line of approach in determining the feasibility and viability of the project. This group should have the responsibility of performing a realistic assessment by interviewing the users and stakeholders, which will allow the task force to set the scope and direction of the project.

Some of the factors that must be considered in project planning include assessing:

- The need for cyclotron produced radionuclides and the requirements of potential users;
- The cost or benefit of having one's own radionuclide manufacturing facility versus purchasing radionuclides or radiopharmaceuticals from a commercial supplier within the country or importing from outside the country;
- The available resources, including technical and scientific expertise, infrastructure supporting the cyclotron facility and the funds for establishing and operating the facility;
- The future availability of cyclotron produced radionuclides and radiopharmaceuticals from commercial suppliers (market competition) within and outside the country;
- The financial balance sheet through a business plan that addresses all factors.

After evaluation of the above factors, the task force must formulate a realistic scope and objectives for the facility. Several questions will be answered after going through the process of critical evaluation including:

- Whether it is advisable to manufacture one's own products or to buy from a supplier;
- What size and type of cyclotron is needed for this facility;
- What resources are required for successful implementation of the cyclotron facility;
- What are the project mission and goals?

Every organization will face dilemmas specific to its own circumstances and needs. Therefore, the questions that must be answered will also be specific to its facility. Regardless of the scope of the planned facility, many generalities do apply. The flow chart in Section 2.6 is a guideline for the prospective cyclotron facility to help define the scope and capabilities of the new facility.

2.2. TASK FORCE

Establishment of a cyclotron facility requires major commitments from the stakeholders. Because of the far-reaching consequences, both in terms of costs and potential benefits, representatives of all parts of the facility must be brought into the decision process from the beginning. The size of the task force should be commensurate with the size of the facility envisioned. However, in addition to the institutional management, there must be input from the end users and operational staff as described below so that the final decision can be made based on the understanding of the demands such a facility will place on the institution. Some members of the task force will have decision making power while others may simply provide critical information to aid in any decision.

2.2.1. Task force composition

Invariably the cyclotron will be used to supply radionuclides to the medical community for diagnostic and perhaps therapeutic purposes. Clearly, an experienced radiochemist and/or a radiopharmacist should be included in the task force to provide information on the state of the art of radionuclide and radiopharmaceutical production technology.

The head of nuclear medicine/radiology must be present in order to define the specific need as relates to type and volume of radiotracers and radiopharmaceuticals required. If there is a substantial likelihood that a basic science faculty will have significant use for the facility, then the appropriate department(s) should have input through representation so that their particular needs will be addressed through the selected facility.

A number of representatives will be required so that the proper advice on practical matters impacting the decision process is supplied. These include radiation safety, both in terms of radiation protection of the staff, and of the public. A cyclotron engineer is required to address the unique characteristics of how such a facility operates. These include the demands on utilities such as power, air conditioning, water cooling and the impact of creating a controlled

environment on the surrounding areas. The cyclotron expert should be brought in as an outside consultant if this expertise is not available in-house.

Either an ex officio member of the relevant regulatory body or at least someone who will be presenting the request to the regulators and understands the law governing the production and use of radioactivity for use in human subjects should be present. There will be multiple stages associated with receiving regulatory approval, starting with the licence to construct through to licence to operate and then to the approvals for using the radioactivity in basic science or more likely as radiopharmaceuticals.

Depending upon the source of funds to construct and operate the facility there may be a need to have potential investors involved if the operation of the facility is to be a *for profit facility*. If the facility is to be supported by the government, then a representative of the appropriate ministry or department must provide guidance as well as to understand the value and limitations associated with such an endeavour.

An architectural engineer is required to advise as to where such a facility can be built and what the infrastructure must provide. Such advice will impact whether renovations are called for or if a new structure must be considered.

Other members of the task force can be added as reflected by the potential user community but the responsible person(s) must recognize that the most efficient committees are the ones that are tailored to the task and do not have superfluous membership. See Section 2.6 for some suggestions concerning the composition of the task force. Once the task force has clearly defined the scope of the facility, it is essential that there be a single person who will be responsible for making operational decisions.

2.3. FACILITY CONSIDERATIONS

The scope of the planned facility will determine the type of cyclotron and the associated resource requirements, which can range from a comprehensive facility manufacturing multiple radionuclides and radiopharmaceuticals to a much smaller facility dedicated only to the production of fluorodeoxyglucose (FDG).

2.3.1. Definition of facility type

In a discussion concerning facility configuration, it is desirable to have a common set of references to ensure that everyone understands what is being discussed. Five categories were formally defined by a task group on PET site and facility planning set up by the American Association of Physicists in

Medicine. It is obvious that there is really a continuum of facilities and the lines of definition are purely arbitrary [2.1]. Here, slightly different categories have been defined based on the assumption that a cyclotron will be in place in the facility and the differences will be in the mission and scope of the facility. The five categories are as follows.

Type I — Facility with only FDG production. This type of facility has a small cyclotron in the proton energy range of 9–19 MeV. The goal of the facility is to produce enough FDG to be used locally and to distribute it to nearby hospitals. There is no involvement with basic radiotracer development research and there is complete reliance on the equipment vendor for repairs, maintenance, and upgrades. Such a facility is much less demanding on resources, technical as well as personnel. Even at a small facility with a small cyclotron, it is quite feasible to manufacture a large quantity of FDG for distribution to other PET centres to which deliveries can be made within a few hours. Furthermore, such a facility can be financially viable.

Type II — Cyclotron facility with radionuclide production for PET. Like the previous example, this type of facility also has a cyclotron in the proton energy range of 9–19 MeV, having the production of FDG as the principal objective. However, this facility is designed to also produce the other short-lived positron emitters (^{11}C, ^{13}N and ^{15}O), convert them into radiopharmaceuticals and distribute them locally. The facility may also distribute FDG to nearby hospitals. There is little involvement with basic radiotracer development research and nearly complete dependence on the vendor for maintenance, equipment upgrades, and new capabilities in the form of new radiotracers.

Type III — Cyclotron facility with a research support staff. Along with a cyclotron in the 13–19 MeV range and automated synthesis modules, this facility has a scientific support staff of chemist(s), physicist(s), or other scientists capable of developing procedures and radiopharmaceuticals that have been described in the literature. The major emphasis is to provide radiopharmaceuticals for routine patient studies, but some independent research can be carried out including biodistribution and biokinetic studies based on a micro-PET. There may be production of more than just the four traditional PET radionuclides mentioned earlier. This can include radionuclides such as ^{64}Cu, ^{86}Y, ^{123}I and ^{124}I.

Type IV — Radionuclide production and distribution facility. This type of facility is devoted to the large scale production of radionuclides, and radiopharmaceuticals, for distribution to users. If FDG is the major product, then the cyclotron is probably a small one. If other radioisotopes (^{201}Tl, ^{123}I, ^{124}I, ^{67}Ga, ^{64}Cu, ^{86}Y, etc.) are being produced, then the cyclotron is typically larger (~30 MeV) than those used only for PET. Separate areas may be required for

target preparation, target recovery, target processing, sterile setup, quality control (QC) and shipping.

There are also possibilities of setting up cyclotron centres dedicated to the production of a single radionuclide such as ^{103}Pd for therapy.

Type V — Cyclotron facility with an extensive research programme. Along with a larger (30 MeV) cyclotron used for the production of PET and SPECT radionuclides and radiopharmaceuticals, the facility will have a team of research scientists performing basic research on developing new radiotracers and procedures. Considerable space is allocated for laboratories and animal facilities. There is little or no pure clinical work done, but there may be an extensive clinical research programme. This programme may involve production of non-traditional PET radioisotopes such as ^{64}Cu, ^{86}Y, ^{123}I, and ^{124}I and many other radionuclides that can be produced by (p, xn), (d, xn) or (α, xn) reactions. Moreover, other research activities including but not limited to radiation physics, chemistry, biology and material science can be performed at this type of facility.

In a national facility, a cyclotron with higher energies (30 MeV and above) and a more flexible configuration in terms of beam lines and targets, makes an attractive tool for applications in the field of physics (determination of nuclear cross sections for (particle, X) reactions), fabrication of micro-optics, chemistry, analytical applications such as particle induced X ray emission (PIXE), biochemistry, geology, etc. Such applications actually require appreciable amounts of beam time, meaning that a careful scheduling for radionuclide production and 'other applications' must be established. Besides, some interesting applications require not only protons, but also deuterons, helium-3 or α particles.

As a conclusion it can be stated that, if the cyclotron is used for both radionuclide production and scientific or industrial applications, a multi-particle, variable energy, and variable beam current (a few nA up to a few hundred μA) accelerator with several beam lines is the preferred cyclotron to be installed. Higher energy accelerators for industrial and specific applications are beyond the scope of this book.

The transition from a smaller, somewhat focused, facility to the more general research facility is often a gradual one, occurring over several years. Some specific examples for these facilities and a few minimum requirements for type I–V facilities are given in Section 6.

2.4. COST–BENEFIT ANALYSIS

Defining the type of facility based upon the considerations discussed above will determine the scope of the project and the required resources. At some stage, discussion with and guidance from an experienced advisor may prove to be quite valuable in not only defining the scope and goals of the facility, but also in identifying and defining the equipment and resource requirements for successful planning and implementation of the project.

In the final assessment, it is the cost–benefit analysis which will provide the basis for the decision whether or not the establishment of a cyclotron facility is justified.

It is generally true that a cyclotron facility and a radiopharmaceutical production programme are expensive both to establish and operate. Return on investment and profits are unlikely except in those cases where there is a substantial customer base paying for the products. For example, a type I facility defined above will be intrinsically financially viable. Moreover, research related to drug development, outsourced by pharmaceutical companies based on ^{11}C labelled tracers, can make type II and III facilities financially viable as well.

2.4.1. Facility benefits

On balance, however, there are several tangible and non-tangible benefits to society from such a facility, which may be viewed as offsetting the fact that the facility is very costly and may operate at a deficit. The benefits are sometimes hard to define, but include:

— Improved health care;
— Advancement of scientific expertise;
— Enhancement of technological competence in the country;
— Increasing self-sufficiency;
— Heightened national pride.

2.4.2. Facility costs

Regardless of the driving force and the financial resources, evaluation of financial viability is absolutely vital for success of the project. It is very important to know if the facility will always operate at a deficit so that a source of operational funds can be identified.

The cost of the facility will entail at least the following:

— Buildings and utilities;
— Equipment;
— Operational costs

Each of these aspects is described below in some detail.

2.4.2.1. Buildings and utilities

Site design and the cost of construction will be dictated by the scope of the programme and the type of cyclotron needed to achieve the goals and objectives as defined by a task force. It is clear that structural and financial requirements for a comprehensive radionuclide and radiopharmaceutical manufacturing facility comprising a 30 MeV cyclotron are quite different from that needed for a small PET radiopharmaceutical production centre. Cyclotron vendors can provide basic information on the space needed and a provisional layout for installing the cyclotron and its utilities. Advice from an operational facility of similar nature would be another way to assess the requirements. From the different programmes which will be supported, one can estimate the space needed for the production and QC laboratories, auxiliary rooms, offices, hot cells, heating, ventilation and air conditioning (HVAC), etc. An experienced architect and HVAC engineer should be involved in this process. With an estimate of the overall space needed and the floor loading, one should assess the possibilities for establishing the centre within an existing building or, alternatively, a green field installation should be evaluated. Renovation of an existing building may be not always the cheaper solution. Factors such as radiation protection issues, weight of the cyclotron, crane access for installing the cyclotron, etc., might make the establishment of the centre in an existing building impractical.

In addition to the space requirements for the cyclotron and the associated infrastructure, the planners should make provision for a GMP compliant radiopharmaceutical manufacturing facility incorporating a pharmaceutical quality clean room environment for control of air quality during production of radiopharmaceuticals.

2.4.2.2. Equipment

In addition to the physical structure, laboratories must be equipped with a range of production and analytical instrumentation. Equipment requirements will depend largely upon the scope and type of facility being developed. For a

production facility, the major equipment will be the cyclotron and the hot cells. For a facility that includes an imaging centre (a PET/CT facility), the scanner will be a major expense. The cost of other specialized equipment can be substantial, forming a significant fraction of the overall cost of the production facility. Some critical pieces of equipment may need backups in case of equipment failure. The following is a typical list (not all inclusive) of equipment which will be necessary for viable operation of the facility. The type of equipment and the quantity will depend largely upon the scope of the facility:

— Cyclotron (9–30 MeV);
— Hot cells (with or without manipulators);
— Radiation protection (shielding, monitoring);
— Synthesis modules;
— Chromatography (HPLC, GC, TLC scanner);
— Pyrogen and perhaps sterility testing (incubators, laminar flow cabinets);
— Gamma spectrometer;
— Gamma counter;
— Dose calibrator;
— QC laboratory equipment (pH meters, weighing balances, osmometers).

2.4.2.3. Operational costs

In addition to facility and major equipment installation costs, sustained operation of facility is also relatively costly, and will play an important role in deciding if the facility can be financially viable. The critical items include:

— Supplies (chemicals, kits, spare parts, etc.);
— Utilities (power, water);
— Staff salaries;
— Maintenance;
— Depreciation (replacement).

Operation of a cyclotron centre requires a continuous supply of various raw materials and spare parts and it might consume significant amounts of electric power. Thus, one should make a reasonable estimate of the running costs summing up all expenses related to the operation of the centre including the salaries of the personnel, depreciation of the facility, and other liabilities (if applicable). The decommissioning costs should also be considered.

Staffing requirements will vary according to the scope of the facility. Concurrently, the cost of hiring qualified individuals will depend upon the number of staff as well as level of expertise required. This includes: cyclotron

engineers, medical physicists, radiochemists, radiopharmacists, QC chemists and administrative staff. The technical staff is likely to require additional specialized training and continuing education. Therefore, cost of such training should also be calculated in the cost–benefit analysis.

2.4.3. Source of funds (sustained support)

Operating funds can have several sources including:

— Grants or government funding and continued support;
— Sale of products;
— User fees.

In order to build and run the cyclotron centre, all possible sources of funding should be identified. The required funds for building the centre should be secured at the planning stage. It is of utmost importance to avoid launching the project before the required funds are assured, regardless of the source (government investment, private investment, loan, grant, or a mixture of all of the above). The self-sustainability of the project should be also evaluated: the sources for covering the operational costs (sales of products, grants, lease of beam time, etc.) should be identified and evaluated.

2.5. BUSINESS PLAN

Regardless of the source of funding (private, governmental or institutional) and scope of the project, the financial viability of the facility must be addressed and formally evaluated through a sound business plan. On one hand, a comprehensive facility with large cyclotron (30 MeV), especially one associated with a national institute or university, requires a very large financial investment which may never be recovered. The financial viability will depend on potential revenues from sales of radiopharmaceuticals and the beam time. On the other hand, a dedicated PET facility with a small cyclotron and lesser resource requirement is very likely to be financially viable.

Having all financial aspects evaluated, one should make an exhaustive business plan, assessing at least the following elements: cost of production, market analysis (potential sales volume and competition from commercial suppliers), organizational structure, personnel plan, financial plan and breakeven analysis. If the breakeven analysis shows that the project is self sustainable, the project planning can continue towards more detailed design issues. Otherwise, the whole project should be revised starting from the

selection of the appropriate cyclotron. Even if the facility is being subsidized by the government, there must be some guarantees as to the continuing funding. Some guidance can be found in articles concerning the establishment of new PET facilities [2.2–2.6].

2.5.1. Business plan

An outline of a business plan might be as follows.

Executive summary. This should include the following elements. It should include a brief description of each element and end with a conclusion that the venture will be self-sustaining:

— Amount requested;
— Purpose;
— Potential market;
— Marketing strategy;
— Potential revenues;
— Management expertise;
— Conclusion.

The executive summary should be no more than two pages, with the key issues and how they will be addressed in the plan. The summary can be followed with a detailed writeup that includes the following elements:

— *Background and vision.* In this section there should be a description of the utility of the radionuclides and nuclear medicine scans which are being considered. If SPECT scans are being done routinely, then the current radionuclide and radiopharmaceutical needs and a projection of future needs should be included. Since these scans are a routine part of nuclear medicine practice, there is not much need to explain the utility of doing these scans. If FDG is a major product, then there should be a summary of the clinical uses of FDG and an analysis of the specificity and selectivity of FDG versus other evaluation of treatment options. This section should also include a typical cost of FDG scans worldwide. Any barriers to the use of these radionuclides should be listed. These might include:

  • The number of qualified physicians who routinely use the diagnostic or therapeutic radiopharmaceuticals or would be anxious to use them in the future;
  • The number of qualified technicians who are available without an extensive training programme;

- The number of scans which must be carried out per month or year to make the facility sustainable;
- The amount of money which must be paid to both the physicians and technicians to carry out these duties;
- The cost of being in compliance with the regulations and having the licences to operate the facility.

Products and services. What products and services are planned? Is it just for the production of FDG or a comprehensive facility for production of PET and SPECT radiopharmaceuticals as well as applications in other fields?

Marketing plan. The key here is to understand the market and how to increase the demand for radiopharmaceuticals. There should be a careful evaluation of any competition both present and future. There should also be a plan to increase awareness among physicians and health care providers of the benefits and costs of imaging studies.

Operational plan and equipment. The operation of the facility and the use of the radiopharmaceuticals consist of five separate operations. The cost of these operations must be included in the overall costs of the facility. In general these operations are:

(1) Production of the radionuclides;
(2) Synthesis of the radiopharmaceutical from the radionuclide;
(3) Quality control and release of the radiopharmaceutical for use;
(4) Distribution of radiopharmaceuticals;
(5) Marketing of radiopharmaceuticals.

Each of these steps is in turn made up of several operations and there are equipment and personnel costs associated with each of them which must be recognized.

There must also be an operational plan for the development of radiation protection documents and of standard operating procedures to cover each of the previously mentioned operations. A plan must be in place to develop these documents and the costs associated with their development need to be included in the operational costs.

Management and organization. This section must include a realistic organizational chart which includes a list of the required staff. Staff requirements will depend largely upon the type of the centre envisioned and scope of the project. Some suggestions are given here although this is not exhaustive and more than one of some of the categories are highly recommended if this facility will be making its own products:

— Facility director;
— Radiation safety officer;
— Industrial safety officer;
— Radiopharmacist (releasing chemist);
— Production radiochemist(s);
— QC chemist(s);
— Cyclotron operator(s);
— Technician(s);
— Transportation personnel or hired company.

Start-up expenses and capitalization. There will be initial costs for equipment which may be amortized over the expected lifetime of that equipment. An estimate of such expenses is given in Refs [2.1, 2.5]. Some examples taken from Ref. [2.1] are given in Section 2.5.2.

2.5.2. Typical costs

Table 2.1 gives some typical costs for equipment and construction. These are ranges which may vary considerably depending on local distributors and construction costs.

2.5.3. Financial plan

There are many factors as discussed in formulating a financial plan. A summary of these considerations would include:

— Initial investment and cost of money, including recovery time;
— Estimate of cost of production based upon cost of operation (materials, labour, utilities, etc.);
— Potential revenues based upon sales volume and value;
— Future growth and expansion;
— A minimum volume of sales to sustain the continued operation;
— Availability of technical staff and cost thereof;
— Estimate of break-even point;
— Risk analysis (including future need for the products manufactured and competition).

In addition to all the above considerations, the key factor for financial success will be the throughput of the facility. The number of radiopharmaceutical doses produced per day will determine the financial viability.

TABLE 2.1. TYPICAL COSTS OF ESTABLISHING A CYCLOTRON RADIOPHARMACEUTICAL PRODUCTION CENTRE [2.1]

Capital expenditure	Original cost (US $)	Lifetime (Years)	Annual cost ($)
Construction			
Shielded vault	1 700 000–2 800 000	20	112 000
FDG synthesis laboratory	700 000	20	56 000
QC laboratory	1 400 000–2 500 000	20	112 000
Radionuclide production and synthesis			
Cyclotron (10–19 MeV)	1 300 000–2 500 000	20	160 500
Cyclotron (25–30 MeV)	3 500 000–6 000 000	20	200 000
Hot cell (per hot cell)	200 000–400 000	10	32 000
Mini-cells for synthesis modules	80 000–150 000	10	20 000
Automated synthesis unit	90 000–150 000	10	17 000
Radiation safety monitoring	100 000–250 000	10	16 000
Radiopharmaceutical QC			
Gamma counter	60 000	10	7800
TLC scanner	30 000	10	7800
HPLC system	50 000	10	10 000
Dose calibrator	20 000	10	2000
GC system	40 000	10	5000
Particle counter	20 000	10	5000
Pyrogen testing equipment	20 000	10	10 000

2.6. DECISION TABLE AND FLOW CHART

Table 2.2 lists some of the factors which need to be considered in the development of a new facility. It is designed to provide some detail for the decision tree flow chart (Fig. 2.1). The list is not exhaustive, but should be a good starting point. If there is insufficient local expertise in cyclotron installation and operations, the best course of action is to get some outside help.

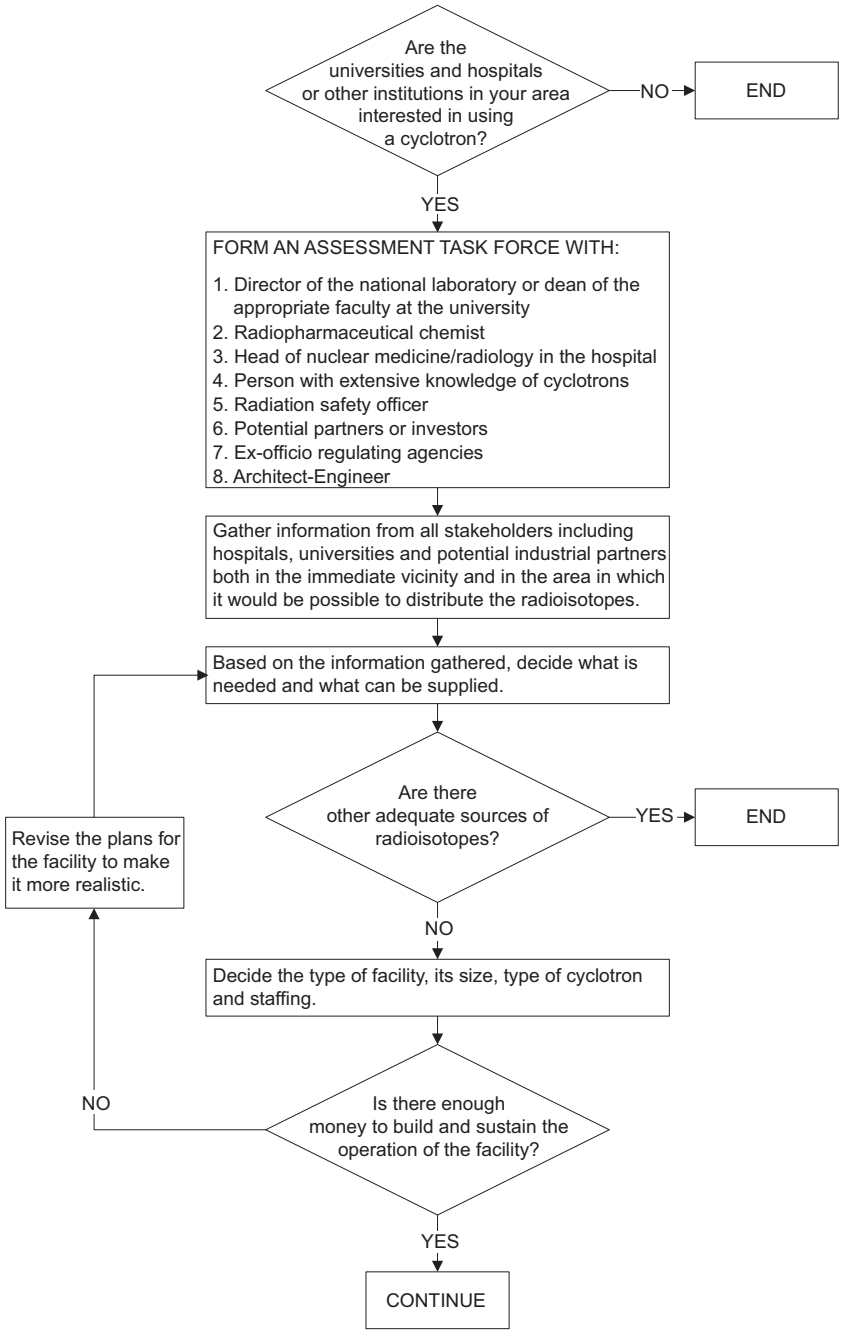

FIG. 2.1. A simplified flow chart of the decision tree.

TABLE 2.2. CONSIDERATIONS FOR THE DEVELOPMENT OF A NEW FACILITY

Assessing the need	Are the national research laboratory, universities and hospitals or other institutions in your area interested in using a cyclotron?	If yes, form a task force
Task force composition	1. Director of the national research laboratory or the dean of the appropriate faculty at the university or designee 2. Radiopharmaceutical chemist 3. Head of nuclear medicine/radiology in the hospital 4. Radiation safety officer 5. Person with knowledge of cyclotron operations (in-house or consultant) 6. Potential partners or investors 7. Ex-officio regulating agencies (radiation, pharmaceutical, etc.) 8. Architect-engineer	
Task force assesses the need		
In the university or radioisotope production centre	Physical science faculty: 1. Which isotopes? 2. What quantities? 3. How frequently? 4. Beam time on the cyclotron? 5. Beam quality (energy, current, size)? 6. Which particles are required?	
In the hospital	1. Survey of the number of gamma cameras. 2. How many patients are planned for cyclotron produced SPECT isotopes? 3. Which SPECT isotopes? 4. Survey of the number of PET cameras. 5. How many patients are planned for PET isotopes? 6. Which PET isotopes? 7. Are other centres within the distribution region interested in using these isotopes?	
Assessing current availability (PET and SPECT)	1. Are there regional distribution centres? 2. Are there problems in importing radionuclides? 3. Are the supplies adequate? 4. Pricing of the radionuclides.	

TABLE 2.2. CONSIDERATIONS FOR THE DEVELOPMENT OF A NEW FACILITY (cont.)

In industry	Industrial applications: 1. Surface analysis 2. Wear studies 3. Tracer applications	
Decision on the type of cyclotron	1. What type of cyclotron is ideal? 2. What is the minimum staffing? 3. What supplies are needed?	Crucial decision
Cost–benefit analysis	Estimated cost of facility (green field, renovations, cyclotron, hot laboratories, etc.) Operational costs 1. Supplies (chemical kits, spare parts, etc.) 2. Utilities (power, water) 3. Salaries 4. Depreciation, maintenance. Source of funds (sustained support) 1. Grants 2. Sales of products 3. User fees Benefit to society 1. Improved health care 2. Scientific expertise 3. Technological competence in the country 4. Self-sufficiency, national pride	
Gap analysis	What must be done to build and operate the facility? 1. Training in outside facilities 2. Appointing consultants How much will it cost?	
Business plan	Will the facility make money, lose money or break even?	
If losing money, revise the scope of the project and start again		
Infrastructure	Are there sufficient resources for a cyclotron: 1. Power, water 2. Technical expertise currently in place	

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3. CYCLOTRON FACILITY DESIGN

3.1. INTRODUCTION

Planning of a facility for production of radioisotopes and radiopharmaceuticals is usually motivated by the need to:

— Design and build a new facility;
— Add on to an existing facility to accommodate anticipated programmatic growth;
— Maintain or renovate an existing facility.

Regardless of which of these options is being considered, careful evaluation of numerous factors is required, most important of which is the overall scope of the facility. The range of activities will depend on the available resources both financial and physical. If a new facility is planned or an expansion is in progress, personnel will need to be added. The number and level of qualification of the new people will depend heavily on the objectives of the facility. Both local and international regulations for the handling of radionuclides and manufacturing radiopharmaceuticals will dictate the policies and procedures.

This section outlines some of the essential considerations in facility development. The main areas covered are the accelerator area, the hot laboratory areas, the dispensing areas and the QC laboratory. There are a few relevant references in the literature describing the planning of new radiopharmaceutical production and/or PET facilities [3.1–3.5].

3.1.1. General planning objectives

Four specific objectives have been defined for site planning:

— Confine specific activities to functional areas and plan these areas to enhance workflow and efficiency;
— Improve and maintain overall environmental quality;
— Ensure that all regulatory requirements are met, including radiation protection, industrial hygiene and radiopharmaceutical manufacture;
— Have sufficient staff to carry out all the required tasks, each with the appropriate level of expertise and experience.

The first point is especially important to the people who are working in the area. The workflow is the most critical consideration in the planning.

3.1.2. General safety planning guidelines

Radiation protection aspects will have to be considered upfront while developing a cyclotron based radiopharmaceutical production facility. The design as well as the operational arrangements proposed will have to be provided to the regulatory body as part of the licensing process. In undertaking a safety assessment of the facility, both protection of the workers and the public will have to be considered including normal operation conditions and from accidents that could arise. In addition to the brief information provided in the subsequent paragraphs, it is highly recommended to implement the standards set by the International Basic Safety Standards for Protection Against Ionizing Radiation and for the Safety of Radiation Sources [3.6].

Protection of the public. The likelihood of unnecessary exposure of the general public to radioactive material will be reduced if certain features are incorporated into the design. These are:

— Areas where radioactive material is used or stored should have restricted access. Members of the general public should not be permitted access to areas where radiation levels are in excess of 2.5 μSv/h.
— All areas which require restricted access should be furnished with adequate security provisions to prevent unauthorized access to the radioactive material.
— Areas where radioactive material is used or stored should be well shielded. Special attention should be given to radionuclides with high energy gamma rays.
— The movement of radioactive material should be minimized and contained. This can be achieved by keeping areas where radioactivity must be stored or handled in close proximity to each other.
— Waste contaminated with radioactive material should be stored and handled in a way that is in compliance with all appropriate regulations.

Protection of workers. The incorporation of several other general design principles will protect workers from unnecessary exposure to radioactive material, for example:

— Radioisotope laboratories must have sufficient floor space, counter space, and hood space to allow people to work safely. The space requirements will depend on the type of work, traffic patterns, and equipment needs. In a well organized laboratory, at least 3 m^2 of free floor area per person should be provided.
— Shielding around radioactive sources should be provided to ensure that workers are not subjected to radiation levels in excess of 25 μSv/h. In most cases, it is advisable to shield radioactive material such that workers are exposed to radiation levels of less than 2.5 μSv/h.
— The facility should be equipped with a radiation alarm system in case of excessive radiation.
— All surfaces in the laboratory should be fabricated from materials that can be readily decontaminated,
— All radiation workers shall be appropriately trained in handling radioactive materials.

3.1.3. Adequate space and movement of materials

The most important consideration in facility planning is to be clear on the scope of the centre. This requires input from the scientists, physicians, and administrators who will be using the centre, as well as the scientists and engineers involved in setting up the centre. It is imperative that everyone clearly understand what a particular facility can do and, more importantly, what it cannot do.

It is common for radiochemistry facilities to gradually increase their scope of operations over time (scope creep). After a time, the facility will need to grow to accommodate these expanded operations. Good planning and foresight will facilitate this growth. Often facilities are sited in an existing space which has little or no room for expansion. For a new facility, the planning committee should assign as much space as possible to the project, particularly if there is a research element to the programme. If there is likelihood for expansion, the layout of the facilities should be planned in a more flexible manner that would allow for changes in the direction and goals of the facility without altering the basic floor plan. This will save time and money when renovations are done. One example would be the incorporation of a central hallway in a new construction, even if there are only a few rooms in the building. This allows an extension of the hallway and rooms to be added on at a later date without extensive renovations to the existing building. The guidelines below give some indications of what is recommended as minimum space requirements. It is possible to operate in less space, but there may be a loss in efficiency.

3.2. FACILITY DESIGN AND FLOOR PLAN

Once the scope has been defined, with a vision of possible expansion in the future, the next logical step is designing a facility that will achieve these objectives. The facility design should encompass not only the physical requirement of space, but also be compatible with regulatory requirements of radiation safety and pharmaceutical manufacturing. Furthermore, integral parts of the facility design are the support services and amenities, including utilities, climate control and equipment. For example, radiopharmaceutical manufacturing necessitates using HEPA filters to ensure air quality conforming to GMP. Radiation protection on the other hand requires that the air released from the cyclotron facility is passed through filters for control of radioactive particulates. With the optimum combination of factors, a well designed facility should serve for a long time.

In addition to the physical structure planning, attention must also be given to the flow of materials and people in the facility as these seemingly minor details will have a profound effect on the efficiency of operation within the domain of regulatory requirements.

In the following sections, the most important factors affecting the facility design and, therefore, the facility floor plan are discussed in more detail. General aspects are presented which provide guidelines for optimum results.

There are a few guiding principles which should be considered when designing a new cyclotron, hot laboratory, and radiochemistry facility. This section contains some advice on laboratory design, followed by some examples of facilities of different types which have features that utilize these principles. Over time, laboratories invariably need to be reconfigured or expanded to meet changing research needs. Electrical and mechanical systems can be fed from a utility chase as illustrated in Fig. 3.1. This arrangement will allow easy extension without taking other laboratories off-line. Foundation walls can be extended beyond the end walls and expansion is possible without disrupting laboratory operations. Modular laboratory units can be used if they are flexible enough to adapt to new programmes and requirements without major alterations or expense.

3.2.1. Overall considerations

There are several overall considerations in the design of a radioisotope production facility which are similar regardless of the type of facility.

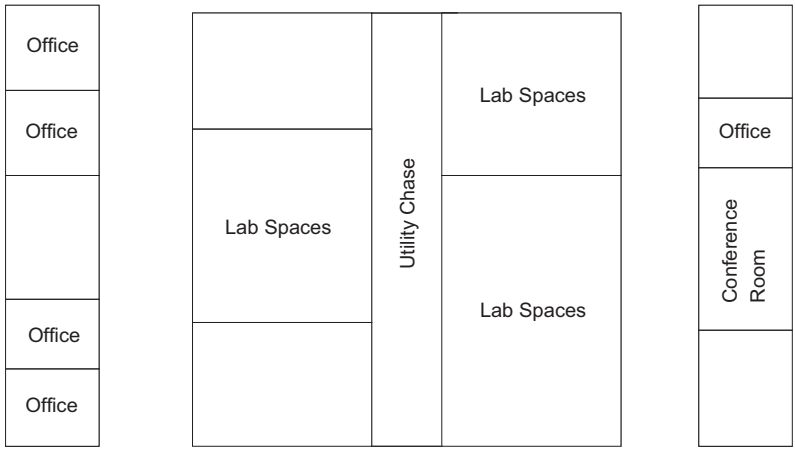

FIG. 3.1. Use of a central utility chase in a laboratory environment to simplify utility access and increase the efficient use of space.

Air flow. The air flow pattern in a facility is one of the most critical parameters to control airborne contamination. The air handling requirements for radiation protection and radiopharmaceutical manufacture are often at odds with one another. For example, to reduce the chance of the spread of contamination, the flow of air in a hood or hot cell should be away from the personnel and up the exhaust stack. In contrast, maintenance of pharmaceutical quality of the products requires air flow out of the hood, away from the product and towards the personnel. To prevent the spread of contamination, the air flow should always be designed so that the cyclotron vault is at the lowest pressure in the building, and the hot laboratories are at slightly higher pressure and the surrounding public areas are at the highest pressure. On the other hand, the area where vials are prepared and product is dispensed is typically a clean room with specified air particle quality needs to be at higher pressure than its surroundings. This ensures that the 'dirty' air particles do not contaminate the product causing degradation of pharmaceutical quality. Furthermore, the area in immediate contact with the open product vials is the most critical and should be controlled for achieving the highest quality of air. An additional requirement for air flow is the number of air changes in unit time, particularly in the clean rooms and hot cells. From this discussion it should be clear that the air flow patterns must be engineered to accommodate these opposing requirements.

If the air pressure gradient is in the direction of the hot laboratory, then some of this material may be drawn into the laboratory and may contaminate

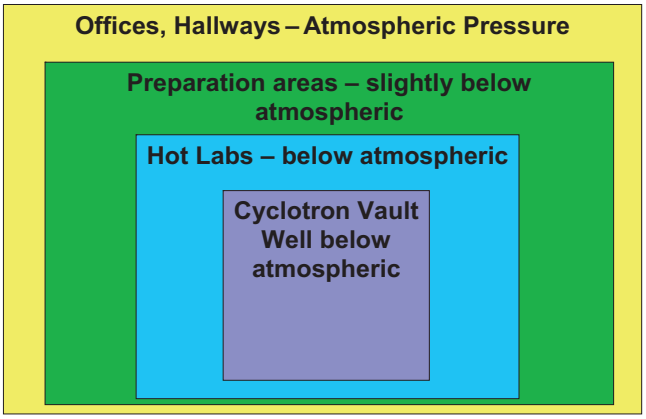

FIG. 3.2. Ideal pressure gradient in a cyclotron facility.

the samples being produced. In the case of PET radiotracers, the contamination could well be long lived material. The air flow should always be designed so that the cyclotron vault has the lowest pressure in the building and the hot laboratories are at slightly higher pressure. An ideal facility pressure gradient is shown in Fig. 3.2.

Radiation level gradient. In a similar fashion to the pressure gradient, there should also be a radiation field gradient. With the cyclotron turned off, the highest level of radiation will be around the txargets. The radioactivity from the targets will be transferred into the hot cells, processed and then transferred to the dispensing (radiopharmacy) and QC units. At each step along this path, the amount of radioactivity being handled is less. The ideal situation is when the facility is set up in such a way that the staff and materials follow this gradient and do not have to pass through a low radiation area on their way from one high radiation area to another. The entrance and exit to the facility should be through only one point. This point is where the transition is made from the radiation areas to the outside. This is where personal protective clothing will be put on and removed, and checking for contamination will be carried out. If there are contamination areas within the facility, there should be a single entrance and exit to these areas as well, so that checking can be minimized. There should be multiple emergency exits in case of fire as is consistent with life safety codes, but they should not be used routinely. The ideal situation is illustrated in Fig. 3.3.

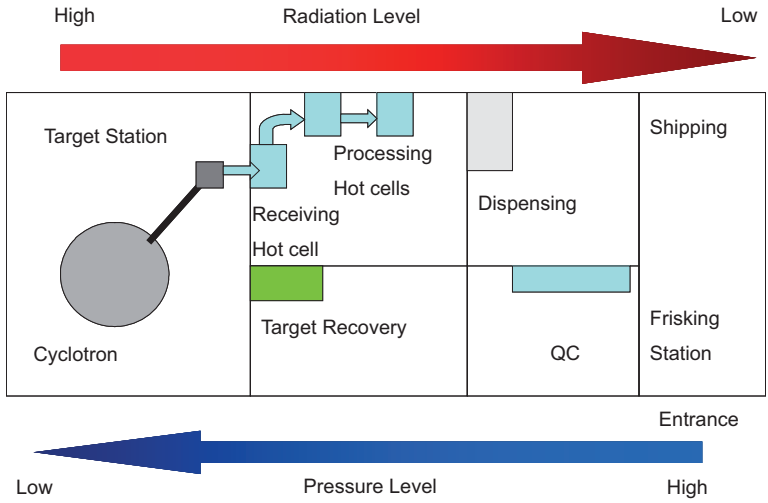

FIG. 3.3. Ideal pressure and radiation gradients in a cyclotron facility.

3.2.2. Workflow

The flow of laboratory operations should be examined in the context of the entire facility. A great deal of consideration should be given to the workflow within the facility. It is important to minimize radiation exposure and to increase efficiency by providing a smooth flow to processing. This can be done by ensuring that the area for each step in the processing is in close proximity to the step before. Another approach is to use a shielded transport system for moving the dose along without human contact. A pass-through in a wall can be an effective means of moving material from one area to another, while minimizing the chance of the spread of contamination.

Control of quality in the radiopharmaceuticals necessitates unidirectional workflow in order to reduce product contamination and mix-ups. Good work habits should be observed while in clean rooms to minimize the chance of product contamination.

3.3. CYCLOTRON OR ACCELERATOR VAULTS AND WORKSPACES

Generally, experienced cyclotron personnel prefer an unshielded cyclotron because the self-shield slows down cyclotron repair and maintenance. An unshielded cyclotron will need to be housed in a dedicated concrete vault. The vault around an unshielded machine will usually require more space than a self-shielded machine. A self-shielded cyclotron can reduce neutron and gamma activity levels outside the shielding to safe levels. This allows the cyclotron to be located in a room with normal building construction. However, with some machines additional shielding in the room walls will be required as well. It should also be noted here that self-shielding needs to be checked for neutron dose rates to ensure there are no gaps in the shielding. There will also be a trade-off in the cost associated with these two options. The design phase with the vault is somewhat more complex. Although concrete is relatively inexpensive, the overall costs may be higher with the vault. However care must be taken in floor loading with the self-shielding option, since the shields alone, typically, weigh about twice as much as the cyclotron.

A cyclotron vault should be reasonably small to minimize cost, but it should include sufficient space to work on the cyclotron and bench space for most maintenance procedures to be carried out in the vault. Major electrical systems cannot reside in the vault since the radiation damage, particularly the neutron flux, will shorten their operating life significantly. The vault floor will contain trenches and conduits, providing pathways for electrical cabling, water, gas, and product supply tubing to and from the cyclotron. The trenches may also provide a pathway to carry the radionuclide delivery lines from the cyclotron targets under the vault floor into the laboratory. Access to the vault may be via a long, angled maze with multiple turns or through a shielding door. The thickness and composition of the concrete should be based on maximum neutron fluxes generated by the cyclotron under various run conditions. The concrete should be low alkali grade to minimize activation through neutron capture reactions of vault walls over the lifetime of the facility. To avoid unnecessary activation of the concrete shielding of the bombardment vault, additional shielding around the target itself could be installed. Especially with high energy irradiation, the formation of secondary high energy neutrons can be problematic. Therefore, ‘sandwich’ shielding consisting of an inner iron layer followed by a wax layer containing boron compounds and finally a lead layer could be useful [3.7].

3.3.1. Utilities

The accelerator will require supplies of electricity, water and air for routine operation. The specifications for each of these parameters will come from the manufacturer. The power requirements given are for a typical PET cyclotron with proton energy of about 17 MeV.

Power. Electrical services supplied to the vault will depend on the cyclotron chosen and its exact configuration. Example values for a typical PET cyclotron are given in Tables 3.1 and 3.2.

Table 3.2 describes the total installed capacity in kVA for the required circuits and breakers. Note that the services outlined above do not include HVAC, wall outlets or safety system power.

Chilled water. The closed circuit, de-ionized water cooling system which serves the cyclotron, beam lines and related equipment usually requires chilled water cooling. This can come from a facility chilled water supply or from a separate chiller, which is dedicated to the accelerator. Some typical operating parameters are given in Table 3.3.

Lighting. Normal lighting services include standard fluorescent fixtures and mercury vapour lights controlled locally. Emergency lighting is provided by battery pack lighting units which are activated upon loss of building power. The intensity of the light should be sufficient to clearly see all parts of the vault. This is important for safety and maintenance procedures, which often require close-in work.

TABLE 3.1. TYPICAL ELECTRICAL SERVICES FOR A PET CYCLOTRON

Installed capacity	100 kVA (115 kVA with a beam line)
Normal operating mode	45–80 kW
Standby mode	5–20 kW
Voltages	480/3 Φ, 208/3 Φ, 208/1 Φ, 120/1 Φ
Voltage stability	±10%
Frequency	50–60 Hz
RF ground	Type and location to be determined in consultation with the vendor
O/L protection	To meet local electrical code

TABLE 3.2. TYPICAL POWER REQUIREMENTS FOR PET CYCLOTRON SUBSYSTEMS

Subsystem	Description	Volts	Phase	kVA
Cyclotron	Main magnet P/S	480	3	30
	Probes	120	1	1.0
	Hydraulic pump	120	1	1.7
	Current amplifiers	120	1	1.7
RF system	Amplifier	208	3	30
	Power	120	1	1.7
Ion source	Iso. transformer	208	3	10
	Quadrupoles	120	1	3
	Ground region	120	1	2.5
Vacuum	Cryopump comp.	208	3	5
	Vacuum forepump	208/120	3/1	2.0
	Vacuum gauge cont.	120	1	1.0
Beam line*	Combination magnet P/S[a]	208	3	8.0
	Quadrupole (2) P/S[a]	208	3	4.5
	Steering magnets P/S[a]	120	1	0.5
Water system	Pumps, etc.	208/120	3/1	10
Control system	Computer system	120	1	1.0
Safety	PLC c/w UPS system	120	1	1.0
Recommended installed capacity	Total			115

[a] If included in supply.

TABLE 3.3. CHILLED WATER REQUIREMENTS FOR A TYPICAL PET CYCLOTRON

Supply temperature	15°C ± 1.5°C at heat exchanger
Heat removal rate	80 kW (excluding beam lines) during operation 20 kW (excluding beam lines) on standby
Flow rate	200 L/min
Maximum pressure at inlet	1.0 MPa
Pressure drop for heat exchanger	35 kPa

Compressed air. A compressed air unit is required for several components on the cyclotron. Some typical supply requirements are a source of instrument quality air with a dew point at least 10ºC below ambient temperature, a particle size below 5 μm, and an oil content not to exceed 1 part per million.

The supply pressure is 550 kPa with a flow rate of 150 L/min and a reserve volume of 100 L. There should be several compressed air outlets with valves located in the cyclotron vault. If there is equipment located outside the vault, one compressed air outlet should be provided in each room.

Gas supplies. Gases are required for the operation of the cyclotron and the production of radioisotopes. There are the ion source gases which must be supplied to the ion source, the target gases which are used for the production of radioisotopes, and helium gas which is used to cool the target windows and to transfer liquids in to and out of the targets. These gas cylinders should be in close proximity to the cyclotron, but not inside the vault. If they are inside the vault, they may become activated through neutron capture reactions or may be inconvenient to change when they are empty.

Hydrogen generator. The basic 'feed-stock' used to produce H^- ions in the cyclotron's ion source is hydrogen gas. In many installations, this is obtained from a tank of 'pure' (so-called 'five-nines' grade of purity) H_2 gas. Unfortunately, hydrogen gas is highly flammable, and many local fire codes — and common sense — prohibit storage of H_2 cylinders inside a building without special (and expensive) safety provisions. Some facilities have tried using small 'lecture' sized H_2 gas cylinders to stay compliant with local safety regulations, but these can be quickly depleted depending on machine utilization and require replacement, always — or so it seems — at an inconvenient time during a busy schedule of operation.

Some facilities elect to store their regular sized H_2 gas cylinders out of doors, with long gas line connections to the ion source. However, this requires long pump-out times and may increase the possibility of vandalism, or small leaks, or contamination during and after service interventions.

The best solution is the use of a 'hydrogen generator' which employs the electrolytic decomposition of pure water, in conjunction with diffusion through a palladium membrane, to obtain very high purity H_2 gas (up to 'seven-nines') without the problems associated with handling and storage of H_2 gas cylinders.

In addition, the purity of H_2 gas in cylinders — even from a reliable and reputable vendor — is sometimes poorer than stated on the certificate of analysis, causing difficult to diagnose problems with ion source operation. This problem is entirely eliminated (assuming the system is free of leaks) by using the H_2 generator.

Air flow. The air flow in the cyclotron vault should be set up so that the air exhaust is in the part of the vault which is most likely to have loose contamination, and the supply should be in the cleanest part of the vault. This will help in maintaining any contamination to the smallest possible area.

3.3.2. Vault construction

The actual construction of the vault is nearly always of concrete, but the entrances, penetrations, floor type, wall coatings, etc. all play important parts in the ease of use and safety of the vault.

Mazes versus doors. One of the considerations in the design of the facility is the use of a maze versus the use of shielding doors for entry into the cyclotron vault. Mazes make entry very simple, but require careful calculation as to the effectiveness of the radiation shielding. Several turns are required to minimize the neutron flux at the entrance of the maze. Another disadvantage is that mazes require the vault to have a larger footprint. As a result, the total cost of the concrete for this larger footprint will be increased. In sliding doors or whenever it is advantageous to reduce the thickness of doors or shields, barite concrete (concrete with added barium sulphate) may be used since it has higher density.

Doors make the design of the vault simpler, but are more costly to build. It may also take longer to access the vault with a door than it does with a maze. There are many types of doors, including elevator type doors, which are sunk into the floor below the cyclotron vault; rotating doors; and sliding doors. Rotating doors may restrict the size of items that can be transferred to and from the cyclotron vault. Sliding doors seem to be the most common.

Concrete type. Concrete is invariably chosen as the practical construction material for permanent structures to shield accelerators. The concrete used to build the vault should contain specific proportion of water to help increase the concrete's neutron absorbing properties. The other important consideration is the activation of the concrete by the neutron or gamma flux from the cyclotron. Short term activities come primarily from manganese-56, sodium-24, potassium-42, potassium-43 and iron-59. These decay away relatively quickly (half-lives ranging from 3 hours to 44 days), but do contribute to the radiation dose to the cyclotron workers doing maintenance, although it is usually small in comparison to the dose from the target components.

The long term activation of the concrete in the walls of the accelerator vault may become a problem during operation and a liability when it is time to decommission the facility. There is some information in the literature on the choice of concrete and how it may affect the walls of the vault [3.3, 3.8]. The use of scrap iron or iron rich minerals as shielding additives to vault concrete

should be avoided because of the inevitable risk of the addition of cobalt and nickel, elements that after long term neutron bombardment will produce ^{60}Co. At a minimum, the cobalt content should be kept low. There are several other chemical elements which may be present in normal concrete that become activated when irradiated by neutrons from a cyclotron target. Fortunately, only a few of the resulting radioisotopes are long lived. These are identified in Table 3.4 [3.8, 3.9].

Some practical steps to minimize activation of the permanent vault material during the planning and design stages are:

— Employ 'local shielding' around the target(s) to absorb neutrons before they can activate the vault walls.
— Employ a 'sacrificial' and easily disposable layer of wall material.
— Use informed judgement in selection of raw materials in concrete. Portland cement is acceptable. Sedimentary aggregates are much preferred over igneous (volcanic) aggregates.
— Mix boron carbide into the concrete. ***Caution:*** *Do not under any circumstances add boron in the form of borate ion (i.e. boric acid, borax) to fresh concrete as it will completely undermine the structural integrity of the material!*
— Avoid barytes and iron loaded aggregates unless combined with boron carbide.

TABLE 3.4. LONG LIVED ACTIVATION PRODUCTS IN CONCRETE

Isotope	Reaction	Half-life	Principal gammas, MeV (%)
^{152}Eu	^{151}Eu(n, γ)^{152}Eu	13.4 y	0.122 (37%), 0.344 (27%) 0.779 (14%), 0.96 (15%) 1.087 (12%), 1.11 (14%) 1.408 (22%)
^{154}Eu	^{153}Eu(n, γ)^{154}Eu	8.5 y	0.12 (38%), 0.72 (21%) 1.00 (31%), 1.278 (37%)
^{60}Co	^{59}Co(n, γ)^{60}Co	5.27 y	1.17 (100%), 1.33 (100%)
^{134}Cs	^{133}Cs(n, γ)^{134}Cs	2.065 y	0.57 (23%), 0.605 (98%) 0.796 (99%)
^{133}Ba	^{132}Ba(n, γ)^{133}Ba	10.5 y	0.356 (62%), 0.303 (18%), 0.384 (9%)

Work surfaces. There should be some work surfaces, either inside the vault or in an area immediately adjacent to the vault, that are set up for carrying out radioactive work. These surfaces are essential for the routine maintenance and repair work on the cyclotron. The work surfaces should be resistant to chemicals and solvents, smooth, and easy to clean. They should not generate dust.

Floor surface. The floor surface should be hard, washable, and smooth. The concrete surface should be painted or covered with an epoxy coating, so that there will be a minimum of dust collected and contamination can be removed.

Floor drains. The floor of the vault must contain drains for water. There will be hoses that break and, during maintenance, it is often necessary to remove water from the water lines. These drains are normally connected to the sanitary sewer system. They may also be tied into a hold up system, for the water to be checked for radioactivity, before it is released into the sanitary sewer system. The holdup system is preferable, but is not always possible.

Floor loading. The weight of a bare cyclotron is of the order of 15–25 t. The weight of the self-shielding system may be 85–100 t. The weight of the vault of a locally shielded cyclotron with 1.2 m thick concrete walls is approximately 300 t. The total weight of a self-shielded cyclotron is much less than an unshielded or locally shielded cyclotron, which must be installed in a vault with thick walls. The floor underneath the cyclotron and vault must be strong and thick enough to bear these weights. A floor thickness of 40–50 cm is typical for the self-shielded version of the cyclotron. The floor loading of the path as the cyclotron is brought into the facility is also a concern, and structural engineers should be consulted before the move is made. Steel plates and other techniques can be used to spread the load if the floor on the path into the facility will not bear the weight of the magnet. The shielding is often installed in pieces, to lessen the problem during transport.

Shielding thickness. The thickness of the shielding around the cyclotron vault will depend on the type of cyclotron, the energy, types of particles, and the targets to be used. The main purpose of the shielding is to reduce the neutron flux during the operation of the machine. Any shielding that will reduce the neutron flux to an acceptable level will also reduce the gamma flux. Final testing should be done using a reaction which produces a lot of neutrons. Typical examples are deuteron on beryllium or protons on ^{18}O enriched water.

Air conditioning and humidity control. Much of the heat load of the cyclotron and associated equipment must be removed by the air conditioning system. The humidity in the room must be maintained low enough so that water will not condense on the cooling water lines. Typical requirements are for

temperature control at 20° ± 2°C, with less than 2°C change/hour and a relative humidity which must not exceed 65%. The air in the cyclotron vault must be clean and free of dust. Typical heat loads that must be removed by the air conditioning system are given in Table 3.5. The cyclotron manufacturer will supply the exact requirements for that specific machine.

There are also some recommendations for the air changes in the vault. It is recommended: that one use filtered make-up air for air coming into the vault; that the air from the vault is exhausted through an active (charcoal or other material) filter; that the room pressure be kept at least 25 Pa less than the adjacent rooms, and that there be at least three air changes per hour (the exact number of air changes per hour will depend on the accelerator and the usage).

Dust contamination. Dust in the vault can be a means of transport of radioactive contamination out of the vault and into other areas and, therefore, should be kept to a minimum. Dust can be kept to a minimum by using epoxy or other sealant on the floors and walls of the vault. This will minimize the number of small particles which flake off the concrete. The other fixtures in the vault should be made of rust resistant materials, and the exposed metal surfaces should be oiled to prevent corrosion if possible.

3.3.3. Control and utility access

There will be a need to provide access to the cyclotron vault from the outside to accommodate power cables, control cables, and gas supply and water lines. These are brought into the vault either through wall penetrations or in trenches.

Penetrations. Penetrations through the wall of the vault should not provide direct line of sight access to the vault. The penetrations should be at an angle or have an S-shaped curve. Some examples of penetration designs are shown in Fig. 3.4.

TABLE 3.5. EXAMPLE OF TYPICAL HEAT LOADS ON AIR CONDITIONING SYSTEMS

Area	Heat load
Cyclotron vault	20 kW for all power supplies in vault during operation 8 kW for all power supplies in vault on standby 2 kW for power supplies outside vault during operation or on standby
Equipment area	15 kW during operation if power supplies installed outside of the vault 2 kW during standby if power supplies installed outside of the vault
Pump area	2 kW (if installed outside vault)

FIG. 3.4. Examples of shielding wall penetrations designed to minimize line of sight radiation.

The number of penetrations of this type should be sufficient to carry all the cables, gas and water lines, etc., with at least 50% excess capacity to allow for additional cabling to be added in the future. One method is to embed a number of curved plastic pipes in the concrete wall during installation to act as conduits. The ducts through the wall should also allow for the voluminous ventilation ducts needed to exhaust the room air. Special attention should be paid to the routing of these wide cross-section openings.

Trenching. Trenches under the shielding wall can be used to carry the required utilities. They can often accommodate much larger cables than wall penetrations and are, therefore, preferred for heavy power cables, large water lines, and other utilities which require a lot of space. Ideally, trenches should be separated based on their function. Power cables should be run in separate trenches from control and signal cables, and the water should be run in a separate trench from the electrical. Again in this situation, larger curved plastic pipes imbedded in the concrete may prove useful.

It is not always possible, but if it is necessary to run more than one type of utility in a single trench, then they should be separated vertically with the water lines on the bottom and the electrical conduits or lines supported at least 3–4 cm above the bottom of the trench. The trenches should have drains to the sanitary sewer system to prevent water leaks from flooding the cyclotron vault.

Conduit and cable tray contents. Conduits and cable trays will carry both power and control signals from the cyclotron to the control room, from the cyclotron and control rooms to the equipment room, and perhaps from the cyclotron to the chemistry laboratory. The cables in the high radiation area should be insulated with a radiation resistant material like Kapton if possible. The position and function of each single cable should be well documented. Power and signal cables should be separately routed. The cyclotron manufacturer should provide recommendations for location, size and number of cable trays that are required, and the location of the connection points for the electrical services to the equipment to be installed. It is usually the

responsibility of the facility to provide and install all conduits and power cables from the main breakers to the cyclotron and related equipment. All electrical services must be installed and made ready prior to the commencement of installation of the cyclotron and related equipment. Cables and piping for building utilities should be laid in different cable trays from the routing that houses the cyclotron utilities. The conduits which are used to carry water should never be used to carry power or signal cables. Figure 3.5 shows a preferred layout for a three tier cable tray with power, signal, and water separated so as to prevent water leaks coming into contact with the electrical cables.

3.3.4. Safety

There are several potential hazards in a cyclotron facility. The normal hazards are high voltage, radiation, oxygen deficiency, high temperatures, and the movement of large pieces of equipment. The hazards associated with a facility should be described in a document specific for each facility. There should be an action plan for all likely emergency situations. There are usually precautions in place for high voltage and radiation, but may be less for the others. Oxygen deficiency caused by nitrogen or helium gas leaks can be mitigated by rapid air turnover in the vault. Postings warning of all these hazards should be clearly visible and the personnel should be trained to be aware of these risks.

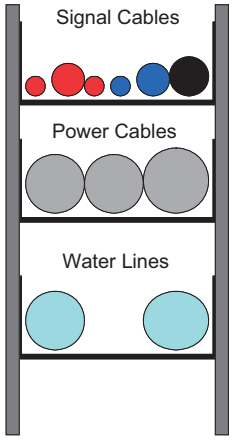

FIG. 3.5. Three tier cable tray with separation of function.

Interlocks. The interlock protection should be provided such that the machine cannot be operated while it is in an unshielded configuration. There should be two sets of independent interlocks. The system may be supplied by the manufacturer or may be installed by the facility. The exact configuration will be determined by the local regulations. Access to the accelerator or target should be allowed only if three independent devices have been turned off which are required to be operating in order to accelerate beam. For example, this could be the high voltage to the RF, the ion source arc, and a beam stop being closed. This results in a 'machine off' condition. The disabled condition for each device is defined as follows:

— The device is in the safe state as determined by a safety system limit switch.
— The device's safety system limit switches are not broken.
— There is no request to enable the device.
— Limit switches are taken to be 'broken' if the limit switches indicating two or more different states are closed at the same time.

A typical interlock system consists of two chains. The first is a chain of microswitches connected in series to shut down the machine if any of the outer doors to the cyclotron are opened. The chain is attached to the power relay on the ion source power supply. The other chain is connected in series with the shielding doors on the cyclotrons and with the inflector power supply. A failure to complete this second chain will keep the power supply from operating. In both situations, there will be no beam produced in the cyclotron. Direct, 'hard-wired' connections, rather than computer or other programmed-logic mediated connections, are preferred for first-line safety interlock systems. A diagram of this system, including the inspection stations, is given in Fig. 3.6.

The inspection procedure before the startup requires the operator to view all sections of the vault prior to closing the doors and starting the cyclotron. During this inspection procedure, a light is visible and there is an audible alarm sounding. The interlock system logic is given in Fig. 3.7.

Magnetic fields. There are magnetic fields associated with cyclotrons. In modern cyclotrons, the field is quite low, more than 30 cm away from the magnet yoke. Magnetic and RF field measurements should be taken in the vicinity of the machine during operation at the acceptance testing. In modern cyclotrons in which the magnet is of the contemporary 'deep valley' style, the external field is typically quite low, beyond several tens of centimetres from the surface of the yoke. However, if the cyclotron has the older, more traditional 'H-style' or 'window frame' yoke and pole construction, the external field can

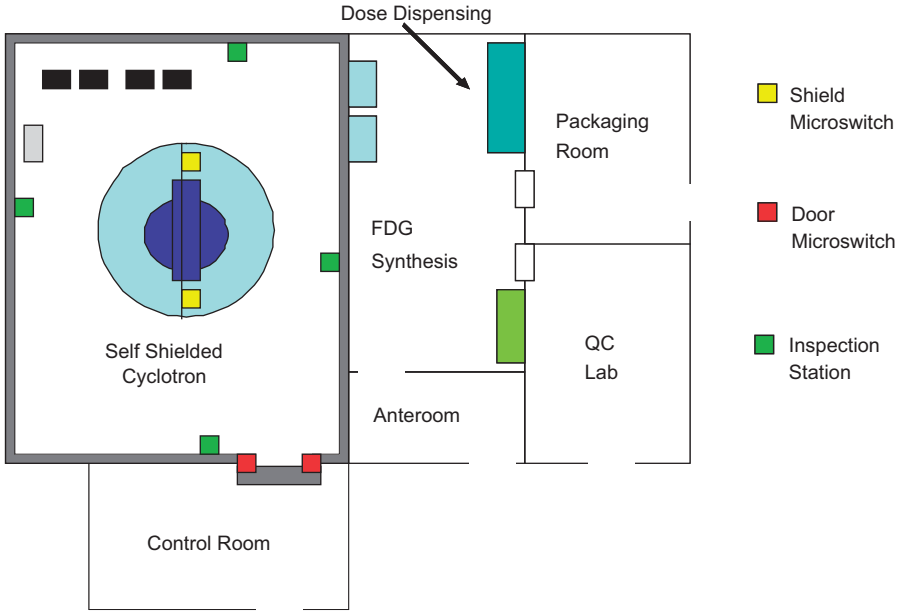

FIG. 3.6. Interlock chain with microswitches on perimeter doors, a second system on shields and inspection stations which must be energized prior to cyclotron operation.

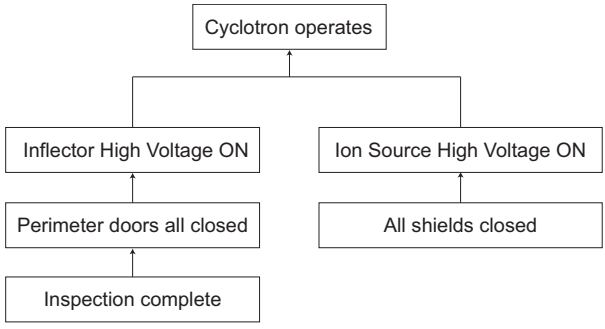

FIG. 3.7. Interlock logic chain for cyclotron operations.

be high enough while the magnet is energized to pose a direct physical hazard if, during maintenance or trouble-shooting, one strays too close to the magnet with steel tools in hand. The intense magnetic field close to the magnet will also render many ion chamber and Geiger–Müller type radiation survey instruments inoperative, creating a potential radiation hazard near close mounted targets and beam-line components due to falsely-low or null instrument readings if one is not forewarned.

The 'far field' — beyond a few metres distance from the H style or window frame style cyclotron magnet — while not a direct physical hazard per se will still be strong enough to affect the readings of sensitive ion chamber or GM radiation survey meters (causing either higher or lower than true readings) and can also perturb CRT type computer monitors, oscilloscopes, and similar instruments, causing a noticeable shift or distortion on the display screen when turning the magnet on and off.

The far field may also be sufficient to perturb the gain of photomultiplier tubes used in analytical instruments (gamma spectrometers, etc., in nearby laboratories) causing instrument readings to change or shift when the magnet is 'on' versus 'off'.

In any case, a careful magnetic field survey after installation is well advised, and the work space near the cyclotron should be posted with appropriate warning signs.

Fire safety. The entire facility should be provided with rate of rise/fixed temperature heat detectors. Manual fire alarm pull stations should be provided at the exits. Smoke detectors are recommended in areas with high value electronic equipment, and areas with programmatic importance. Smoke detectors are typically provided in the control room, and fire extinguishers are located in the control room and in the vault. The combustible material inventory in the facility should be kept low. This means removing cardboard boxes, papers, etc., that could aid in the spread of a fire. Fire extinguishers should be of the type which will not cause excessive damage to the electronic circuits. Carbon dioxide type extinguishers are ideal, although no longer readily available. The dry type extinguishers are most common.

Tritium production. Tritium can be produced in small amounts, by passage of the proton beam through water or by the neutrons generated in the target interacting with the groundwater. For low energy cyclotrons, these processes are usually not significant, but may become important for higher energy accelerators.

Radiation monitoring. Commercial area monitoring packages are readily available for radioisotope production facilities, but at a fairly significant cost. These systems measure activity levels in areas where radioactive material is handled, or where there is potential leakage of gaseous or volatile radioactive materials. Ideally, there should be a monitor inside the cyclotron vault to indicate the radiation levels before entry. There should also be radiation monitors inside each hot cell and in the general areas around the hot cells to detect any leakage. In addition, a monitoring device should be installed on all the exhaust ducts from the cyclotron and hot cells to warn of any emission escaping from the facility to the outside. These detectors can, when properly calibrated, give the integrated amount of activity being released from the

facility, which is often a regulatory requirement. If the hot cell and the cyclotron exhaust ducts are bundled close together, detectors in the exhaust ducts should be placed carefully to avoid one detector reading activity from the adjacent duct. Cross-talk between detectors can lead to an erroneous calculation of total emissions from the facility.

3.4. EQUIPMENT ROOM

Electrical equipment may be located in the same area as a self-shielded cyclotron, but a dedicated area is required for an unshielded cyclotron. This room should contain the cyclotron magnet power supply, radio frequency amplifier system, other power supplies, the deionized cooling water recirculation system, the secondary cooling water system (if required), and the compressed air supply system.

3.4.1. Noise levels

The noise levels in the room can be quite high, especially with the air compressor running. Hearing protection is often required. At a minimum, the area should be surveyed for noise levels and the noise levels posted if necessary. Noise levels above 85dbA require some hearing protection in order to avoid hearing loss.

3.4.2. Floor drains

Floor drains are essential to the room as there will be leaks and accidents with the water system. It may be necessary to refurbish the heat exchanger after a few years and this will require emptying the active cooling area of all water.

3.4.3. Trenches

Trenches are required from this area to the cyclotron vault for water cooling lines, control lines, and gas lines. They should be kept separate if possible, and should be well shielded to prevent leakage of radiation out of the vault.

3.4.4. Distance to cyclotron

The equipment room should be relatively close to the cyclotron, since water pipes and a substantial quantity of cabling will run from the various supporting units into the vault.

3.5. WORKSHOP AND STORAGE

All facilities require some storage area for supplies and spare parts. This area should be more than a single closet. A workspace is also required for maintenance operations and for the fabrication of small parts for the cyclotron or targetry.

3.5.1. Simple machining

There should be an area within the facility for doing simple machining. This could consist of a drill press, a mill, and some polishing and grinding equipment. A more extensive shop may be required if there are no facilities nearby for working on radioactive parts. Machining of activated or contaminated parts should be in a controlled area, and areas for machining these parts should be kept separate from areas dedicated to machining non-radioactive parts. There should be a clean area for simple electronic repairs.

3.5.2. Storage

Several storage areas are required for smooth operation of the facility. The spare parts for the cyclotron should be stored in the vicinity of the machine. The list of spare parts should be generated in collaboration with the manufacturer and other users. There should be a storage area for solvents, wipes/towels, polishing cloths, and tools. There will also need to be a separate area for the storage of radioactive parts and irradiated targets. This area must be shielded and could be in the vault or be located very near by, as to avoid excessive radiation exposure when storing the parts.

3.5.3. Waste disposal

There should also be an area for waste waiting to be removed from the facility. This process is usually referred to as decay in storage, and one should

wait at least ten half-lives or until the radioactivity in the sample has decayed to levels authorized for clearance [3.10].

3.5.4. Spare parts and self-service

3.5.4.1. Consumable spare parts

The facility is responsible for purchasing and maintaining a stock of 'consumables' — small parts such as ion source cathodes and insulators, O rings, extractor and target foils, etc., which are expected to wear out and to be replaced regularly during normal operation of the cyclotron. At the beginning of the installation, and probably through the first year or two of operation, it is assumed that these consumables would be purchased in 'kit' form from the original equipment supplier.

However, with the necessary extra work and investment in time and effort in identifying and characterizing these parts, many of the items (or their functional equivalents) can also be found and purchased in normal commerce at a considerably lower price. The resulting savings in overall operating cost over the life of the system may be substantial.

3.5.4.2. Proprietary, non-consumable spare parts

The most common routine service interventions are replacement of ion source cathodes or filaments, replacement of extractor foils, and maintenance and repair of the target(s). In the ideal case, these interventions are carried out on a scheduled basis, after a pre-determined number of 'beam-on' hours, or after observing a (hopefully) gradual degradation in performance.

The small parts which are actually changed and replaced are drawn from the stock of consumable components which is maintained on-site. We recommend — in addition to the normal complement of standard consumable spare parts — that a specific set of spare, fully assembled vendor proprietary components also be purchased by the owner. Routine, scheduled system repairs are then easily done by 'swapping' these complete subassemblies and implementing the actual repair or replacement of worn out consumable components in the parts which are removed from the cyclotron, the work performed on the laboratory bench, at one's leisure.

In the case of the ion source and target(s), it is highly advantageous and recommended to have a fully assembled spare *ion source assembly* and — depending on how many different types of targets are being used routinely — one or more spare target assemblies.

At least one — and preferably two — extractor foil-holder carousel assemblies should also be kept on hand.

3.5.4.3. Non-proprietary, non-consumable spare parts

With the exception of a half dozen or so proprietary subsystems and assemblies, such as the ion source, target changer and targets, extractor mechanism(s), etc., mentioned above, many component parts are non-proprietary and are available for purchase in normal commerce. However, identifying and characterizing these will require some work and investment of time and resources by the facility — and possibly some help from the outside — as it is generally not in the interest of the original equipment supplier to provide this information. There may be no particular reason or incentive to worry about this while the manufacturer's warranty is in force, but once the warranty has expired this can be very important in maintaining economical operation and maximizing 'up-time' of the system.

Essential non-proprietary spare parts. The RF system final amplifier and intermediate power amplifier vacuum tubes, high voltage ceramic coupling and bypass capacitors should be kept in hand at all times as these items can take a significant amount of time to be delivered from the manufacturer.

3.5.4.4. Essential service tools, instruments and fixtures

First year warranty notwithstanding, it is vital that the owner purchase and maintain the tools, instruments, and other resources (including in-depth training of local, resident technical personnel) so as to conduct as much of the routine — as well as urgent, non-routine — service as possible to minimize the delays, down-time, expense, and aggravation associated with having to wait for technical support from abroad.

Having the right tools and instruments in hand can, at the very minimum, facilitate resident troubleshooting and diagnostic capability to the extent that support and advice from afar, especially on the more common problems, becomes feasible by telephone or email.

The following is a short list of recommended tools and instruments, arranged by category. The list is not necessarily all-inclusive, but is intended to serve as a general guide wherein the most important items are covered. It is always better to have too many — rather than too few — tools.

Small hand tools. For normal day-to-day mechanical equipment maintenance, a complete 'mechanics tool assortment' in a roll-about cabinet with locking drawers may be purchased through catalogues or from large department stores.

An assortment of 'electronics technician' hand tools is needed, including: jeweller's screwdrivers, small needlenose pliers, diagonal cutters, tweezers, wire strippers, crimpers (for attaching terminal lugs and assembling coaxial and multi-pin cables, etc.), soldering iron, and 'solder-sucker' (for repair of printed wiring boards).

Also needed are: precision calipers with digital read-out; portable, a battery operated drill motor with an assortment of 'English' and metric drill bits; tap and die set ('English' and metric threads); small hacksaw, tubing cutter, assortment of files, including miniature jeweller's files; small flashlight; portable, high intensity work lamp.

Small portable electronic and laboratory test instruments. Continuity tester, two and three phase mains tester; digital multi-meter with accessories, including: high voltage DC probe (20 KV), clamp-on ammeter, and (optional) temperature probe. A 100 MHz oscilloscope with probes; frequency counter; signal generator with vernier frequency adjustment covering 70–80 MHz.

Specialized test and diagnostic instruments. Helium leak checker; residual gas analyser; Gow-Mac leak detector for leak testing high pressure targets; RF 'dummy load' resistors for high and medium power (one each required for 10 KW and 500 W power ratings); medium power (500 W) RF directional coupler and power meter; an array of 50 ohm RF cable adaptors, tees, miniature directional couplers, attenuators; dual channel analog chart recorder or equivalent digital data logger.

Electronic components. If there is no convenient local supplier for common, small electronic components such as resistors, capacitors, semiconductor products, fuses, lamps, terminal lugs, etc., then a selection must be purchased and stocked on-site.

3.5.4.5. Special topics

There are some specific technical support issues which may be unfamiliar to those who are new to the field, or which are particularly important and must be emphasized and understood in advance — particularly for cyclotron systems which will be installed overseas or in remote areas, far from the manufacturer.

Bead blaster. This is a particularly useful accessory for maintenance of the ion source and its internal components. It is used for cleaning oxidation and 'invested' contaminants from metal and ceramic surfaces by means of tiny (micrometre sized) glass beads driven at high velocity by a jet of air supplied by a small compressor. The action takes place inside a transparent, sealed glove-box compartment with an internal, recirculating air filter and reservoir to maintain cleanliness and to prevent leakage of glass particles into the room.

Vacuum leak detection: Leaks in the cyclotron vacuum system may occasionally occur due to operator error or a momentary lapse during a service or maintenance intervention. Often such leaks can be fixed by simply 'back-tracking' to correct the mistake. However, vacuum leaks can also occur due to mechanical wear of shafts or other penetrations, or radiation damage or overheating of elastomer O-ring seals. In these cases it can be very difficult to pinpoint the problem, and a methodical and systematic process of 'leak chasing' must be undertaken.

The general subject of methods and techniques for leak detection is best covered in a 'hands-on' training course, supplemented by technical documentation and textbooks such as Basic Vacuum Practice by Varian, Inc.

If not repaired in a timely manner, a vacuum leak can get worse and may lead to overall degradation in system performance, severe wear and tear on other subsystems such as the ion source and RF system, and possible further damage or disruption and shut down of the entire cyclotron system.

Fortunately, severe vacuum leaks do not occur often, but it is the very rarity of the problem that can also render vacuum leaks among the most difficult and frustrating problems to resolve. Generally, the instrument which is used to find a vacuum leak is the 'classic' helium leak detector. The overseas customer should either purchase — or at least have ready access to — a good quality helium leak detector. The choice of which leak detector depends on how one chooses to trade off between the most automated, high end (and highest price) systems versus manual, lower end (and substantially lower priced) systems.

The high end, fully automated systems are, of course, easier for the novice or occasional user to learn and operate — especially when used only occasionally — with advanced features like 'auto-calibration'. The less expensive manual systems will require an extra investment of time and effort in operator training, but are entirely satisfactory for the job at hand. Moreover, test equipment also needs occasional service and maintenance; the less expensive manual systems can generally be maintained by the user, on-site, with kits of replacement parts available from the manufacturer, while the fully automated systems may require factory only service. One should always, if at all possible, choose a leak detector system which incorporates the newer turbomolecular type of vacuum pump, as opposed to the oil diffusion pump. The turbopump systems are more easily started up from a 'cold' state whenever they are actually needed, whereas the diffusion pump systems often have to be left plugged in and running at all times (24 hours per day, seven days per week) in order to maintain these machines in a reliable 'ready' state.

Finally, one does not necessarily have to purchase a new leak detector, as they are also available used — but carefully reconditioned and guaranteed by reputable suppliers.

Residual gas analyser: An extremely useful and valuable supplement to the helium leak detector is a new, relatively inexpensive, very rugged and compact 'residual gas analyser' (RGA) which provides additional information which, in turn, can significantly enhance the speed and efficiency of finding and fixing vacuum leaks. The fully configured RGA (approx $7500) also incorporates a 'leak detector' operating mode, which may often substitute for — though not entirely eliminate — the need for access to a 'classic' helium leak detector.

Dual channel analog chart recorder. A digital data logging facility is usually included in the cyclotron's control system software, but the temporal sampling rate may not be sufficient for characterizing every problem; the solution to some problems may require recording two or more operational parameters in real-time. A compact, relatively inexpensive, dual channel analog strip-chart recorder is very useful for this task. Alternatively, a dual or multi-channel analog to digital data logger with 1 s or less sampling interval may also be used.

Special test fixtures. After finishing repairs or replacing consumables on an ion source or extractor assembly, it is highly recommended that these components be checked for vacuum integrity before they are stored or have to be reinstalled in the cyclotron itself. This will require some simple vacuum test fixtures which may be designed and built locally by qualified engineering/metal fabricating shops.

Additional recommended spare parts are:

— RF coupling loop assembly;
— Mechanical pump oil and filters;
— Diffusion pump oil;
— Spare diffusion pump heaters;
— Diffusion pump temperature switches;
— Spare solenoid coils;
— Spare pneumatic valves;
— Spare high vacuum gauge filaments;
— Spare TC gauges.

3.6. DECOMMISSIONING

There will come a time to decommission the cyclotron and replace it with a newer version. The plans for this should be made when the facility is built [3.11] and money should be put aside for this process. Many Member States now require that the funds be allocated for this purpose during construction.

One can expect the cyclotron to last for 20 years although there are cyclotrons which have been operated for more than 50 years. At some point, the cyclotron may start to show signs of age. The repairs will be more frequent and the time the cyclotron in not operational start to increase. When this time comes, the effort spent in planning the decommissioning of the cyclotron will be well worth while. Leaving a service access to the vault such that the cyclotron can be removed whole is much less expensive than having to cut up the main magnet into pieces for removal as is sometimes the case. Since the iron in the magnet will be radioactive for many years, the entire magnet assembly must be treated as low level waste and the disposal is expensive. If the magnet can be removed whole, it may be sold to another facility willing to put in the work to maintain the cyclotron, or at a minimum it might be a single piece for disposal.

The planning of the vault to minimize the activation will also be very beneficial at this point since the outer layers of the concrete (away from the cyclotron) can often be disposed of as regular waste whereas the inner layers will probably be low level waste. There is an extensive decommissioning study available on the Web which covers many of the aspects of decommissioning. The title of this report is 'Evaluation of the Radiological and Economical Consequences of Decommissioning Particle Accelerators' [3.12].

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4. LABORATORY DESIGN

4.1. HOT LABORATORIES

The laboratory should be planned as a suite of rooms, the complexity depending on the extent of the proposed work and the number of workers. A larger suite might include a separate radioactive store, two main laboratories for handling different levels of activity, and an office for record keeping and the processing of results. In many countries there are certain requirements for the design and construction of adequate radioisotope laboratories. Conformance with these regulations will be required from any applicant for a license to manipulate unsealed radioactive material. The next two sections contain suggestions on utilities which may not always be in compliance with local regulations. Of course, the local regulations will take precedence and local authorities must be consulted during the planning.

4.1.1. Utilities

There are guidelines which can make the laboratory safer and easier for the chemist to use. A few of these guidelines are listed below. More of these can be found in the literature [4.1, 4.2].

Heating and cooling system. The heating and cooling system must maintain the temperature, the humidity and the particulate level in the laboratory. The ventilation requirements of the laboratory will be dictated by the heat load in the room and the environmental requirements for the experiments. All laboratories should, preferably, be air-conditioned. Ideally, ventilating air should enter a laboratory at the doorway or 'clean' side of the room, and be exhausted at the far or 'dirty' side of the room. The air passing through the laboratory in this manner will tend to transport atmospheric contaminants across the room to the exhaust point. For heavier than air vapours, the clean air should be introduced at a high level near the ceiling of the room with the exhaust at a lower level, preferably near the floor. A rule of thumb for ventilation is that there should be an air flow of 3–6 L/s of air per square metre of floor space in the room.

An adequate supply of clean, cooled or heated air will be required in a laboratory equipped with one or more fume cupboards. Control of the temperature of the incoming air and the removal of its dirt load require that the bulk of this air should be filtered. Cross-drafts adversely affect fume hood performance. Air coming into the laboratory should ideally be at the opposite side of the laboratory from the fume hoods or hot cells, to ensure that the entire

laboratory volume will be swept by the air flow which will transport contaminants across the room from the 'clean' side to the 'dirty' side at the fume cupboard or hot cell where it will be exhausted.

High efficiency filters. High efficiency particulate air (HEPA) filters offer a significant benefit when they are used to filter out dust particles and other contaminants from the air coming into the laboratory space. When used on the exhaust, they will not remove radioactive gases from the air.

Electrical. Utility shut-off controls should be located outside the laboratory. Laboratories should have an abundant number of electrical supply outlets to eliminate the need for extension cords and multi-plug adapters. A good rule of thumb is to have at least two receptacles for every metre of bench space. Electrical panels should be placed in an accessible area not likely to be obstructed. Ground fault circuit interrupters should be installed near sinks and wet areas.

Loss of electric power can create hazardous situations. Flammable or toxic vapours may be released as a chemical warms when a refrigerator or freezer fails. Fume hoods may cease to operate, allowing vapours to be released into the laboratory. If magnetic or mechanical stirrers fail to operate, safe mixing of reagents may be compromised. Fume hoods should be equipped with flow monitors and audible alarms to indicate an unsafe condition. Hot cells should be equipped with both flow and pressure differential monitors and auditory and visual alarms.

Lighting. The lighting should be sufficient to be able to see clearly, and should illuminate the entire area of the laboratory as evenly as possible. The standard requirements in each type of workspace are set by national regulations.

Vacuum and gases. Central vacuum systems should not be used, since they are vulnerable to contamination. Local vacuum pumps are preferable. All vacuum lines should have cold traps or filters to prevent contamination. High air flow Venturi pumps may be used for solvent evaporation. These require an air supply of at least 675 kPa. Most laboratories need built-in supplies of nitrogen gas, argon, helium and perhaps hydrogen for flame ionization detectors used in GC analysis. Gas lines from highly toxic gases should use coaxial tubing for double containment. Hydrogen gas supplies should be run in all metal tubing with spark arrestors at the tank. Gas storage rooms should be accessible from the outside whenever possible.

4.1.2. Work surfaces and floors

Ideally, the work surfaces should be finished in hard, impervious, heat resistant, stain resistant, chemically resistant and easily cleaned material, which

can be applied in large sheets with a minimum of joints. Tables 4.1 and 4.2 provide data on ease of decontamination and on chemical resistance. Grade 316 stainless steel is frequently used for laboratory sinks, draining racks, and bench tops. To aid in decontamination, the surface of the steel should be finished to a 'bright polish' rather than the more common satin finish. The 316 grade is more resistant to chemical attack than the 304 grade; however, it is still prone to attack by hydrochloric acid and some other chemicals.

The whole floor covering should be watertight and effectively act as a tray, so that the building structure and the space on the floors below the laboratory suite are protected against water, whether it is contaminated with radioactivity or not. The covering should be bonded to the floor to prevent liquids spreading underneath in case it is punctured, and it should be extended about 100 mm up the walls. The usual material chosen for floor covering is seamless vinyl sheet which can be welded at joints and readily coved up walls. Vinyl tiles are not recommended because of the large number of joints.

TABLE 4.1. EASE OF DECONTAMINATION OF THE SURFACE OF VARIOUS MATERIALS (8 cm × 9 cm AREA)

Material	Decon [a]
Stainless steel	0.01
Industrial polyvinylchloride, grey	0.01
Industrial polyvinylchloride, white	0.05
Polypropylene on glass fibre base	0.2
Plastic laminate	1.5
Plastic laminate with abraded surface	1.4
Plastic laminate treated with hypochlorite abrasive cleaner	5.7
Plastic laminate, aged	4.5
Polyurethane-varnished hardwood	33.2
Vinyl flooring	0.03
Vinyl flooring plus asbestos filler	4.4
Vinyl flooring plus rubber filler	10.0
Linoleum	6.9

[a] Percentage of contaminant (^{60}Co/^{137}Cs) remaining after decontamination by British Standard procedure [4.3].

TABLE 4.2. CHEMICAL RESISTANCE OF SOME TYPICAL MATERIALS USED IN LABORATORY COUNTERTOPS

Chemical	HDPE	Epoxy resin	Teflon	Aluminium	Stainless steel 304	Stainless steel 316
Acetic acid, glacial	A	A	A	A	C	A
Acetonitrile	A	A	A	B	A	A
Acetone	D	B	A	A	A	A
Ethanol	A	A	A	B	A	A
Hydrochloric acid 37%	nt	A	A	D	D	D
Mineral oil	A	A	A	A	A	A
Sodium hydroxide 60%	C	A	A	D	B	B
Sulphuric acid 96%	B	D	A	D	D	D
Toluene	B	A	A	A	A	A
Trichloroethlyene	D	B	A	A	B	B

A: excellent; B: good; C: fair; D: not recommended; nt: not tested.

It should be noted that the radiochemical processing of many elements (among which the radio-metals, some even of importance to PET) requires handling and evaporation of hot mineral acids, most notably hydrochloric acid. Hot cells, fume hoods and ventilation systems for such operations (either present or foreseeable) should be specified and constructed of acid resistant materials. Normal 316 stainless steel will not tolerate such operations over long periods of time, and costly, operation-interrupting maintenance and repair will be required.

4.1.3. Hot cell design

Hot cells are exhausted and shielded enclosures usually used for processing radioactive materials. Hot cells are based on the principle that shielding is the cheapest and most effective if it is as close as possible to the radiation source.

Hot cells have to provide shielding for personnel against radiation from gamma emitters [4.1]. Various types of concrete, lead, lead glass, steel and depleted uranium can be used as shielding materials. The thickness of the shielding must be calculated on the basis of the type, energy and activity of radiation to keep doses received by the operators within the internationally accepted limits. The shielding material must be supported by a rigid frame. The

interior surface of most hot cells is made of good quality stainless steel (grade 316 is preferred since it is less susceptible to corrosion). Operations are either done with a remote or automated system, or carried out by using manipulators. Connections for services are welded into the bottom of the box or service lines may be brought in through a panel in the top face. Windows are common on most hot cells with the size depending on the operations which need to be observed from the outside. A 5 cm thick lead wall requires 10 cm thick windows of standard density of 5.2 g/cm^3. The windows are mounted in frames in the shielding wall. Remote-handling tongs and manipulators of various types may be obtained from commercial suppliers. Prior to putting a newly constructed hot cell into operation, a dose map indicating potential leakage of the radiation should be drawn up using a sealed source containing similar isotopes as intended to be handled inside the hot cell and having known radioactivity. There have been no recent dramatic changes in hot cell design since the design considerations and dose calculations have been well established for a long time.

The hot cells constructed for the production of radiopharmaceuticals need to maintain negative pressure to prevent radioactive contamination. The hot cells should be leak tight according to accepted international standards. The walls of the hot cells should be smooth, impervious and unbroken and the corners curved. Permanent installation of components, which cannot be sufficiently cleaned, should be avoided. Stainless steel and clear plastics are recommended as construction materials. The stainless steel surface inside the hot cell should be polished and made from good quality stainless steel. The hot cells need to meet the general recommendations for GMP. During their operation, the hot cells are under negative pressure with a 20-fold air change per hour. The in-air and exhausted air should pass through HEPA filters to prevent introduction of dirt and exhaust of any contaminated particles. The hot cell can be equipped with double door air locks. It is desirable to have the front and/or back wall movable in order to clean or change the devices inside the hot cell. The so-called mini-cells are commercially offered especially for PET technology. The mini-cells are used for the automatic synthesis of PET pharmaceuticals, the dispensing of pharmaceuticals in vials and syringes. The mini-cell is a completely closed hot cell with controlled air flow (clean room class C and A are possible). The mini-cell is designed without manipulators.

The introduction of radioactive material and reagents, and removal of product and waste require transfer systems that are reliable and safe. Safety encompasses radiation protection, radioactive contamination and conventional laboratory safety in handling reagents and solvents. Liquid waste can be handled through shielded drains or absorbed on some suitable material and treated as solid. Although the latter appears to be inefficient, it may be

advantageous when small volumes are produced. The drain method may require expensive maintenance.

Hot cells come in many configurations and the best choice depends on the intended use. For remote or automated synthesis, a sliding central pane with solid panels on either side is a common design. An example of a hot cell with sliding glass central door used for chemical synthesis is shown in Fig. 4.1.

There are two basic designs the devices used to handle materials or equipment inside the hot cell. These are the tong and master–slave manipulator. The tong, which could be seen as a fixed or manoeuvrable rod (with two degrees of freedom) is usually limited to shielding walls up to 150 mm thick as the lead ball, which gives it the swivel action, becomes too heavy in thicker walls. The master–slave manipulator provides far greater articulation but requires greater maintenance and is more costly. Both types of manipulator require a seal to maintain an airtight seal with the box. These seals should be easily replaceable. Examples of hot cells are shown in Fig. 4.2.

In order to prevent the release of radioactivity, the hot cell needs to be held at a controlled negative pressure, the magnitude of which is dependent on the toxicity and volatility of the radioisotopes. Pressures of –200 Pa to –500 Pa are normally chosen. Both inlet and outlet HEPA filters are required; the inlet determines the rate of air drawn into the box and the outlet filter must be able

FIG. 4.1. Sliding leaded glass shield hot cell design.

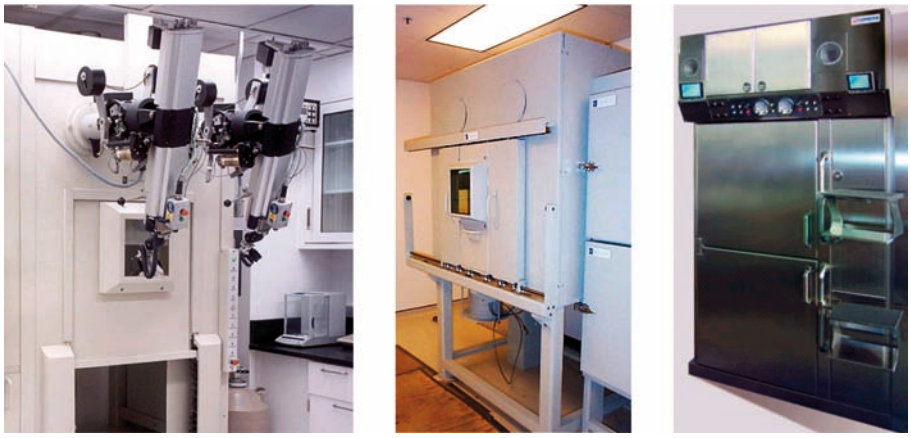

FIG. 4.2. Hot cells with different opening designs. The one on the left with the door up also has two master–slave manipulator arms installed; the one in the centre has a central sliding door. The ones on the right are mini-cells with hinged doors designed to house automated synthesis units.

to handle the air flow when the door is opened. A face velocity of air through the door of about 0.5 m/s is usually adopted as the minimum in an enclosure used for handling radioactive materials.

4.1.4. Laminar flow hot cells

The hot cells and laminar flow hoods used in the laboratory need to be sufficiently shielded to minimize the radiation exposure to the chemist working at the face of the hot cell. Shielded hot cells are commercially available or can be produced in-house. Likewise, shielded laminar flow hoods are commercially available. There should be radiation monitoring equipment in the laboratory for both area monitoring and personnel checking. More details can be found in the section on radiation safety. A typical example of the mini-cell and associated laminar flow hood is shown in Fig. 4.3.

4.2. SHIELDING AND RADIATION EXPOSURE REDUCTION

Shielding is required around all areas where radioactive material is being stored, processed, or used in synthesis. The amount of shielding will depend on the decay mode of the radioisotope being used, the quantity, and the type of

FIG. 4.3. Two mini-cells next to a laminar flow cell in a new PET installation.

area in which it is being used. For positron emitters where the 511 keV gammas are the primary source of radiation exposure, the half-value layer thickness for lead is 4.1 mm and 3.4 cm for concrete [4.5].

Shielding consisting of lead or other high density material in the form of bricks, panels, L-shields, storage containers, or other shapes may be used on bench tops, in fume hoods, or in glove boxes to reduce radiation exposure from gamma-emitting radioactive materials.

Remote handling tools, such as forceps or extension handles, should be used to provide distance in the handling of radioactive materials. In addition, shielded handling devices, such as shielded syringes, can be used to protect workers from materials that cannot be handled remotely. Pipetting should be done using appropriate devices. Pipetting by mouth is strictly forbidden.

Observation of activities conducted behind shielding with remote tools (or with extended arms and hands, within limits consistent with permissible occupational exposures) can be accomplished by using mirrors, through shielded (e.g. leaded glass) windows, through transparent plastic beta shields, or by remote video monitoring. The combination of containment, shielding, and handling devices proposed for any use of radioactive materials should be appropriate to the type and quantity of the materials to be used, and to the type and duration of the operations to be conducted.

Gases coming from the target into the hot cell for synthesis should be in a closed system. The gas should pass into the synthesis vessel or trap and the outlet of this vessel should be connected to a system such that the radioactivity will have a chance to decay to acceptable release criteria before venting to the

atmosphere. This can be done with either a flow delay or storage may be used depending on the half-life and quantity. In a flow delay system, the gas is passed through a large volume or a very long length of tubing before being exhausted to the atmosphere. In the storage system, a balloon or large sealed vessel is used to hold the gas until the level of radioactivity will allow the vessel to be vented to the atmosphere. Activated charcoal filters (shielded) on hot cell exhaust can significantly reduce atmospheric release of activity.

4.3. EQUIPMENT PLACEMENT AND WORKFLOW

4.3.1. Equipment placement

In a radiopharmaceutical production facility, placement is even more important than in a normal chemistry laboratory. The need to keep operations separate and prevent both radioactive and chemical contamination is essential. A list of hints on equipment placement is given in Table 4.3.

4.3.2. Workflow

Careful thought should be given to the workflow as the radioisotope passes from the cyclotron target to the chemical synthesis, to the packaging area, and finally out for distribution. The facility should be arranged so that the transfer from the cyclotron to the hot laboratory minimizes the radiation exposure, and minimizes the chances of transfer failure. The transfer should be carried out in ways that there is an easy access to the transport vessel in case of failure. An idealized scheme is shown in Figs 4.4 and 4.5. In Fig. 4.4, the orange arrows represent the raw material flow into the facility and the purple arrows represent the final product flow out of the facility.

Laboratory space should be physically separate from personal desk space, meeting space and eating areas. Workers should not have to go through a laboratory space where hazardous materials are used in order to exit from non-laboratory areas. Consider making visible separation between laboratory and non-laboratory space, for instance with different flooring.

In the same facility (Fig. 4.5), the personnel flow is shown as blue arrows with a clear boundary between the limited access areas and the free access areas.

TABLE 4.3. LOCATION MATRIX FOR PLACEMENT AND ACCESS OF EQUIPMENT (ADAPTED FROM REF. [4.6])

Radioactivity and contamination levels			Laboratory location and access
None	Low	High	
■	■	■	Separated from public areas by door.
	■	■	Access limited to authorized personnel.
	■	■	Laboratory doors have appropriate signs for level of radioactivity.
■	■	■	Size of door openings to allow passage of all anticipated equipment.
	■	■	Doors have locks which are locked when room is not occupied.
		■	Doors have restricted entry access (e.g. key card).
■			Office areas located in free access areas.
		■	Access to area is through an anteroom or lower level area.
	■	■	Exit from the area through a frisker or whole body counter.
■	■	■	Utilities are located in close proximity.
		■	Laboratories located away from outside walls.
	■	■	Surface material designed to minimize movement of gases or liquids outside the perimeter walls.
■	■	■	Working surfaces to be non-absorptive.
■	■	■	Surfaces are scratch, stain, moisture, chemical and heat resistant.
	■	■	Surfaces should be continuous (no seams).
	■	■	Drawers to be of one piece construction.
■	■	■	Reagent shelving to be equipped with lips to contain spills.
	■	■	100% outside air supplied.
	■	■	Flow from areas of low contamination to high.
■	■	■	Visual pressure differential monitoring devices at doorway to room.
■	■	■	Audible and visual alarms for air system failure.
	■	■	Supply air to be HEPA filtered.
	■	■	Supply air system interlocked with exhaust to prevent overpressure.
	■	■	Exhaust air to be HEPA filtered.

TABLE 4.3. LOCATION MATRIX FOR PLACEMENT AND ACCESS OF EQUIPMENT (ADAPTED FROM REF. [4.6]) (cont.)

Radioactivity and contamination levels			Laboratory location and access
None	Low	High	
	■	■	Supply and exhaust systems outside radioactive areas for ease of maintenance.
	■	■	Mixed hazardous waste disposal system in place.
	■	■	All penetrations sealed with non-shrinking sealant at the containment barrier.
	■	■	All conduits and wiring sealed with non-shrinking sealant at the containment barrier.
	■	■	Windows do not open to the outside.
■	■	■	Observation windows installed at the containment barrier.
■	■	■	PPE hooks and supplies at containment barrier.
	■	■	Hand washing sinks provided with 'no-hands' operation.
■	■	■	Emergency eye wash facilities provided at every sink.
■	■	■	Emergency showers provided in accordance with regulations.
		■	Drains to containment or hold-up vessels.
	■	■	Compressed gas cylinders located outside laboratory space.
	■	■	Portable vacuum pumps available.
■	■	■	Emergency lighting provided.
	■	■	Electronic data transfer to outside areas.
■	■	■	Laboratory equipped with a communication system between high activity areas and outside areas.

Fire rated hallway doors should have magnetic hold-open features, such that the door will close in the event of an alarm. Doors to laboratories should not be fire-rated unless necessary. Entryways should have provisions for mounting emergency information posters and other warning signage immediately outside the laboratory (for example, on the door). Each door from a hallway into a laboratory space should have a view panel to prevent accidents from opening the door into a person on the other side and to allow individuals to see into the laboratory in case of an accident or injury. Even in the anteroom where there is a purposely straight path, a window can be installed in the wall to allow people in the hallway to see inside the synthesis area in case of accident or emergency.

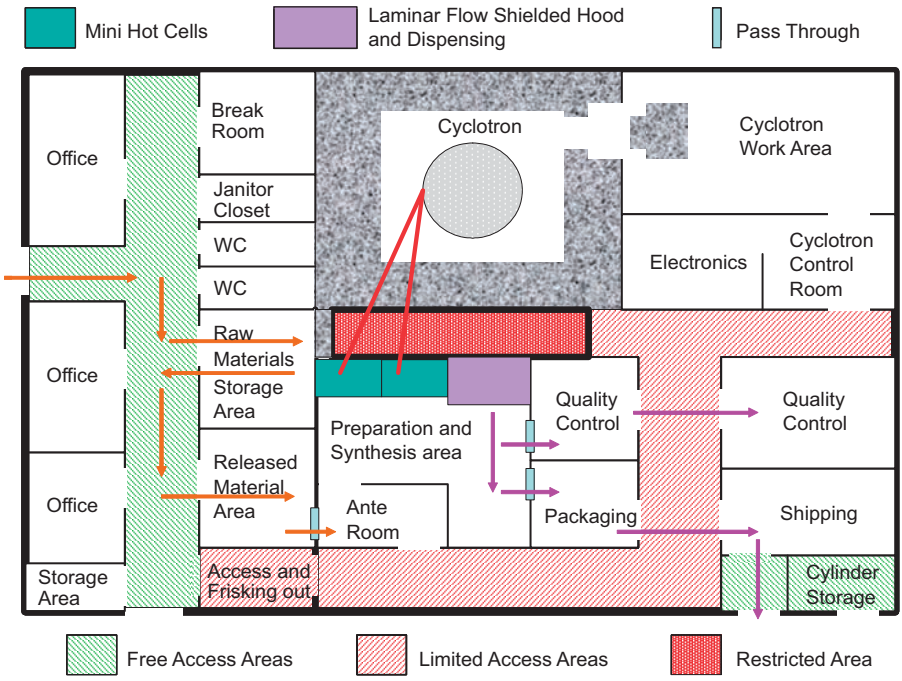

FIG. 4.4. Schematic diagram showing the unidirectional flow of materials through the facility. Raw materials are shown as orange arrows and the finished product is marked by purple arrows.

Laboratory areas with autoclaves should have adequate room to allow access to the autoclave and clearance behind it for maintenance. There should also be adequate room for temporary storage of materials before and after processing. Autoclave drainage should be designed to prevent or minimize flooding and damage to the floor. When using radioactive material, there must be separate spaces for eating and drinking which are outside the laboratory space. Security of laboratory and materials is a concern and there should be safeguards in place for this. If possible, the laboratory should be designed to allow separation of radioactive material use from other laboratory activities.

The requirements for placement of the hot cells must meet the two important criteria of workflow and air flow. The hot cells: should be placed so that they are near the source of the radioactivity coming from the cyclotron vault; should be placed so that they are near the air exhaust from the room; and should be within easy access of the hot cells when they are not in use to facilitate cleaning and maintenance. The hot cells provide additional shielding; thus, their placement against a vault wall offers a considerable advantage. In

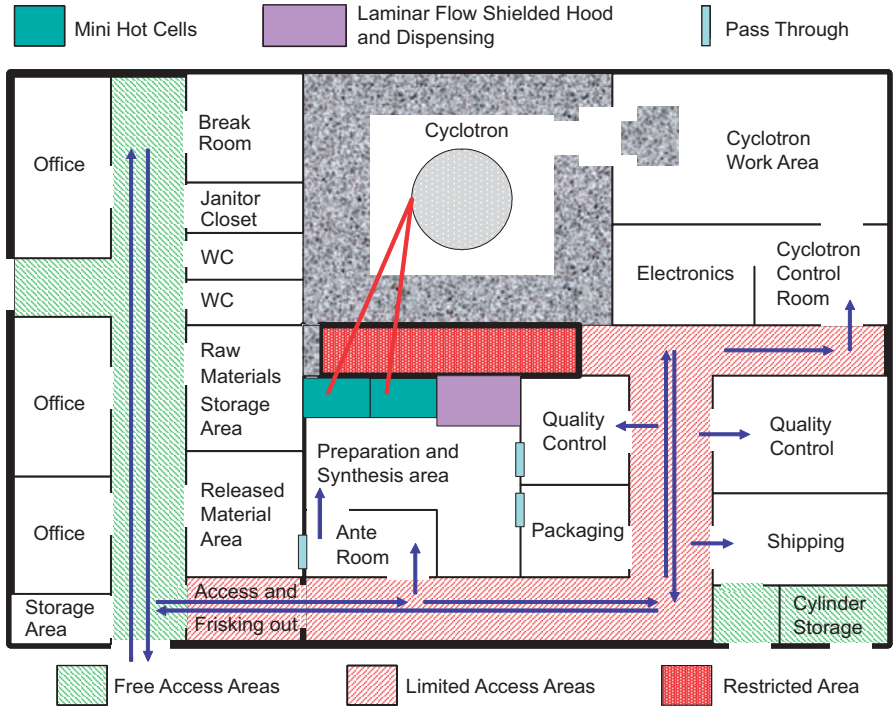

FIG. 4.5. Schematic diagram showing the flow of people from the free access areas to the limited access areas. The personnel flow is shown in blue.

the above diagrams, there is access to the hot cells from the rear through the restricted area. This area should be interlocked with radioisotope transfer so that there is never anyone in that area when there are high levels of radioactivity present.

4.4. TRANSPORT OF RADIOACTIVE MATERIAL

Radioactive gases and liquids will normally be transferred out of the accelerator vault into the hot laboratory. Gases will be transferred through small internal bore tubing extending from the cyclotron vault to the chemistry laboratories. This tubing will be contained within larger bore tubing as secondary containment to enclose any radioactivity in case of a leak in the lines. Liquids will be transferred in a similar fashion from the vault to the chemistry laboratories. These tubes will also be contained with secondary containment. Both sets of lines should be shielded so that radiation levels will allow normal

occupancy during transfer. Radioactivity may also be transferred with the use of shielded containers. The radioactivity would typically be placed in a multi-injection vial and sealed in the shielded container for transport. The composition of the tubing used to transport the radioactivity should be consistent with the chemical form of the radionulide being transported. In many applications for liquids and some gases, PEEK tubing serves well since it is chemically inert and has good radiation resistance.

4.4.1. Security

Radioisotope laboratories should have a lockable cupboard or a lockable refrigerator to hold chemicals. It is advisable to have locks on the laboratory door and windows on the ground level, to prevent unauthorized access when the facility is not occupied.

4.4.2. Emergency equipment

Laboratories using hazardous materials should have an eye wash and safety shower within 30 m, or 10 s travel time from the areas where chemicals are being used. Eye wash and safety shower types and locations should be standardized, at least within a laboratory building, so that one can be found quickly in an emergency. The flooring under the safety showers should be slip-resistant and should have plumbed drains. Fire extinguishers, safety showers, and eye washes should be conspicuously labelled, particularly if recessed.

Fire extinguishers appropriate for the chemicals and equipment in use should be placed near the entrance of each laboratory, mechanical and electrical room. Some chemical operations (for example, distillation) may benefit from hood fire suppression systems. Windowless laboratories and environmental chambers should have emergency lighting. Alarm enunciator panels should be descriptive of the area where the alarm has activated. Laboratories using highly toxic gases should be equipped with alarmed vapour sensors, preferably with automatic shutdown systems. Gas lines from highly toxic gases should use coaxial tubing for double containment. Fire rated hallway doors should have magnetic hold-open features, such that the door will close in the event of an alarm. Doors to laboratories should not be fire rated, unless it is required. The entryways should have provisions for mounting emergency information posters and other warning signs immediately outside the laboratory (for example, on the door). Each door from a hallway into a laboratory should have a view panel to prevent accidents from opening the door into a person on the other side, and to allow individuals to see into the laboratory in case of an accident or injury.

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5. EQUIPMENT AND PERSONNEL

5.1. INTRODUCTION

Radiopharmaceutical production areas include: clean room(s); QC laboratory(ies); glassware preparation room; radiotracer development laboratory(ies); and raw materials storage room. Not all facilities will need these areas, since the space allocation will depend largely upon the scope of the facility as discussed in Section 2.3.1. The following discussion pertains to more specific requirements to achieve compliance with the regulatory requirements and also in relation to the product quality. Radiation protection requirements must always be an integral part of production area planning.

5.2. PERSONAL PROTECTIVE EQUIPMENT (PPE)

As part of personal radiation protection, the staff should wear laboratory coats over the normal garments and eye protection with side shields at all times when entering the laboratory space. Entry into an area with potential contamination should require shoe covers. Working with radioactivity requires double gloves and forearm protection (gauntlets). Coat hooks should be provided within the laboratory close to the entrance to hang laboratory coats prior to leaving the laboratory. Latex or other disposable gloves should be in a container near the doorway so they can be donned on entry. There should also be boxes of gloves near every potential contamination site so that gloves may be changed frequently. There also must be cartons for the disposal of gloves which are separate from all the other garbage so that they may be easily segregated. More extensive protective clothing, such as overalls, should be readily available in areas where they may be needed. Extra clothing should be available at the exit in the event of some contamination of clothing that cannot be removed from the facility. It is a common practice in some facilities to have a complete set of clothing available in case of contamination.

The PPE should be stored away from radiation areas and in a closed cabinet. Exposure to light and radiation will shorten the lifetime, and often cause small cracks to develop, particularly in latex gloves which may not be noticeable but will allow contamination to seep onto the skin.

Different gloves should be worn depending on the specific use. A guide to materials is given in Table 5.1.

TABLE 5.1. GLOVE MATERIAL TYPES AND THEIR CHEMICAL RESISTANCE [5.1]

Glove material	General uses
Butyl	Offers the highest resistance to permeation by most gases and water vapour. Especially suitable for use with esters and ketones.
Neoprene	Provides moderate abrasion resistance but good tensile strength and heat resistance. Compatible with many acids, caustics and oils.
Nitrile	Excellent general duty glove. Provides protection from a wide variety of solvents, oils, petroleum products and some corrosives. Excellent resistance to cuts, snags, punctures and abrasions.
PVC	Provides excellent abrasion resistance and protection from most fats, acids, and petroleum hydrocarbons.
PVA	Highly impermeable to gases. Excellent protection from aromatic and chlorinated solvents. Cannot be used in water or water-based solutions.
Viton	Exceptional resistance to chlorinated and aromatic solvents. Good resistance to cuts and abrasions.
Silver shield	Resists a wide variety of toxic and hazardous chemicals. Provides the highest level of overall chemical resistance.
Natural rubber	Provides flexibility and resistance to a wide variety of acids, caustics, salts, detergents and alcohols.

Eye and face protection. All staff and visitors must wear appropriate eye and/or facial protection in all areas:

— Where hazardous materials, or substances of an unknown nature, are stored, used, or handled.
— Where the possibility of splash, flying objects, moving particles, and/or rupture exist.
— Where there are other eye hazards, for example, UV, or laser light.

5.3. EQUIPMENT AND CHEMICALS

In any radiochemistry laboratory, there will be a substantial amount of equipment which is used in doing the chemical synthesis and quality control. This equipment is identical to that used in any normal chemistry laboratory and needs the same care in selection and maintenance. Table 5.2 provides a brief list

TABLE 5.2. EQUIPMENT SELECTION AND USE (ADAPTED FROM REF. [5.2])

Equipment type	Consideration
Autoclave	Adequate space for use, maintenance and materials storage. Drainage nearby to minimize flooding.
Fume hood	Use the bypass style. Do not use auxiliary air hoods. Located to minimize cross-drafts and turbulence. Face velocity of 0.5–0.6 m/s. Needs a continuous face velocity monitoring device. No fire dampers should be placed in the exhaust ducts. Debris screen to prevent small pieces from being sucked up by the exhaust. Single vertical sash. Hood fire suppression system. Visual or audible local alarm if regular alarm system cannot be heard inside the room.
Cryogenic liquid tanks	Controls secured or located to prevent accidental opening. Not below grade or near glass doors or windows to prevent oxygen deficiency.
Equipment needing cooling	Chilled water loops.
Vacuum lines	Local pumps preferred over central systems. Cold traps or filters to prevent contamination.

of typical laboratory equipment along with some considerations in the selection and use of particular equipment.

In addition to the equipment, there are some standard safety precautions which should be observed when handling both inorganic and organic chemicals. Some of these precautions are given in Table 5.3.

In addition to these considerations, there are some more general items which should be considered in setting up a laboratory handling different levels of radioactive materials. Table 4.3 (Section 4.3.1) gives some guidelines for various levels.

TABLE 5.3. SAFETY PRECAUTIONS FOR EQUIPMENT AND MATERIALS (ADAPTED FROM REF. [5.2])

Chemical type	Consideration
General	Solvent resistant coved flooring. Possibly needs ventilated storage. Solid, sturdy shelving for storage. Space for chemical waste storage. Plumbed, conspicuously labelled eye wash and safety shower within 30 m or 10 s travelling distance. Fire extinguishers mounted near entrance of work or storage area and conspicuously labelled.
Flammable liquids	More than 40 L in a laboratory needs flammable liquid storage cabinet. Storage not allowed below grade.
Corrosives	Storage in low cabinets or shelves.
Radioactive material	Physically separated eating and drinking areas. Separate radioactive material areas from other areas. Space for radioactive waste storage.
Biological agents	Hand washing sinks with electronic controls. Space for medical waste storage.
Highly toxic chemicals	Hand washing sinks with electronic controls.
Highly toxic gases	Vented gas cabinet. Coaxial tubing. Vapour sensors with alarms.

5.4. CLEAN ROOM AND ASEPTIC PROCESSING

Unlike the conventional pharmaceuticals, radiopharmaceuticals are often not heat sterilized prior to patient use. Application of aseptic processing is, therefore, of primary importance for microbiological purity of the radiopharmaceutical preparation. This is achieved through production in clean room environment where airborne particles are controlled to reduce the possibility of contaminant particles entering the product, and ultimately the patient. ISO 14644-1 defines the clean room as "a room in which the concentration of airborne particles is controlled, and which is constructed and

used in a manner to minimize the introduction, generation and retention of particles inside the room, and in which other relevant parameters, for example, temperature, humidity, and pressure are controlled as necessary." Therefore, the facility must provide clean rooms with specified air quality for production of radiopharmaceuticals.

Typically, production areas where the vial or product is exposed to atmosphere (critical site) must be a class 100 (class a) laminar flow cabinet, which is enveloped in a Class 10 000 (Class C) room (supporting clean areas). Entrance to the main clean room area is usually through anterooms of Class 10 000 (Class C), and is interlocked. The facility should be designed and engineered to achieve the required cleanliness. The critical components in design are: HEPA filters for incoming air; more than 20 air changes per hour (>20); and a pressure differential between rooms of different classes of 10–15 Pa. The pressure differential between classified and non-classified rooms should be 12.5 Pa (the pressure should be higher in the cleaner area).

5.4.1. Air purity

In clean rooms, the entire room should have overall positive pressure in relation to the adjacent room. An access to the aseptic areas should be through anterooms with airlocks, pass-through windows, and interlocking doors with appropriate pressure gradients if possible. Typically, the room would be of air Class 10 000 (Class C) and the production area within this room where the product is exposed to air would be of Class 100 (Class A). The local regulations should be used as the guiding principle while planning the clean rooms. Classifying the entire room as Class A would ensure product purity but is not necessary and will become too expensive.

5.4.2. Personnel ingress and egress

There should be a single means of ingress and egress. This entrance should be as far as possible from the laminar flow hood or area where the sterile preparations are occurring, to avoid stray air currents from interfering with the air flow inside the hood. It should also be as far as possible from the front faces of the hot cells. This will reduce the chance that rapidly opening the door will cause some contamination in the hot cells from being sucked into the room if the cell door is open.

5.4.3. Room surfaces

The selection of proper materials for the walls and floors, and the care of the scientific instruments, is an important concern as they can affect the safety and efficiency of the workplace.

Walls. The walls should be covered with a seamless material or painted with a smooth surface paint which will not catch dust. The surfaces should be washable with a disinfectant solution.

Floors. Likewise, the floors should also be covered with seamless vinyl or other material which can be washed and does not offer any cracks or crevices for the accumulation of dirt particles.

Pipes, tubing, etc. All exposed tubing and pipes should be covered when possible to avoid the buildup of dirt on the surfaces or between tubes. This is particularly true for overhead pipes where they are not in clear view and dust may accumulate on the top of the pipes. A good practice is to place some type of covering over the pipes which can be easily cleaned. Materials used in production should be introduced into the clean room in a controlled manner to reduce the bioburden. The use of pass-through windows is usually the best means of maintaining a clean environment within the clean room. Provision should be made for gowning in an anteroom prior to entering the clean room.

5.4.4. Aseptic processing hoods

There are a large number of commercially available aseptic processing hoods on the market. They should provide an environment of Class 100 (Class A) for the sterile preparation of the vials.

There are a number of considerations which should be in place for clean aseptic processing areas. Table 5.4 provides a checklist for clean areas of differing classes.

5.4.5. Monitoring

The clean room should be monitored round the clock for pressure differential, temperature and humidity. Also, the air quality within the rooms should be monitored for compliance at a regular interval (typically, semi-annually). Regular monitoring will prevent the HEPA filters becoming clogged over a period of time. There should be audible alarms if there is an air handling system failure and the pressure differentials are not maintained.

TABLE 5.4. CLEAN ROOMS AND ASEPTIC PROCESSING LEVELS (ADAPTED FROM REF. [5.3])

Open	Class C	Class A	Laboratory location and access
		■	Anteroom located between the processing area and the outside.
		■	Outside door and inner door interlocked so only one can be opened at a time.
		■	Interlocked doors have manual overrides for emergency exit.
		■	Clothing change area located in anteroom.
■	■	■	Doors, frames, casework and bench tops to be non-absorptive (use of organics should be avoided if possible).
■	■	■	Surfaces are scratch, stain, moisture, chemical and heat resistant.
	■	■	Surfaces should be continuous (no seams).
	■	■	Drawers to be of one piece construction.
	■	■	Reagent shelving to be equipped with lips to contain spills.
	■	■	100% outside air supplied.
		■	Benches, doors, drawers, door handles, etc., have rounded rims and corners.
		■	Visual pressure differential monitoring devices at doorway to room.
	■	■	Audible and visual alarms for air system failure.
	■	■	Supply air to be HEPA filtered.
	■	■	Supply air system interlocked with exhaust to prevent overpressure.
	■	■	Exhaust air to be HEPA filtered.
	■	■	Supply and exhaust systems outside radioactive areas for ease of maintenance.
■	■	■	Mixed hazardous waste disposal system in place.
	■	■	All penetrations sealed with non-shrinking sealant at the containment barrier.
	■	■	All conduits and wiring sealed with non-shrinking sealant at the containment barrier.
	■	■	Windows do not open to the outside.

TABLE 5.4. CLEAN ROOMS AND ASEPTIC PROCESSING LEVELS (ADAPTED FROM REF. [5.3]) (cont.)

Open	Class C	Class A	Laboratory location and access
	■	■	All piping and conduits are contained within sealed areas so there are no upper ledges or surfaces for dust accumulation.
		■	Anteroom door interlocked with laminar hood operation so there is no entry during sterile preparation or dispensing.

Radiopharmaceutical production related materials including chemicals and supplies should be stored according to the storage conditions required for specific products. GMP guidelines are very clear on segregation of materials which have been qualified for use in pharmaceuticals production. Most of these supplies and chemicals are to be controlled in terms of inventory and usage.

5.5. QUALITY CONTROL AREA

5.5.1. Quality control laboratory

The quality control laboratory will have the responsibility of assessing and monitoring quality in all aspects of radiopharmaceutical production. The test functions include: quality of the raw materials and supplies used in production of radiopharmaceuticals; in-process materials; and the finished products. The laboratory of adequate size should be equipped with instrumentation for performing the quality assessment functions. Also, sufficient bench space should be available within the laboratory for sample manipulation and preparation of reagents. Non-radioactive raw materials should be tested in a separate location from the radioactive materials. Additional space requirements may arise from documentation storage in fulfilment of GMP regulations. Radiation protection requirements should also be integrated into the planning and layout of the QC laboratory.

5.5.2. Pyrogen and sterility testing

In addition to the routine chromatography and other tests for determination of radiochemical and radionuclidic purity, qualification of radiopharmaceuticals entails pyrogen and sterility testing. If performed in-house, these tests will require appropriate equipment and environmental

conditions. Alternately, the samples can be sent out to an outside laboratory for testing although most national regulations require the tests to be started before the product is injected.

5.5.3. Raw materials storage

Space should be allocated for proper storage of raw materials with control of receipt, qualification, and inventory. Qualified materials should be segregated from the non-qualified materials to avoid mix-ups and inadvertent use of unqualified materials in production. For a small facility with only a limited number of products, the laboratory where the syntheses are being carried out may have sufficient storage facility. However, for a larger facility, a formal storage area may become necessary. The best solution is to put a tag or marker on the qualified materials indicating a control number and an expiration date.

5.5.4. Analytical equipment

The minimum equipment necessary for a QC laboratory would include: high performance liquid chromatography (HPLC) system with radioactive and mass detectors; gas chromatograph with FID and TC detectors; a thin layer chromatography (TLC) scanner; ionization chamber; gamma spectrometer; and small laboratory equipment such as the hot plates, incubators, and pH meters. Sufficient space and utilities and gases must be supplied to operate this equipment.

5.6. DISPENSING AND PACKAGING OF RADIOPHARMACEUTICALS

At some stage, the radiopharmaceuticals manufactured in the planned facility may be supplied to more than one end user. Fractionation of the bulk radiopharmaceutical into smaller doses (dispensing) is likely to become a daily routine. Two important factors to consider while dispensing are: controlling product quality and radiation protection. It is obvious that the dispensing of radiopharmaceuticals must be done in an aseptic area which may be in the same area as the synthesis modules. Automated dispensing devices are available from several manufacturers which combine a well shielded laminar flow hood with an automated dispensing unit. These devices will allow the production of both unit doses and bulk radiopharmaceutical preparations. During the process of dispensing, it is possible to get a very large extremity

radiation dose. The equipment must be well designed and the processing well thought out in order to minimize the radiation dose, and to maximize the efficiency.

The packaging area can vary in size depending on the type of PET radiochemistry facility. If the facility is packaging only a few doses for distribution to nearby hospitals, the room can be rather small. On the other hand, if a large number of doses are being distributed, then a much larger operation is required. The packaging area should be located close to the dispensing room to minimize the transport of radioactive material.

5.7. PERSONNEL

The facility for production of radioisotopes and radiopharmaceuticals/ radiotracers will require staff representing a wide range of qualifications. It is the scope of the project that will determine the number as well as the qualification level of personnel that will be needed in order to maintain smooth operation of the facility. In general, the staff should have the formal education, training and experience that are relevant to the assigned tasks. Table 5.5 represents a list of personnel that should be considered depending upon the size of the facility. While most of these employees would be required to be regular employees, some may be contracted from outside sources (e.g. radiation safety officer and pharmacist).

For a facility Type I, for example, the staff requirement will be the minimum which may be limited to only a cyclotron operator and a chemist. On the other hand, a comprehensive facility manufacturing and distributing to various other centres the PET and SPECT radiopharmaceuticals will require a large number of staff with greatly varying education and experience requirements. The technical supervisors and scientists should possess sufficient experience in their respective fields to guide and train the junior technical staff. The facility management should ensure that ample continuing education opportunities are provided for staff training to maintain and enhance performance.

The senior and supervisory staff should have sufficient insight and in-depth understanding of the field to properly supervise and train the technical staff. Production of radioisotopes may be considered primarily a technical task, while production of radiopharmaceuticals using GMP protocols is a culture which must be developed within the facility by the management and the senior staff. Radiation safety for all is a culture which must be developed and maintained.

TABLE 5.5. PERSONNEL REQUIRED FOR OPERATION OF A RADIOISOTOPE FACILITY

Type of personnel	Minimum education	Specialized training
Cyclotron operator(s)	Two year technical degree or equivalent	— Factory training. — On the job training. — Supervised training for six months. — Extensive mechanical and electrical repairs. — Radiation safety.
Radiation safety officer	Degree in medical physics, health physics or radiation physics	— Supervised training for six months. — Radiation safety.
Production chemist(s)	Diploma or degree in chemistry or equivalent	— Board certified or as required by local regulations.
QC chemist	Diploma or degree in chemistry, pharmacy or biological sciences	— Experience in GMP. — Synthesis of radiotracers. — Experience in target preparation. — Courses in laboratory operations. — Radiation safety.
Electronic engineer	Diploma or degree in electronics, electromechanical engineering or equivalent	— Experience in analytical methodology. — Experience in GMP and QA. — Courses in laboratory operations. — Radiation safety.
Mechanical engineer	Diploma or degree in mechanical or electromechanical engineering or equivalent	— Radiation safety.
Manager	Advanced degree in physical or biological sciences	— Experience in GMP. — Experience in laboratory operations. — Radiation safety.

Personnel may perform multiple functions in the list of job responsibilities. The only restriction is that the QC person must be independent of the production operations or must have independent oversight on these duties. The product cannot be qualified by the production chemist without additional oversight.

REFERENCES

[5.1] AIHA Laboratory Health & Safety Committee web site: http://www2.umdnj.edu/eohssweb/aiha/technical/labequipment.htm.

[5.2] GOVERNMENT OF CANADA, Laboratory Biosafety Guidelines, 3rd edn, Centre for Emergency Preparedness and Response, Ottawa (2004).

6. EXAMPLES OF CYCLOTRON FACILITIES

6.1. INTRODUCTION

There are a large number of cyclotron facilities around the world and nearly all of them have unique floor plans. Nevertheless, a radiation facility layout should comply with the regulations pertaining to radiation protection and radiopharmaceutical production. In this section, there are some examples of floor plans which attempt to follow the regulatory guidelines as well as common laboratory practices. These examples should be examined not only for what is good, but also where they might be improved.

In general, cyclotron facilities shall be made up of three clearly separated areas (zones):

(1) Non-controlled area, which houses the offices for the staff, storage rooms and restrooms.
(2) Controlled area, which is built and classified according to the local regulations and international recommendations as an area for work with open radioactive sources. The cyclotron with its utilities, the radionuclide production and quality control laboratories and rooms for temporary storage of radioactive waste shall be all within the controlled area.
(3) Clean rooms within the controlled area, which are used for the production of radiopharmaceuticals.

The following sections provide examples of the five facilities discussed in Section 2.3.1. The space requirements will be taken as indicative only (i.e. minimum functionally required space for normal operation). In the design phase care should be taken that the local architectural, ergonomic, safety (for example fire protection, mechanical, electrical and compressed gas safety) and regulatory (e.g. radiation protection and GMP) aspects of facility design are strictly followed.

6.2. EXAMPLES

6.2.1. Type I facility

This facility (Fig. 6.1) is designed to produce FDG and then to use it locally and/or distribute it to nearby hospitals. For this purpose a 9–19 MeV cyclotron is adequate. If the volume of planned production is low (or if FDG is

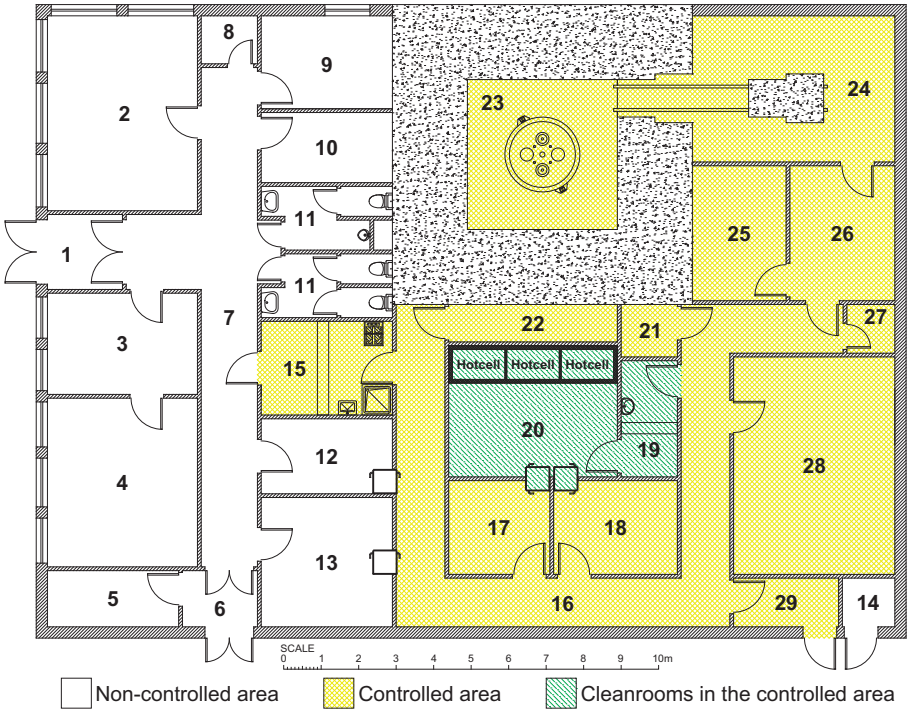

FIG. 6.1. Simple FDG radiopharmaceutical production and distribution centre (type I facility). The numbers in the figure are explained in Table 6.1.

used only locally) a small 9–11 MeV cyclotron could be sufficient. There is a single product being made and, therefore, the layout is relatively simple. There will be a small number of employees at this facility, thus there is only one personnel airlock for entering the controlled area. The cyclotron in this example is an unshielded one. Alternatively, one may place a self-shielded cyclotron within the same footprint of the presented shielding vault into a lightly shielded room. The dose dispensing, sterile preparation and synthesis boxes are all in a clean room separated from the rest of the facility by a personnel airlock. The raw materials and synthesizer kits enter the clean room through a material airlock, from a preparatory laboratory. The doses can be passed out of the synthesis area to the packaging area for distribution and for QC through a material airlock. There is a convenient service corridor behind the hot cells, which might be omitted if not required by the particular design of hot cells. The hot cells are located as close to the cyclotron vault as possible, for keeping the transfer lines as short as possible. This suggested floor plan has a

TABLE 6.1. BRIEF DESCRIPTION OF ROOMS OF A TYPE I FACILITY PRESENTED IN FIG. 6.1.

Room No.	Function	Classification	Area (m^2)	No. of air changes (h^{-1})	Room pressure (Pa)
1	Entrance for the personnel	Non-controlled area	4	—	—
2–4	Staff offices	Non-controlled area	50	—	—
5	Quarantine storage room	Non-controlled area	5	—	—
6	Material entrance	Non-controlled area	3	—	—
7	Corridor	Non-controlled area	24	—	—
8	Janitorial room	Non-controlled area	2	—	—
9	Kitchen	Non-controlled area	9	—	—
10	Data centre (archive)	Non-controlled area	7	—	—
11	Toilets	Non-controlled area	12	—	—
12	Storage room for transport containers	Non-controlled area	7	—	—
13	Storage room for released raw materials	Non-controlled area	12	—	—
14	Storage room for technical gases	Non-controlled area	2	—	—
15	Personnel airlock for entering the controlled area	Controlled area	9	5–10	–5
16	Corridor	Controlled area	34	5–10	–10
17	Preparatory laboratory	Controlled area	7	5–10	–10
18	Packing room	Controlled area	8	5–10	–10
19	Personnel airlock for entering the clean room	Controlled area, GMP Class C	5	10–20	+5

TABLE 6.1. BRIEF DESCRIPTION OF ROOMS OF A TYPE I FACILITY PRESENTED IN FIG. 6.1. (cont.)

Room No.	Function	Classification	Area (m^2)	No. of air changes (h^{-1})	Room pressure (Pa)
20	Radiopharmaceutical production laboratory	Controlled area, GMP Class C	16	10–20	+20
21	Storage for radioactive waste, recalled products and retention samples	Controlled area	3	5–10	–25
22	Service corridor for hot cells	Controlled area	5	5–10	–25
23	Shielding vault for the cyclotron	Controlled area	64 (16 internal)	10–20	–60
24	Service room	Controlled area	21	10–20	–30
25	Power supply room	Controlled area	9	10–20	–30
26	Control room for the cyclotron	Controlled area	10	5–10	–10
27	Janitorial room	Controlled area	2	5–10	–10
28	QC laboratory	Controlled area	25	5–10	–10
29	Material airlock/emergency exit	Controlled area	4	5–10	–5

400 m^2 footprint. The HVAC system of the facility can be conveniently placed on the roof of the building, adding an additional ~30 m^2 to the total space requirements.

6.2.2. Type II facility

This facility (Fig. 6.2) is designed to produce a range of common radiopharmaceuticals based on short lived positron emitters (^{11}C, ^{13}N, ^{15}O and ^{18}F) and then to use them locally and distribute FDG to nearby hospitals. For this purpose a 9–19 MeV cyclotron is adequate. If the volume of planned production is low, a small 9–11 MeV cyclotron could be sufficient. There are multiple products being made and, therefore, the layout is a bit more complex and the overall size of the facility is also larger than that of a Type I facility. There will be more employees at this facility; however, one personnel airlock for entering the controlled area should be generally sufficient. The cyclotron in this example is an unshielded one. Alternatively, one may place a self-shielded cyclotron within the same footprint of the presented shielding vault. The dose

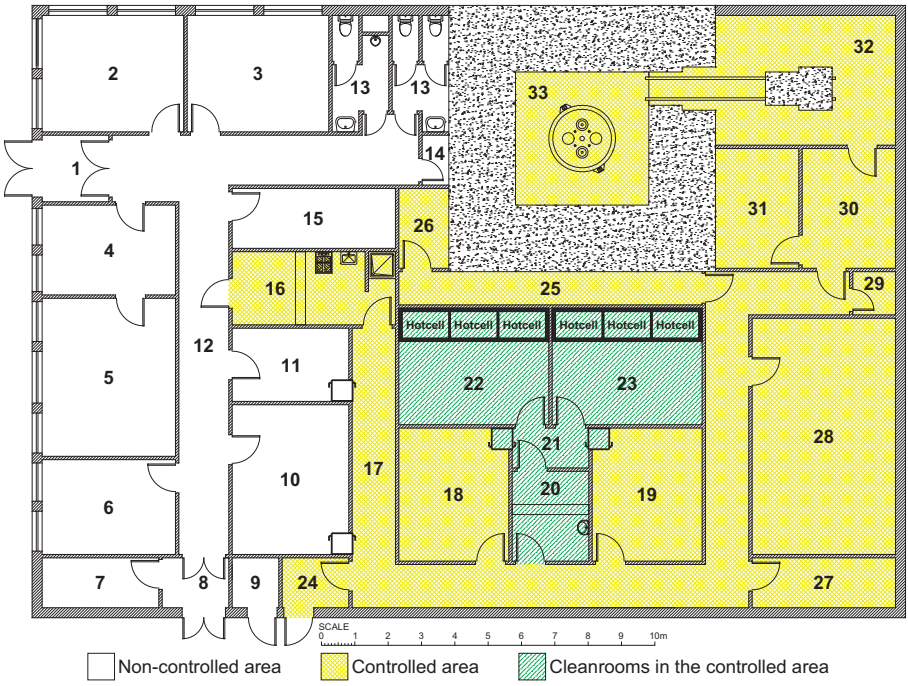

FIG. 6.2. PET radiopharmaceutical production and distribution centre (Type II facility). The numbers in the figure are explained in Table 6.2.

dispensing, sterile preparation and synthesis boxes are all in clean rooms separated from the rest of the facility by a personnel airlock. There are two separate clean rooms for radiopharmaceutical production, in order to reduce the congestion of material flow and personnel traffic in the clean rooms. The raw materials and synthesizer kits are entering the clean area through a material airlock, from a preparatory laboratory. The doses can be passed out of the clean rooms to the packaging area for distribution and for QC through a material airlock. There is a convenient service corridor behind the hot cells, which might be omitted if not required by the particular design of hot cells. The hot cells are located as close to the cyclotron vault as possible, for keeping the transfer lines as short as possible. This suggested floor plan has a 450 m^2 footprint. The HVAC system of the facility can be conveniently placed on the roof of the building, adding additional ~35 m^2 to the total space requirements.

TABLE 6.2. BRIEF DESCRIPTION OF ROOMS OF A TYPE II FACILITY PRESENTED IN FIG. 6.2

Room No.	Function	Classification	Area (m^2)	No. of air changes (h^{-1})	Room pressure (Pa)
1	Entrance for the personnel	Non-controlled area	4	—	—
2–5	Staff offices	Non-controlled area	60	—	—
6	Kitchen	Non-controlled area	11	—	—
7	Quarantine storage room	Non-controlled area	5	—	—
8	Material entrance	Non-controlled area	3	—	—
9	Storage room for technical gases	Non-controlled area	2	—	—
10	Storage room for released raw materials	Non-controlled area	16	—	—
11	Storage room for transport containers	Non-controlled area	8	—	—
12	Corridor	Non-controlled area	31	—	—
13	Toilets	Non-controlled area	12	—	—
14	Janitorial room	Non-controlled area	2	—	—
15	Data centre (archive)	Non-controlled area	9	—	—
16	Personnel airlock for entering the controlled area	Controlled area	11	5–10	–5
17	Corridor	Controlled area	40	5–10	–10
18	Packing room	Controlled area	13	5–10	–10
19	Preparatory laboratory	Controlled area	13	5–10	–10
20	Personnel airlock for entering the clean room	Controlled area, GMP class C	6	10–20	+5
21	Clean corridor	Controlled area, GMP class C	3	10–20	+10

TABLE 6.2. BRIEF DESCRIPTION OF ROOMS OF A TYPE II FACILITY PRESENTED IN FIG. 6.2 (cont.)

Room No.	Function	Classification	Area (m^2)	No. of air changes (h^{-1})	Room pressure (Pa)
22, 23	Radiopharmaceutical production laboratories	Controlled area, GMP class C	32	10–20	+25
24	Material airlock/emergency exit	Controlled area	3	5–10	–5
25	Service corridor for hot cells	Controlled area	9	5–10	–25
26	Storage for radioactive waste	Controlled area	4	5–10	–25
27	Storage for recalled products and retention samples	Controlled area	6	5–10	–25
28	QC laboratory	Controlled area	30	5–10	–10
29	Janitorial room	Controlled area	2	5–10	–10
30	Control room for the cyclotron	Controlled area	10	5–10	–10
31	Power supply room	Controlled area	9	10–20	–30
32	Service room	Controlled area	21	10–20	–30
33	Shielding vault for the cyclotron	Controlled area	64 (16 internal)	10–20	–60

6.2.3. Type III facility

This facility (Fig. 6.3) is designed to produce a range of common radiopharmaceuticals based on short lived positron emitters (^{11}C, ^{13}N, ^{15}O and ^{18}F) and then to use them locally and distribute FDG to nearby hospitals. In addition, this facility provides for the production of long lived positron emitting radionuclides and for the preparation of various radiotracers for research purposes used locally or to be distributed to other research centres. For this purpose a 13–19 MeV cyclotron is adequate and the installation of a variable energy cyclotron would be advantageous. There are multiple products being made combined with research activities, therefore, the layout is more complex and the overall size of the facility is also larger than that of a Type II facility. There will be a large number of employees at this facility, thus two personnel airlocks for entering the controlled area should be provided (separated male

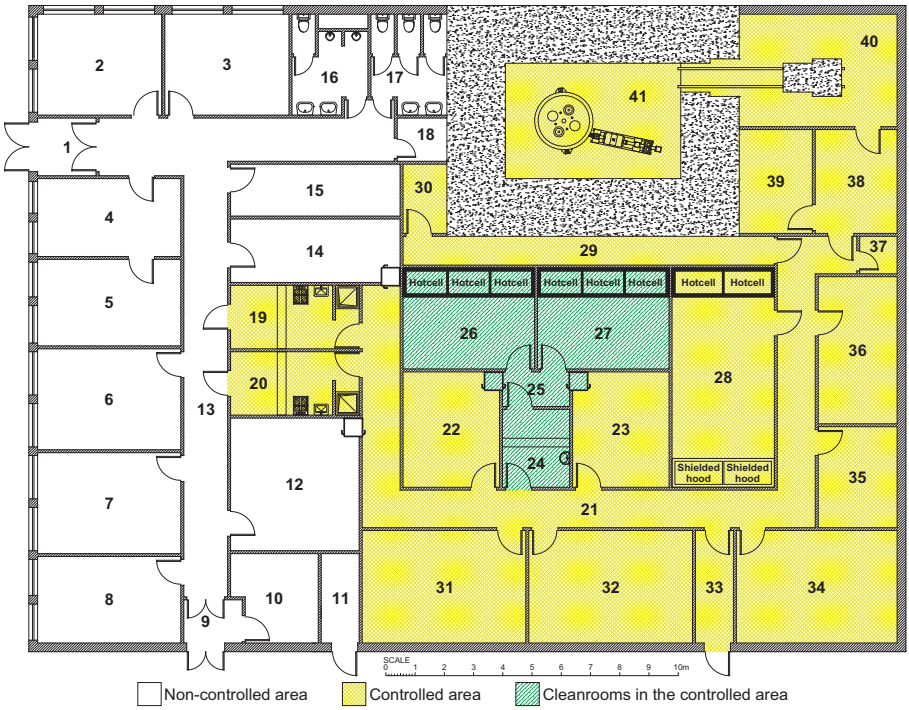

FIG. 6.3. PET radiopharmaceutical production, distribution and research centre (type III facility). The numbers in the figure are explained in Table 6.3.

and female airlocks). The cyclotron in this example is an unshielded one, equipped with a short external beam line at whose end a solid target station might be installed. The dose dispensing, sterile preparation and synthesis boxes are all in clean rooms separated from the rest of the facility by a personnel airlock. There are two separate clean rooms for short-lived radiopharmaceutical production, in order to reduce the congestion of material flow and personnel traffic in the clean rooms. The raw materials and elements of the kits are entering the clean area through a material airlock, from a preparatory laboratory. The doses can be passed out of the clean rooms to the packaging area for distribution and for QC through a material airlock. There is a separate hot laboratory housing hot cells and shielded hoods for processing the irradiated solid targets, separation of radionuclides from the target material and for the preparation of various radiotracers. There is a convenient service corridor behind the hot cells, which might be omitted if not required by the

TABLE 6.3. BRIEF DESCRIPTION OF ROOMS OF A TYPE III FACILITY PRESENTED IN FIG. 6.3

Room No.	Function	Classification	Area (m^2)	No. of air changes (h^{-1})	Room pressure (Pa)
1	Entrance for personnel	Non-controlled area	4	—	—
2–6	Staff offices	Non-controlled area	75	—	—
7	Meeting room	Non-controlled area	17	—	—
8	Kitchen	Non-controlled area	15	—	—
9	Material entrance	Non-controlled area	3	—	—
10	Quarantine storage room	Non-controlled area	9	—	—
11	Storage room for technical gases	Non-controlled area	4	—	—
12	Storage room for released raw materials	Non-controlled area	20	—	—
13	Corridor	Non-controlled area	40	—	—
14	Storage room for transport containers	Non-controlled area	13	—	—
15	Data centre (archive)	Non-controlled area	10	—	—
16	Male toilets	Non-controlled area	9	—	—
17	Female toilets	Non-controlled area	9	—	—
18	Janitorial room	Non-controlled area	3	—	—
19	Male personnel airlock for entering the controlled area	Controlled area	10	5–10	–5

TABLE 6.3. BRIEF DESCRIPTION OF ROOMS OF A TYPE III FACILITY PRESENTED IN FIG. 6.3 (cont.)

Room No.	Function	Classification	Area (m^2)	No. of air changes (h^{-1})	Room pressure (Pa)
20	Female personnel airlock for entering the controlled area	Controlled area	10	5–10	–5
21	Corridor	Controlled area	33	5–10	–10
22	Preparatory laboratory	Controlled area	13	5–10	–10
23	Packing room	Controlled area	13	5–10	–10
24	Personnel airlock for entering the clean room	Controlled area, GMP class C	6	10–20	+5
25	Clean corridor	Controlled area, GMP class C	3	10–20	+10
26, 27	Radiopharmaceutical production laboratories	Controlled area, GMP class C	32	10–20	+25
28	Research production laboratory	Controlled area	27	10–20	–20
29	Service corridor for hot cells	Controlled area	13	5–10	–25
30	Storage for radioactive waste	Controlled area	4	5–10	–25
31, 32	QC laboratories	Controlled area	44	5–10	–10
33	Material airlock/emergency exit	Controlled area	5	5–10	–5
34	Research laboratory	Controlled area	22	10–20	–10
35	Storage for recalled products and retention samples	Controlled area	10	5–10	–25
36	Workshop	Controlled area	14	10–20	–10
37	Janitorial room	Controlled area	3	5–10	–10
38	Control room for the cyclotron	Controlled area	10	5–10	–10
39	Power supply room	Controlled area	9	10–20	–30
40	Service room	Controlled area	21	10–20	–30
41	Shielding vault for the cyclotron	Controlled area	80 (24 internal)	10–20	–60

particular design of hot cells. The hot cells are located as close to the cyclotron vault as possible, for keeping the transfer lines as short as possible. There are two separate QC laboratories (separating the QC of radiopharmaceuticals based on short lived radionuclides from those of longer lived radionuclides). There is an additional research laboratory, which might be used for cell studies, or for housing a micro-PET. There is also a small workshop for maintaining and modifying targets and other research equipment (for instance modules under development). This suggested floor plan has a 700 m^2 footprint. The HVAC system of the facility can be conveniently placed on the roof of the building, adding additional ~40 m^2 to the total space requirements.

6.2.4. Type IV facility

This type of facility (Fig. 6.4) is designed for large scale commercial production and distribution of a wide range of SPECT and PET radiopharmaceuticals, leaving very limited space for research activities. It is based on a 30 MeV cyclotron with four beam lines and three types of target stations (two solid target stations, one ^{124}Xe gaseous target station for ^{123}I production and a target station with several targets for PET radionuclide production) placed in separate shielding vaults. The solid target station is connected to a receiving hot cell by a rabbit target transport system.

The non-controlled area of this facility would house the offices for the staff, meeting room, toilets, lounge, different storage areas, workshop, power supplies of the cyclotron and its control room, and utilities. The space requirements for the non-controlled area will depend on the number of staff and ergonomic requirements. In any case, it is wise to design the layout in such a way that the non-controlled area can be extended at a later time.

The controlled area would consist of four blocks: (a) the cyclotron block with its utilities, beam lines and target stations; (b) the SPECT production block housing the hot laboratories needed for the production and quality control of SPECT radionuclides and radiopharmaceuticals; (c) the PET production block consisting of three clean rooms for the production of PET radiopharmaceuticals; and (d) utilities, including the active janitorial, temporary storage of solid and liquid waste, storage of recalled products and retained product samples.

The layout presented in Fig. 6.4 outlines the design principles; the actual layout should take into account the radiopharmaceutical production programmes of the particular facility. However, when designing such a facility, it is important to make the design in such a way that it can be easily extended in the future, for instance for the implementation of research and

development programmes. It is also important to leave free access to the cyclotron vault, as it might be necessary to upgrade or even replace the cyclotron in the future. Typically, such facilities will have 2000–3000 m^2 footprints.

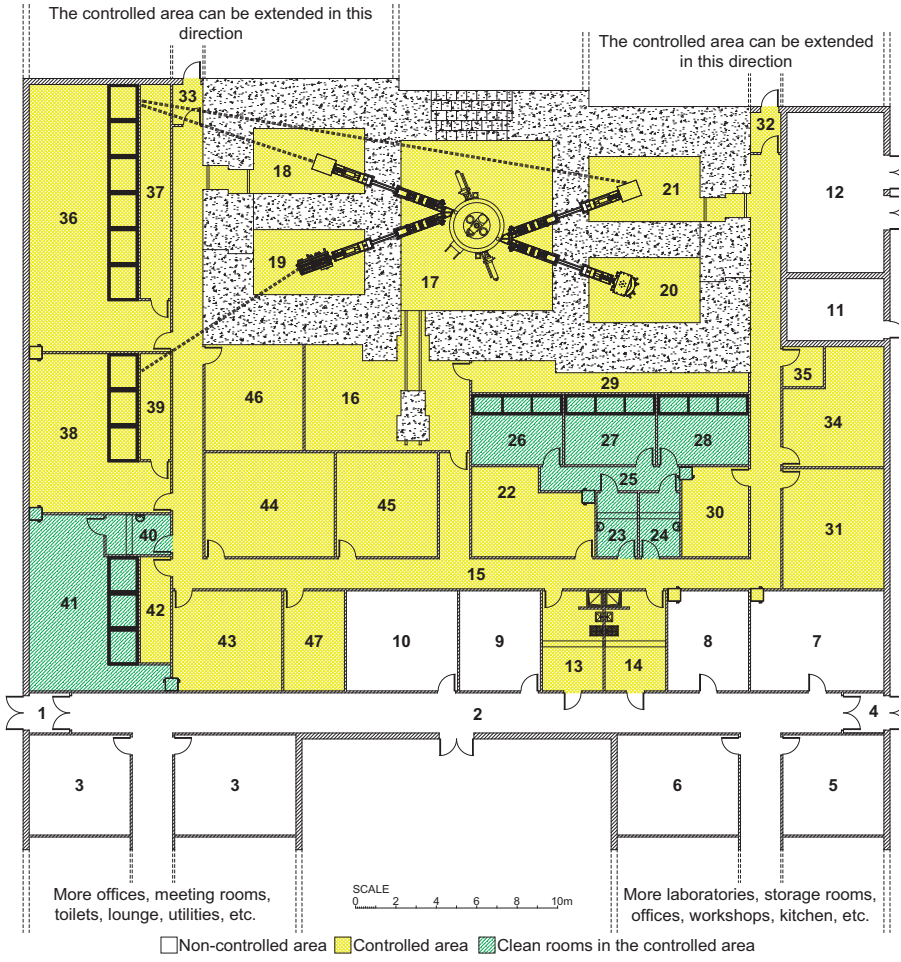

FIG. 6.4. Large scale commercial radiopharmaceutical production centre (type IV facility). The numbers in the figure are explained in Table 6.4.

TABLE 6.4. BRIEF DESCRIPTION OF ROOMS OF A TYPE IV FACILITY PRESENTED IN FIG. 6.4

Room No.	Function	Classification	No. of air changes (h^{-1})	Room pressure (Pa)
1	Entrance for personnel	Non-controlled area	—	—
2	Corridor	Non-controlled area	—	—
3	Offices, meeting rooms, toilets, janitorial, data centre, archive, utilities, workshop, etc.	Non-controlled area	—	—
4	Material entrance	Non-controlled area	—	—
5	Quarantine storage room	Non-controlled area	—	—
6	QC laboratory for raw materials	Non-controlled area	—	—
7	Storage room for released raw materials	Non-controlled area	—	—
8	Storage room for transport containers	Non-controlled area	—	—
9	Control room of the cyclotron	Non-controlled area	—	—
10	Room for the power supplies and control system of the cyclotron	Non-controlled area	—	—
11	Storage room for technical gases	Noncontrolled area	—	—
12	Transformer station	Non-controlled area	—	—
13	Male personnel airlock for entering the controlled area	Controlled area	5–10	–5
14	Female personnel airlock for entering the controlled area	Controlled area	5–10	–5
15	Corridor	Controlled area	5–10	–10
16	Utility room for the cyclotron (closed loop heat exchanger, etc.)	Controlled area	5–10	–30
17	Shielding vault for the cyclotron	Controlled area	10–20	–60

TABLE 6.4. BRIEF DESCRIPTION OF ROOMS OF A TYPE IV FACILITY PRESENTED IN FIG. 6.4 (cont.)

Room No.	Function	Classification	No. of air changes (h^{-1})	Room pressure (Pa)
18	Shielding vault with the first solid target station for radionuclide production	Controlled area	10–20	–60
19	Shielding vault with the gaseous ^{124}Xe target station for ^{123}I production	Controlled area	10–20	–60
20	Shielding vault with a target station for four–five targets for PET radionuclide production	Controlled area	10–20	–60
21	Shielding vault with the second solid target station for radionuclide production	Controlled area	10–20	–60
22	Preparatory laboratory for PET radiopharmaceutical production	Controlled area	5–10	–10
23	Male personnel airlock for entering the clean rooms for PET radiopharmaceutical production	Controlled area, GMP class C	10–20	+5
24	Female personnel airlock for entering the clean rooms for PET radiopharmaceutical production	Controlled area, GMP class C	10–20	+5
25	Clean corridor	Controlled area, GMP class C	10–20	+10
26	Clean room for the production of ^{11}C based radiopharmaceuticals with GMP class C hot cells	Controlled area, GMP class C	10–20	+25
27	Clean room for the production and dispensing of FDG	Controlled area, GMP class C	10–20	+25
28	Clean room for the production of other PET radiopharmaceuticals (^{18}F-elctrophilic synthesis $[^{13}N]NH_3$, $[^{15}O]H_2O$, etc.)	Controlled area, GMP class C	10–20	+25
29	Service corridor for the PET hot cells	Controlled area	5–10	–30
30	Packing room for PET radiopharmaceuticals	Controlled area	5–10	–10

TABLE 6.4. BRIEF DESCRIPTION OF ROOMS OF A TYPE IV FACILITY PRESENTED IN FIG. 6.4 (cont.)

Room No.	Function	Classification	No. of air changes (h^{-1})	Room pressure (Pa)
31	QC laboratory for PET radiopharmaceuticals	Controlled area	5–10	–10
32	Material airlock (dispatch of products)/emergency exit	Controlled area	5–10	–5
33	Alternative material airlock/ emergency exit	Controlled area	5–10	–5
34	Temporary storage of radioactive waste (solid waste, recalled products, retention samples, underground liquid waste tanks)	Controlled area	5–10	–25
35	Janitorial room	Controlled area	5–10	–10
36	SPECT production laboratory with GMP class D hot cells	Controlled area	5–10	–10
37	Service corridor for the SPECT hot cells	Controlled area	5–10	–25
38	^{123}I production laboratory with GMP class D hot cells	Controlled area	5–10	–10
39	Service corridor for the ^{123}I hot cells	Controlled area	5–10	–25
40	Personnel airlock for entering the SPECT dispensing clean room	Controlled area, GMP class C	10–20	+5
41	SPECT dispensing clean room	Controlled area, GMP class C	10–20	+25
42	Service corridor for the SPECT dispensing hot cells	Controlled area	5–10	–25
43	Packing room for SPECT radiopharmaceuticals	Controlled area	5–10	–10
44	QC laboratory for SPECT radiopharmaceuticals	Controlled area	5–10	–10
45	General purpose laboratory	Controlled area	5–10	–10
46	Laboratory for solid target preparation (electroplating)	Controlled area	5–10	–10
47	Workshop	Controlled area	10–20	–10

6.2.5. Type V facility

This type of facility (Fig. 6.5) is designed for large scale production of a wide range of SPECT and PET radiopharmaceuticals, as well as for extensive research basically in the field of radiopharmaceutical sciences, but it can be used for other types of research, for example, for radiation physics, chemistry and

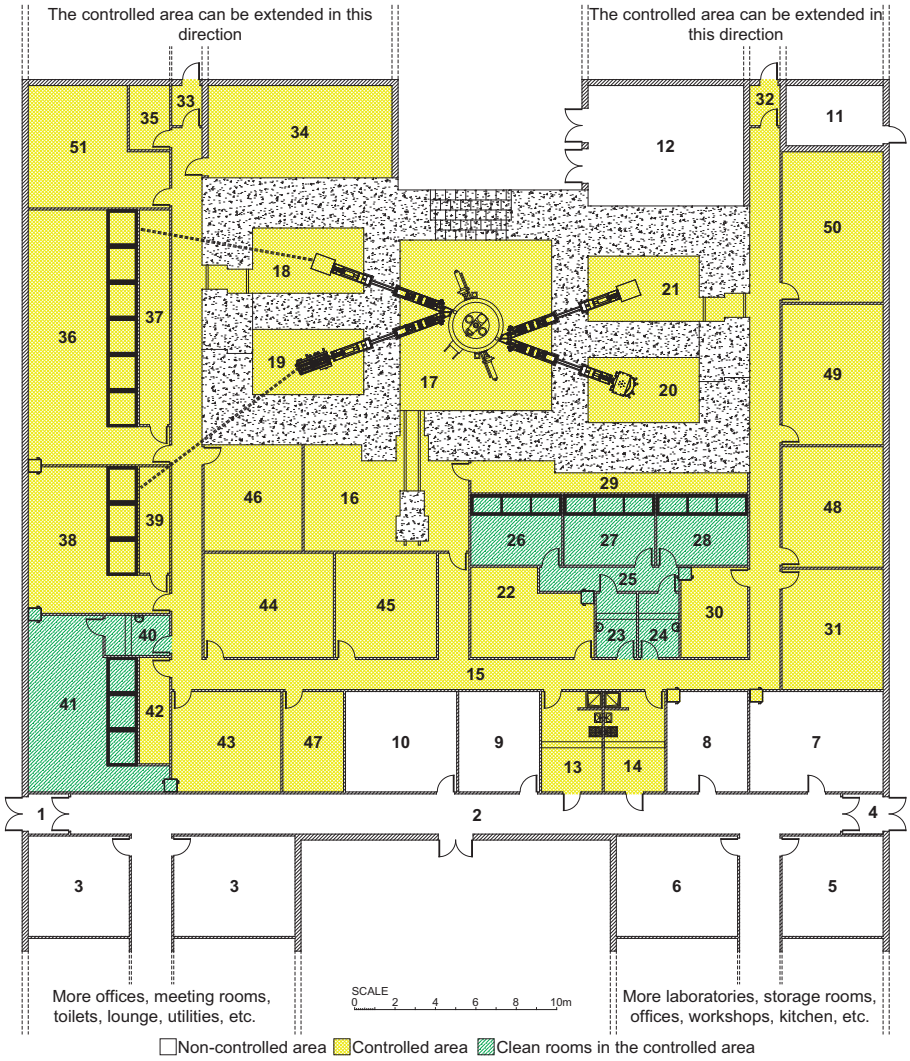

FIG. 6.5. Radiopharmaceutical production, distribution and research centre (type V facility). The numbers in the figure are explained in Table 6.5.

biology, modification and analysis of materials, etc. The radiopharmaceuticals produced in this facility can be used locally in a nearby hospital and in addition they can be widely distributed as the production capacity of such a facility is rather high. The facility is based on a 30 MeV cyclotron with four beam lines and four different target stations (one solid target station, one ^{124}Xe gaseous target station for ^{123}I production, one target station equipped with a number of targets for PET radionuclide production and a universal target station for research purposes) placed in separate shielding vaults. The solid target station should be connected to the receiving hot cell by a rabbit target transport system. If a higher energy cyclotron is to be installed and the variety of planned research programmes requires more beam lines, the facility would become much more complex, but the basic principles of its construction would have to be the same.

The non-controlled area of this facility would house the offices for the staff, meeting room(s), toilets, lounge, inactive laboratories, different storage areas, workshop(s), power supplies of the cyclotron and its control room, various utilities, etc. The space requirements for the non-controlled area can be very different, depending on the number of permanent staff (extensive collaboration with a university or some large institute would demand less space on-site) and planned uses of the facility. In any case, it is wise to design the layout in such a way that the non-controlled area can be extended at a later time.

The controlled area would consist of five blocks: (a) the cyclotron block with its utilities, beam lines and target stations; (b) the SPECT production block housing the hot laboratories needed for the production, quality control and research related to the SPECT radionuclides and radiopharmaceuticals (typically, the production of ^{123}I and radiopharmaceuticals labelled with it will be placed in a separate laboratory); (c) the PET production block consisting of several clean rooms for the production and research related to the PET radiopharmaceuticals; (d) the block dedicated to research, which might include but is not limited to laboratories for cell and animal studies, a micro-PET, precursor and tracer development laboratories, physics laboratory for material science, etc.; and (e) the utilities, including the active janitorial, temporary storage of solid and liquid waste, storage of recalled products and retained product samples.

The layout presented in Fig. 6.5 outlines the design principles; the actual layouts should take into account the radiopharmaceutical production and research programmes of the particular facility. However, when designing such a facility, it is important to make the design in such a way that it can be easily extended in the future. It is also important to leave free access to the cyclotron vault, as it might be necessary to upgrade or even replace the cyclotron in the future. Typically, such facilities will have footprints of several thousands of m^2.

TABLE 6.5. BRIEF DESCRIPTION OF ROOMS OF A TYPE V FACILITY PRESENTED IN FIG. 6.5

Room No.	Function	Classification	No. of air changes (h^{-1})	Room pressure (Pa)
1	Entrance for personnel	Non-controlled area	—	—
2	Corridor	Non-controlled area	—	—
3	Offices, meeting rooms, toilets, janitorial, data centres, archives, utilities, workshops, laboratories, lounge, etc.	Non-controlled area	—	—
4	Material entrance	Non-controlled area	—	—
5	Quarantine storage room	Non-controlled area	—	—
6	QC laboratory for raw materials	Non-controlled area	—	—
7	Storage room for released raw materials	Non-controlled area	—	—
8	Storage room for transport containers	Non-controlled area	—	—
9	Control room of the cyclotron	Non-controlled area	—	—
10	Room for the power supplies and control system of the cyclotron	Non-controlled area	—	—
11	Storage room for technical gases	Non-controlled area	—	—
12	Transformer station	Non-controlled area	—	—
13	Male personnel airlock for entering the controlled area	Controlled area	5–10	–5
14	Female personnel airlock for entering the controlled area	Controlled area	5–10	–5
15	Corridor	Controlled area	5–10	–10
16	Utility room for the cyclotron (closed loop heat exchanger, etc.)	Controlled area	5–10	–30

TABLE 6.5. BRIEF DESCRIPTION OF ROOMS OF A TYPE V FACILITY PRESENTED IN FIG. 6.5 (cont.)

Room No.	Function	Classification	No. of air changes (h^{-1})	Room pressure (Pa)
17	Shielding vault for the cyclotron	Controlled area	10–20	–60
18	Shielding vault with the solid target station for radionuclide production	Controlled area	10–20	–60
19	Shielding vault with the gaseous ^{124}Xe target station for ^{123}I production	Controlled area	10–20	–60
20	Shielding vault with a target station for four–five targets for PET radionuclide production	Controlled area	10–20	–60
21	Universal target station for research purposes	Controlled area	10–20	–60
22	Preparatory laboratory for PET radiopharmaceutical production	Controlled area	5–10	–10
23	Male personnel airlock for entering the clean rooms for PET radiopharmaceutical production	Controlled area, GMP class C	10–20	+5
24	Female personnel airlock for entering the clean rooms for PET radiopharmaceutical production	Controlled area, GMP class C	10–20	+5
25	Clean corridor	Controlled area, GMP class C	10–20	+10
26	Clean room for the production of ^{11}C-based radiopharmaceuticals with GMP class 'C' hot cells	Controlled area, GMP class C	10–20	+25
27	Clean room for the production and dispensing of FDG	Controlled area, GMP class C	10–20	+25
28	Clean room for the production of other PET radiopharmaceuticals (^{18}F-elctrophilic synthesis, $[^{13}N]NH_3$, $[^{15}O]H_2O$, etc.)	Controlled area, GMP class C	10–20	+25
29	Service corridor for the PET hot cells	Controlled area	5–10	–30
30	Packing room for PET radiopharmaceuticals	Controlled area	5–10	–10

TABLE 6.5. BRIEF DESCRIPTION OF ROOMS OF A TYPE V FACILITY PRESENTED IN FIG. 6.5 (cont.)

Room No.	Function	Classification	No. of air changes (h^{-1})	Room pressure (Pa)
31	QC laboratory for PET radiopharmaceuticals	Controlled area	5–10	–10
32	Material airlock (dispatch of products)/emergency exit	Controlled area	5–10	–5
33	Alternative material airlock/ emergency exit	Controlled area	5–10	–5
34	Temporary storage of radioactive waste (solid waste, recalled products, retention samples, underground liquid waste tanks)	Controlled area	5–10	–25
35	Janitorial room	Controlled area	5–10	–10
36	SPECT production laboratory with GMP class D hot cells	Controlled area	5–10	–10
37	Service corridor for the SPECT hot cells	Controlled area	5–10	–25
38	^{123}I production laboratory with GMP class D hot cells	Controlled area	5–10	–10
39	Service corridor for the ^{123}I hot cells	Controlled area	5–10	–25
40	Personnel airlock for entering the SPECT dispensing clean room	Controlled area, GMP class C	10–20	+5
41	SPECT dispensing clean room	Controlled area, GMP class C	10–20	+25
42	Service corridor for the SPECT dispensing hot cells	Controlled area	5–10	–25
43	Packing room for SPECT radiopharmaceuticals	Controlled area	5–10	–10
44	QC laboratory for SPECT radiopharmaceuticals	Controlled area	5–10	–10
45	General purpose laboratory	Controlled area	5–10	–10
46	Laboratory for solid target preparation (electroplating)	Controlled area	5–10	–10
47	Workshop	Controlled area	10–20	–10

TABLE 6.5. BRIEF DESCRIPTION OF ROOMS OF A TYPE V FACILITY PRESENTED IN FIG. 6.5 (cont.)

Room No.	Function	Classification	No. of air changes (h^{-1})	Room pressure (Pa)
48	Laboratory for cell and/or animal studies	Controlled area	5–10	–10
49	Micro-PET	Controlled area	5–10	–10
50	Physics (material science, etc.) laboratory	Controlled area	5–10	–10
51	Precursor and/or tracer development laboratory	Controlled area	5–10	–10

6.3. CONCLUDING REMARKS

As stated in the introduction, the examples provided are derived from experience of various facilities in the world. The primary design purpose for the facility is to conform to the regulatory (radiological and pharmaceutical) requirements. Concurrently, the facility should also be efficient and user friendly. Not every facility is suggested to be identical to the examples presented here. These are only the indicative layouts which could certainly be modified as per the circumstances specific to the new facility. The examples emphasize separation of areas according to functions, control of materials and people movements and fulfilment of regulatory requirements. In addition, facility planners should be aware of the need for optimum bench spaces, storage areas, laboratory equipment and furniture placement.

7. QUALITY MANAGEMENT SYSTEM

7.1. INTRODUCTION

In line with modern management practice, the assurance of quality in services and products is considered to be a prime responsibility of facility management, and management systems in place should make provision accordingly. A radioisotope production facility manufactures radioisotopes for subsequent use in a wide spectrum of applications, including radiopharmaceuticals for clinical applications. Radiopharmaceuticals may be produced only for one's own institution or for distribution to other sites. In some instances such as a national centre, bulk radiochemicals may be produced for distribution to other sites where these are converted into radiopharmaceuticals. Regardless of the scope of the facility, radiopharmaceuticals are pharmaceutical products, and therefore must be manufactured according to the GMP guidelines which require product manufacturing and testing in a specified and controlled manner ensuring the application of validated processes and procedures. While the GMP guidelines (detailed in Section 8) are the basis for manufacturing radiopharmaceuticals, the management of quality in the finished product and integration of the internal policies and procedures of the organization are achieved through a well defined and executed quality management system (QMS). In this respect, GMP is essentially a subcomponent of QMS, and both concepts are critical for facility operations. The definitive goal for the manufacturer should be to establish a well defined and sound quality management system to not only ensure maximum confidence in product quality conforming to the national (and/or international) specifications of purity, efficacy, and safety in the radiopharmaceutical product, but also to continually improve the quality of operations.

The aim of this section is to provide readers with a basic understanding of a facility's quality requirements (within the scope of applicable national regulations), and guidelines to construct their own set of procedures to achieve the desired and consistent quality in their products. In defining the QMS requirements, it is assumed that the radioisotopes handled in the facility are intended for end-use in radiopharmaceutical manufacturing. Relatively less strict guidelines may be acceptable for radioisotopes intended for non-medical use (for example, radiotracers for research). Additional reading on QC/QA is highly recommended, particularly, for QC/QA managers within the facility who will bear the responsibility of implementation of the guidelines. Several references are cited at the end of this section for further perusal. Moreover,

QMS and GMP have a number of overlapping attributes. Therefore, discussion in this section and the one on GMP (Section 8) will have substantial common characteristics.

This section also addresses the features of a QMS that should be addressed and dealt with when establishing a new facility, or to improve the existing facility. Consulting other QMS such as ISO is highly recommended. It is also suggested that quality management policies and principles are established as soon as possible in the project and that the quality manager should be an integral part of the planning and building process. Moreover, it is important to recognize the necessary staffing requirements to implement a working, useful QMS, which can be a serious investment in personnel initially, but will pay back in the long run.

7.1.1. Purpose of a QMS

Unlike conventional pharmaceutical products, radiopharmaceuticals necessitate special handling during their manufacturing, owing mainly to the short half-lives of the incorporated isotopes, aseptic processing and radiation protection requirements. Invariably, the products are utilized in the patients prior to full quality testing of the product batch. Hence, it is mandatory that quality is built into the system from beginning to the end of the manufacturing process, providing greatest assurance that each unit of the batch represents the one that was tested and found to conform to the required specifications.

A QMS is a set of policies, processes and procedures required for planning and execution to achieve the objectives of the manufacturer. QMS is also a sum total of actions, reviews and records, the purpose of which is to ensure that the manufacturing facility achieves consistently high quality results. QMS integrates the various internal processes within the manufacturer and intends to provide a process approach for project execution. It enables the organization to identify, measure, control and improve the various core business processes that will ultimately lead to improved business performance.

Regardless of any external requirements, control of quality in a product should be an operational philosophy of any manufacturer. Design and implementation of a detailed and rigorous QMS greatly enhance the probability that all products will conform to the required quality standards. It should be emphasized that the QMS adopted by the manufacturer should be appropriate for the specific and intended purpose. This is particularly true if the radioisotope batches will subsequently be transformed into injectable radiopharmaceuticals as opposed to oral products. In either case, the QMS

should be linked directly to the GMP guidelines governing pharmaceutical manufacturing (see Section 8).

A comprehensive QMS is an operational and management tool that encompasses everything having a bearing on quality of the product, including such attributes as the quality philosophy of the manufacturer, and its policies and procedures. A QMS places greater emphasis on prevention than on detection. The primary objective of any QMS is to demonstrate beyond a reasonable doubt that the radioisotope/radiopharmaceutical batch being manufactured satisfies the established and required specifications. This means that the manufacturer must remain in control of its operations since through these systematic actions and efforts the manufacturer can attain and maintain a high level of consistency and uniform quality.

Recent advances in the new applications of radionuclides, development of new radiopharmaceuticals; for example, radiopharmaceuticals for PET, and increasingly greater awareness for application of GMP regulations for control over manufacturing processes, are presenting new challenges in the control of quality. Consequently, greater demands are made on the manufacturer's quality system that must cope with new developments. (The term "manufacturer" has been used throughout this section for any facility, commercial or otherwise, engaged in the production of radioisotopes or radiopharmaceuticals.)

As an increasingly large number of facilities in Member States are embarking upon radiopharmaceutical manufacturing, it is recommended that a practical QMS be an integral part of their project planning and implementation.

7.2. QUALITY MANAGEMENT SYSTEM

The structure of a QMS will largely depend upon the scope and objectives of the facility, product volume and variety, and whether or not the facility is operating under the guidelines of an international quality standard, such as ISO, in addition to the requisite GMP. Whatever the system that is adapted by the manufacturer, it should be suitable for the intended purpose and clearly defined and communicated to the staff.

The two facets of quality management are QC and QA. In a nutshell, QC is concerned with measurements, analysis and evaluation of results whose purpose is to ensure that the product conforms to all the quality requirements. QA, on the other hand, is a wide ranging concept that covers all aspects that individually or collectively influence the quality of the product. It is, therefore, the sum total of planned systematic activities, including policies and procedures

that are necessary for the organization (legal entity responsible for the facility) to provide confidence that the products will indeed conform to the required quality. One of the simplest ways to manage quality is to divide the quality related responsibilities into a QA unit and a QC unit. For a small production facility, it may be sufficient to establish a QC unit that looks after all matters concerning quality. This is particularly true for a facility with limited scope and limited staff as would be the case for a PET only facility. On the other hand, in a sizeable facility, quality may be managed by two separate units — QC and QA — each with well defined roles to play within the manufacturing facility. The manufacturer should ensure the functional separation and, if possible, the administrative separation of the QC/QA unit from the production unit. Concepts such as QA, QC and GMP are all interrelated aspects that make up the total QMS.

The discussion that follows describes the fundamental importance of these concepts and their implementation in radiopharmaceutical manufacturing and product quality.

7.2.1. Quality control

The purpose of QC is to analyse all materials (whether a raw material or a finished product) and ensure that their quality is judged to be satisfactory, and conforms to the pre-determined and appropriate specifications. Furthermore, the group that performs these functions, the QC unit, is not confined to laboratory operations only, but should be involved in all decisions concerning quality of the product.

A QC unit would, therefore, typically be responsible for these functions:

— Performing tests and analyses on all materials concerning manufacturing.
— Approving or rejecting all raw materials, containers, closures, radiochemical bulks and finished products.
— Approving specifications for all materials;
— Approving all procedures (standard operating procedures).
— Reviewing production records, ensuring compliance with written procedures without deviations or errors. If deviations or errors have occurred, these should be systematically investigated prior to approving or rejecting a product.
— Approving validation and product stability study protocols and procedures.
— Monitoring the environmental conditions.

— Maintaining reference standards and equipment.
— Investigating customer complaints related to product quality and resolving issues.

In general, QC approves all specifications, procedures, and materials having direct impact on the identity, strength, quality, and purity of the finished product. In order to achieve the desired results, the responsibilities of the QC unit within the facility should be clearly stated in writing and communicated to the staff to avoid any ambiguity.

7.2.2. Quality assurance

While QC is practically a day to day testing and monitoring activity, QA is a measure of overall performance of the manufacturing facility, and hence, encompasses a much wider scope and has greater implications. In this context, QA is the sum total of all activities whose purpose is to provide assurance that the facility meets the defined standard of product quality with the highest level of confidence in the results. Quality assurance is, in fact, a management tool with wide ranging concepts covering all matters that individually or collectively influence the quality of the product.

Some of these quality management functions of the QA unit include:

— Designing and developing products and the associated procedures in collaboration with the QC and production units;
— Controlling all documentation and taking custody of records and reports;
— Reviewing production and test records prior to release;
— Issuing and controlling product labels;
— Assuring adherence to prevailing regulatory procedures;
— Evaluating and monitoring the processes for their performance, and modifying, if necessary, for continuous improvements;
— Reviewing and approving procedure validations and product stability studies;
— Performing or coordinating quality audits;
— Promoting manufacturer's quality policy and monitoring adherence;
— Identifying deficiencies and arranging staff training.

In the presence of a QA unit, the responsibilities of the QC unit may be restricted basically to activities of testing only. Then, the QA unit would typically perform the tasks of monitoring the compliance and managing quality throughout the facility.

It is very important for there to be a clear separation of responsibilities between the QC and QA units and this distinction is clearly communicated to the staff. Furthermore, it is important for the manufacturer to define the organizational structure, such that the QC/QA unit is independent of the production unit. In other words, production produces, and QC/QA confirms the quality. For a very small outfit (for example, a PET facility), lacking sufficient personnel, it may be acceptable for staff to perform overlapping functions, ensuring no vested interest (e.g. person performing production should not be doing QC on the same batch. However, the roles may be switched as per organizational needs). The manufacturer has the ultimate responsibility to release a safe product and must define the requirements of the person qualified to release the product according to national regulations.

Quality assurance is the decision making unit within the manufacturing facility. In case of a dispute regarding quality matters, there should be a collective discussion between the various units to understand the problem and its implications. However, the ultimate decision should be the responsibility of the QA unit.

7.3. DEVELOPMENT AND IMPLEMENTATION OF A QMS

A facility's QMS is derived from the quality policy. The quality policy is the structured approach to develop, implement and maintain a high standard of quality for its products. This policy can be as simple as products meeting the general criteria of quality and being manufactured as per GMP regulations, or it can be quite complex entailing for example, an ISO 9001:2000 QMS. It is this operational philosophy, depending upon the size and function of the facility, which will determine if the QMS will take the shape of a few SOPs or a full blown QMS such as the ISO standard.

7.3.1. Development

While developing a QMS, the manufacturer should focus on its function and objectives. Broadly speaking, a good starting point is to define products and the specifications that must be achieved, and then engineer quality into the product through a development strategy. Activities leading up to the products of required specifications may be divided into distinct processes, subprocesses and procedures. Processes are a broader version of an activity, while the procedures are the step by step actions. For instance, the process of isotope production may be divided into subprocesses of target irradiation and radiochemical separation. Each subprocess can be further divided into

procedures with exact details for execution. For example, irradiation of the target may comprise preparation of target for irradiation, tuning the cyclotron beam, irradiation (time and current) for isotope production, and unloading of the target.

For a facility engaged in radiopharmaceutical manufacturing, the GMP guidelines are the most appropriate basis for establishing the quality policy. A larger facility distributing products to external users may want to consider the ISO 9001:2000 quality management standard, which would further enhance the reliability and consistency of product manufacturing, and also promote continuous quality improvements and customer satisfaction. Although such an undertaking is relatively costly and time consuming, it is well worth the effort. ISO's philosophy of monitoring processes and continuous quality improvement is a great way to achieve and maintain high production standards.

7.3.2. Implementation

Having developed the QMS, the manufacturer should review and make available the required resources (staff, facilities, equipment, etc.) to achieve its objectives. The responsibilities of various staff levels should be clearly defined and communicated in an unambiguous manner as written documents. Success of any quality system depends heavily on the commitment of the management, and then the staff taking responsibility for it. In other words, management should define the quality policy, which becomes the basis for deriving the objectives.

7.3.3. Achieving quality

An effective approach in achieving quality is to design the quality in a product. It must be realized that QC testing on a radiopharmaceutical is performed after production, and also that product quality is assessed from only a small sample of the entire lot. Therefore, a high level of confidence in quality in the product necessitates emphasis on adherence to the established procedures and process protocols which have been extensively validated for the desired outcome. The expected outcome of a well-designed and correctly implemented QMS is that the products conform to the required specifications with greater degree of consistency.

Achievement of quality is made simpler if the entire organization operates as a quality-aware team, in which every individual carries out his or her duty with a focus on quality policy and objectives. Quality testing then becomes just a support and quality confirming activity. This is easier said than

done. Such perfection can only be achieved through commitment of all individuals, from top to bottom.

The sections that follow deal with the various aspects of product manufacturing and control of quality. Much of the discussion has an overlap with GMP protocols. If procedures and policies are correctly implemented and regularly monitored, a quality system will yield good quality products with a high level of consistency and reliability.

A model checklist (Appendix III) for a QMS is included as guidance.

7.4. PRODUCT SPECIFICATIONS AND TEST PROCEDURES

7.4.1. Product specifications

Radiochemicals/radiopharmaceuticals, must conform to the pre-determined specifications at the end of batch manufacturing. Specifications for radiopharmaceuticals are derived from the national or an international pharmacopoeia. Specifications for a radiochemical, on the other hand, depend largely upon the end-use of the product, and may be less restrictive.

Typical specifications for a radiochemical batch include at least the following:

— Radionuclidic purity;
— Radiochemical purity;
— Chemical purity;
— Radioactivity concentration (radioassay);
— Specific activity;
— pH.

The radiopharmaceutical batch includes the additional requirements of:

— Pharmaceutical quality (e.g. particulate matter, osmolality);
— Microbiological purity (e.g. apyrogenic, sterile);
— Activity at reference time and expiration (shelf-life).

It should be noted that the radiopharmaceuticals are usually formulated as sterile and apyrogenic injections; hence, they are not different from the conventional parenteral medications in their requirement of strength, purity, efficacy and safety.

In addition to these finished product specifications, all components (containers, closures, reagents, chemicals) that come in contact with the product or become an integral part of the product are also subject to certain specifications (see Section 7.6).

In the case where specifications are to be established for a new product not yet in any pharmacopoeia, the scientific literature, other monographs for similar products and the generic texts in the pharmacopoeias should be consulted prior to setting the specifications.

7.4.2. Test procedures

There are several variables to consider while developing QC test procedures. The degree of freedom in a measurement depends on the purpose of a test and the allowed tolerance. Therefore, an optimal test procedure is developed according to these requirements. For example, in a pH measurement of a sample, an acceptable range of 2 pH units renders the use of a pH strip quite acceptable. On the other hand, a tighter pH range of 0.5 pH units may necessitate the use of a pH meter that is accurately calibrated or a narrow range pH strip that is validated for the purpose.

An important consideration in test procedure development is that reliable results are obtained every time the procedure is applied to a sample being analysed. More importantly, all test procedures must be validated for the intended outcome (see Section 7.7) and well documented as SOPs. Typical attributes of such procedures include:

— Specificity;
— Reliability;
— Accuracy;
— Precision.

One may also need to consider other aspects of the procedure, including speed, cost, ease and robustness. Extended discussion of each of these subjects can be found in numerous textbooks on pharmaceutical analysis. An added aspect of radiation protection of the operator handling the test samples should also be considered as part of good radiation practice (as low as reasonably achievable (ALARA) principle).

Developing test procedures for radiopharmaceuticals necessitates specific attention to the fact that unlike the conventional pharmaceuticals, the radiopharmaceuticals pose challenges of their own due to the very short half-lives of the radioisotopes associated with them. Therefore, it is customary to

develop test procedures producing results in a very short time and minimum radiation burden to the operator.

7.4.2.1. Radionuclidic purity

Radionuclidic purity is defined as the ratio, expressed as a percentage, of the radioactivity of the radionuclide compared to the total radioactivity of the source. It is important to know, in some detail, the expected impurities (emissions, energy, half-life) in order to understand artefacts arising from these during the use of the primary isotope. For example, the presence of a particle emitting or a long lived impurity causes unnecessary radiation exposure to the patient or may cause other clinical complications (the presence of a high level of an ^{124}I impurity in an ^{123}I preparation is one such example). Furthermore, the manufacturer should take into account these impurities while establishing the shelf-life of the product. The relative percentage of longer half-life impurity increases over a period of time, while a shorter half-life impurity may preclude the primary isotope from being used immediately after production and hence require some period of 'wait time' prior to use.

For radiopharmaceuticals, limits of impurities of unwanted radioisotopes are well-defined in various pharmacopoeias. Consequently, the radiochemical derived from irradiation of a target in the cyclotron must conform to the ultimate radionuclidic purity requirement in the radiopharmaceutical. Moreover, the process design should anticipate and alleviate the possible radionuclidic impurities to begin with.

Typical irradiation of a target in a cyclotron often results in co-production of a number of radionuclides other than the primary radioisotope of interest, due to the impurities present in the target material. Radionuclidic impurities may also arise from competing nuclear reactions at the energy of the bombarding particle during production. Therefore, the manufacturer should carefully plan the radioisotope production with particular attention to isotopic enrichment in the target material and the incident beam energy. Both should be controlled in order to produce the radioisotope of required radionuclidic specifications. In a well designed QMS, the raw materials (enriched isotopes) used in production would be required to be of certain specifications with an acceptable range of enrichment, and the cyclotron beam energy clearly defined.

The radionuclidic purity of a radiochemical solution is generally determined by gamma spectrometry, since the gamma or X ray emitting radioisotopes display a unique spectrum which can be used in identification of the radionuclide. The gamma spectrum can be obtained with a germanium/lithium (GeLi) detector, high purity germanium detector (HPGe) or an NaI

crystal scintillation detector. The HPGe detector in conjunction with a multi-channel analyser is the equipment of choice due to its higher resolution. The more readily available NaI detector is of lower resolution, which may obscure the detection of impurities. The application of software for the acquisition and analysis of the spectrum facilitates data collection and presentation of the results in an understandable and usable format.

In a well defined QMS, the equipment would be calibrated at the appropriate interval and with regularity for assurance of system stability, and for reliability of measurement data. For example, use of a standard source (such as ^{152}Eu) of known radioactivity and gamma energy will ensure that the equipment output can be trusted. Furthermore, the equipment should be calibrated for detector efficiency for reliable radioactivity measurements (radioassay).

7.4.2.2. Radiochemical purity

Radiochemical purity is defined as the fraction, expressed as a percentage, of the stated radioisotope present in the stated chemical form. A radiopharmaceutical is designed to be used in a specific chemical form in order for it to localize in the target organ. Therefore, other chemical forms (impurities) present in a radiopharmaceutical product having a different biodistribution pattern may interfere with the scintigraphic image and the clinical findings, and should be avoided.

Radiochemical impurities may arise during radioisotope bulk preparation (for example Tl^{+1} being contaminated with Tl^{+3}), or during a chemical synthesis (e.g. presence of unhydrolysed impurities in a 2-FDG preparation), or resulting from decomposition of a high level of radioactivity in solution (e.g., radiolysis of a concentrated ^{123}I iodide solution causing impurities of iodates and periodates). A manufacturer should develop preparation procedures and storage conditions through validations taking into account the potential pitfalls. The radiochemical purity may be determined in a variety of ways depending upon the nature of the material used for the analysis and the laboratory set-up. The most convenient and popular means of radiochemical purity determination is the application of chromatography or some other type of separation technique. The most often used chromatographic methods are paper chromatography (PC), thin layer chromatography (TLC), and high performance liquid chromatography (HPLC). Gas chromatography is also used in some instances, such as, assessing organic solvents in a 2-FDG radiopharmaceutical. Paper electrophoresis also finds application to determine the radiochemical purity of certain labelled preparations.

Paper and thin layer chromatography are the simplest of the chromatographic techniques, and are also the least expensive. A considerable amount of time may be required in search for a suitable solvent system that provides adequate separation (resolution) of the impurities from the primary component. It is important to validate each procedure in relation to the individual laboratory circumstance.

Undoubtedly, the HPLC method has an advantage over PC and TLC in terms of better resolution, and may become the method of choice in some instances. An advantage with HPLC is that the eluate from the column can be channelled through a radioactivity detector and a mass detector (refractive index, UV) connected in series to detect the radioactive as well as non-radioactive species simultaneously. Calibration of the detectors must be established experimentally for a reliable measurement. It is important to note that the HPLC methodology is generally more expensive and requires a well-trained staff for operation and interpretation.

An advantage of the PC and TLC methods is that there is no loss of radioactivity which is likely to happen in a column chromatography technique (HPLC). In PC and TLC, all radioactivity applied on the plate is present for full detection and accountability. On the other hand, in a column type of chromatography (HPLC), it is possible that the strongly adsorbed fraction of the applied sample will remain on the column and not be detected, causing a false estimate of radioactivity distribution. Therefore, it is important while developing a HPLC method to compare the eluted activity with the injected activity. The bottom line is that the method to be applied should be validated prior to application.

7.4.2.3. Radioassay

Radioassay is the concentration of the radioisotope in solution per unit volume at a defined time. This information is readily available from the results of tests performed for radionuclidic purity by germanium (or NaI) gamma spectrometry, where radionuclidic composition data are expressed as counts or MBq per mL of the test sample. A dose calibrator is used to measure the radioactivity in the entire test sample.

7.4.2.4. Chemical purity

In a radiochemical bulk or a pre-formulation radiopharmaceutical, chemical impurities in the form of metal ions or unreacted chemicals may arise from the target material or the chemicals used in synthesis of the principal component, respectively. Therefore, the procedures for isolation of the formed

radioisotope from the irradiated target should separate the target material with high efficiency, and the unreacted chemicals should be effectively removed during purification steps. Prior to further utilization of the radiochemical bulk or the pre-formulation radiopharmaceutical, it should be tested (in-process sampling) for metal ions and other chemical entities that may potentially be present as impurities, and the 'purified' product should be tested for absence of stray chemicals. It should also be realized that several ions present in greater than the minimum quantity may interfere with subsequent radiopharmaceutical or radiotracer preparation. In the end, the radiochemical bulk or the pre-formulation radiopharmaceutical should conform to the required specifications of chemical purity.

In certain radiopharmaceutical preparations (for example, FDG), it is important to demonstrate the absence of degradation products and organic solvents. Methods should be developed to identify and quantify the impurities.

7.4.2.5. Pyrogen testing

Production of radiopharmaceuticals necessitates control of microbial contamination in the finished product. One of the tests that must be performed on a radiopharmaceutical batch is the demonstration of no more than the acceptable level of pyrogens in the preparation. Pyrogens (also called endotoxins or lipopolysaccharides) are substances that, when injected in sufficient quantity into the human or animal body, will cause an untoward reaction, most notably a rise in body temperature. Therefore, the radiopharmaceutical batch must conform to the requirement of apyrogenicity. It is important to note that neither steam sterilization, nor filtration sterilization (0.22 μm), normally used in radiopharmaceutical preparations, will remove pyrogens. Therefore, the manufacturing must be well controlled throughout the process to ensure that the preparations are pyrogen free. Use of pyrogen burned product containers and closures, and the application of aseptic processing techniques during product manufacturing to avoid accidental introduction of pyrogen in the product will increase assurance of a product conforming to specifications.

The pyrogen test is designed to detect the level of pyrogens in a pharmaceutical preparation. Classically, the test entailed injection of the preparation in rabbits, but it is now acceptable to perform the test (endotoxin test) using limulus amebocyte lysate (LAL), which is simpler and less expensive, with results within acceptable time frame. The test must be validated for each product with the positive and negative controls to ensure that the test solution does not interfere with the test. It should be noted that complexity of the tests warrants strict control and adequate staff training.

Except for the very short half-life products, all radiopharmaceutical batches should be tested for pyrogen prior to approval for use. The manufacturer should attempt to develop pyrogen test procedures of short duration through validations for such products as FDG. All batches should be tested, even retrospectively, to demonstrate apyrogenicity of the radiopharmaceutical batch.

7.4.2.6. Sterility testing

In addition to the pyrogen test just described, a radiopharmaceutical batch must also be subjected to sterility testing to demonstrate the microbiological purity of the preparation. Freedom from the presence of viable microorganisms is a strict requirement of an injectable solution. The presence of radioactivity, small batch production and the relatively short half-life of the products pose constraints in assessing the presence/absence of microorganisms in the test sample. Most of the time, cyclotron produced radiopharmaceuticals are administered to the patient prior to knowing the sterility test results (this is an acceptable practice). Consequently, adherence to the aseptic processing protocols and controlling raw materials are of paramount value in manufacturing sterile radiopharmaceutical products, particularly in those instances when the finished product is not terminally sterilized.

Furthermore, it is important to realize that when a batch is said to be sterile, it means that the sample that was tested is sterile, not necessarily every vial in the batch. From the QMS point of view, the test for the absence of microorganisms should be viewed as a measure of the entire manufacturing process, not merely the tested batch being sterile. Consistent manufacturing of 'clean' products can be viewed as an indication of the system working well.

7.5. EQUIPMENT

A typical radioisotope/radiopharmaceutical production facility will have several different types of equipment intended for specific purpose:

— Preparation equipment (e.g. pyrogen oven, electroplating);
— Production equipment (e.g. autosynthesizer, dispenser);
— Measurement equipment (e.g. dose calibrator, pH meter);
— Analytical equipment (e.g. HPLC, GC).

Equipment selection should take into consideration the design and installation specifications, and suitability for the intended application. Furthermore, equipment should be qualified for the operation and performance, calibrated at regular interval, and monitored for its continued suitability.

7.5.1. Quality control equipment

The QC laboratory should be supplied with proper equipment to carry out the necessary tests. While performing a QC test, measurement data are carefully collected and subsequently utilized to determine whether the material being tested conforms to the required specifications. The approval or rejection of a material requires that the equipment is working properly. This necessitates close control of the equipment so that a non-conforming material is not approved, or a perfectly acceptable material is not rejected. Consequently, the measurement equipment must not only be suitable for the intended purpose, but also provide results with a high degree of confidence.

7.5.2. Equipment validation

Confidence in the output of the equipment, particularly the equipment which directly influences the quality of the product, is achieved through validation of the specified application. The degree of validation depends on how critical the particular equipment is in assessing the quality of the final product. For example, dose calibrators, gamma spectrometers and dispensers are critical equipment, as their performance has a direct influence on assessing the quality of the product being manufactured. In contrast, some production equipment has a greater level of tolerance. All equipment should be regularly calibrated, inspected and revalidated after long use or following major repair work.

Equipment validation generally entails: design qualification (DQ); installation qualification (IQ); operation qualification (OQ); and performance verification (PQ). Since the equipment is selected for specific functions and performance characteristics, a validation study should be designed to provide the evidence that the equipment indeed conforms to the required functionality and meets the performance criteria. These studies should be well documented and referred to for revalidation and for performance comparison as equipment becomes old.

7.5.3. Equipment log

All equipment necessitates adequate control to ensure reliability of the output. The degree of control varies depending upon the application and how critical the operation is to the process. Keeping active logs of calibration, validation, equipment use, deviations and repairs, etc., is necessary to maintain the equipment in the best working order.

7.5.4. Repairs and maintenance

The periodic preventive, and the occasional reactive maintenance (breakdowns) performed on the equipment should be recorded in the equipment specific log for maintaining the history of the equipment and frequency of malfunction. Furthermore, for some equipment, it is necessary to perform calibration and even revalidation prior to use in analysis following a major maintenance job.

7.5.5. Equipment calibration

Equipment tends to drift over a period of time, making calibration a mandatory process for reliability. The frequency of calibration is determined from experience and how critical is the measurement. For example, a repeated analysis using a chromatography method may require only occasional use of a calibration standard for reassurance, since the daily use and acceptable results can be used as a measure of equipment function. However, for some equipment, calibration just prior to use is required. As an example, determination of osmolality with an osmometer in an injectable preparation may need to be calibrated prior to the equipment being used for a measurement. Calibration procedures should include specific directions and acceptable level of variation from the standard value. When measured values are not within the specified limits, remedial actions must be taken to re-establish the acceptable values.

The calibration standards used for inspection and measurements should, preferably, be traceable to certain national or international standards. The manufacturer may, however, use in-house prepared standards in a controlled manner. These standards should remain secure ensure their integrity and non-contamination, and should be accessible to authorized employees only.

7.5.6. Equipment monitoring

In a radioisotope/radiopharmaceutical production facility, it is not unusual to find equipment dedicated to a single repeated use. Variations from batch to batch can be used for monitoring and evaluating the equipment performance. For example, in a PET facility, HPLC may be used for the radiochemical purity assessment of the FDG product. A problem with the column or the mobile phase can usually be detected from the retention time of the material being analysed, observing the drift over a period of time, and inspecting the peak shapes. Such observations and control impart a greater level of confidence in results reported by the QC unit.

7.6. MATERIALS CONTROL AND TESTING

Production of radiochemicals or radiopharmaceuticals will entail management of materials at various stages of production. These are raw materials, in-process materials and the finished product. A QMS should clearly define the sampling plan, test procedures and acceptance criteria for each.

7.6.1. Raw materials testing

When a finished radiopharmaceutical product fails to meet the predetermined specifications, one can often trace the problem back to one of the materials used in production. It is therefore imperative that all production related raw materials are traceable, and are received, sampled and analysed by the QC unit prior to approval for use. The QC unit has the responsibility of developing definitive test and analysis procedures for these materials. Whenever a new product or a procedure is being developed, discussion with the QC unit regarding the process and the raw materials specifications can save a lot of headaches at a later stage. The QC unit should also qualify the suppliers through maintaining a track record of material quality and post-sale services.

For all items being tested in a QC laboratory, it is essential to establish acceptable specifications, bearing in mind the required specifications of the finished product. Theoretically, every raw material must be qualified in the QC laboratory prior to use in production. However, raw materials procured from reliable sources need not be subjected to the rigor of full testing. In such cases, accompanying certificate of analysis (COA) along with one identifying test is usually sufficient. The manufacturer should determine the acceptability of the COA and the extent of testing from past experience.

The QC unit must maintain a proper log of materials received and tested, and keep a record of materials rejected for a procurement decision in the future. Concurrently, the user sections should maintain an inventory log of materials received, used and reordered.

7.6.2. In-process testing

In a typical radiopharmaceutical manufacturing facility, the radioisotope is produced in the cyclotron, followed by radiochemical separation. The radiochemical bulk so obtained should be analysed prior to transformation into a radiopharmaceutical batch. This in-process sample should meet certain quality criteria to establish the continued suitability of the radioisotope batch. The following process chart (Fig. 7.1) illustrates in-process sampling during manufacturing of a ^{201}Tl radiopharmaceutical.

7.6.3. Finished product testing

The finished product, a radiopharmaceutical, must conform to all the required specifications prior to being approved for patient use. The sterility test cannot be performed prior to releasing the product batch due to the long time required to obtain the test results. The product batch is released without this test, but with the understanding and assurance that manufacturing was

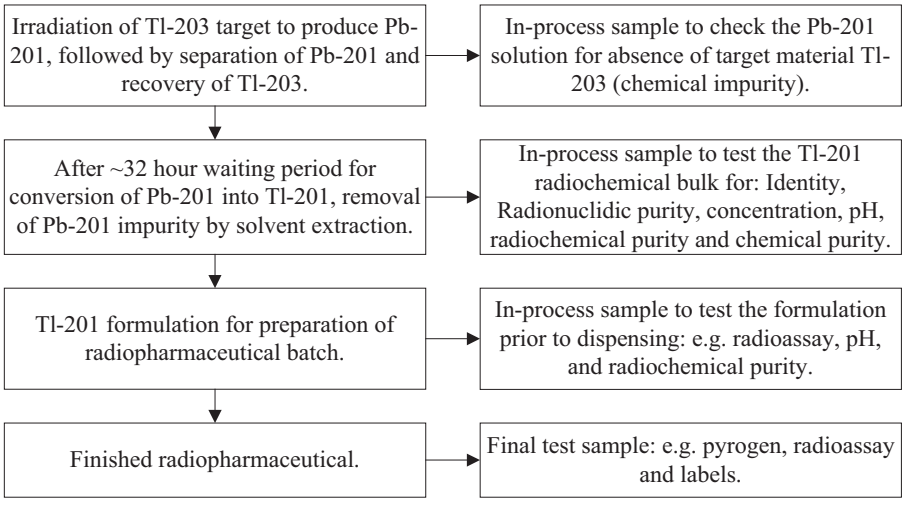

FIG. 7.1. Process flow for ^{201}Tl production.

performed aseptically, following the guidelines of GMP and that all precautions were taken to ensure product safety. Furthermore, the product must be correctly labelled with such information as: product name; calibration and expiration dates; radioassay; and the product lot number.

It should be understood that approval of the finished product does not depend solely on the results of the QC tests. A product conforming to all specifications may still be rejected if it is evident to the QC unit that it was manufactured in non-conformation of the established procedures (e.g., use of non-qualified raw material). The QC/QA units have collective responsibility to ensure that, in addition to product conformity, the batch was manufactured according to the approved SOPs without deviation, production and test protocols have been adhered to, and that the documentation is in proper order.

A qualified product batch conforming to the required specifications should be approved for release by the QA unit. In the absence of a QA unit, the responsibility belongs to the QC unit. A manufacturer should have written procedures describing the product batch release criteria and the authorization. Procedures should also be in place for an action plan if the radiopharmaceutical batch fails to meet the required specifications. Decision to reprocess a salvageable batch requires careful consideration of a number of factors (product safety, radiation protection), and should be performed as per written procedures agreed upon between the production, QC and QA units. The reprocessed batch should be subjected to the same testing routine prior to approval.

7.6.4. Test reagents

One often missed aspect of QC is control of the test reagents themselves. Accuracy and reliability of the measurement depend upon the correct reagents being used in performing the analysis. Therefore, it is essential that the reagents are prepared, preserved and used in a controlled manner so as not to introduce an artefact in the results of an analysis.

7.7. VALIDATION

A prerequisite for achieving consistent and accurate results is to develop the processes/procedures that perform as expected time after time. This assurance can only be achieved through validation of the applicable procedures and processes, which means attaining sufficient experimental evidence to give reasonable assurance that the process/procedure under consideration does

what it is intended to do, and will continue to do so repeatedly when applied as written.

In a radioisotope/radiopharmaceuticals manufacturing facility, the applicable processes and procedures are generally derived from the published literature. However, it is reasonable to assume that the methodology is not always directly reproducible, requiring subtle modifications to suit the prevailing environment. During this development stage, the critical parameters affecting results should be identified. The final format of the procedure/process which repeatedly yields the desired outcome becomes the basis for the validated standard operating procedure. The number of process runs required for validation depends upon the complexity and the critical nature of the process. As a general guide, three consecutive successful operations should be used as the procedure becomes finalized. Often it becomes necessary to modify the existing procedure/process based upon experience and as part of the continuous improvements. Again, the modification should be controlled and validated prior to implementation. It is understood that the QC/QA unit would take the responsibility in development and validation of every process and procedure used in product realization.

7.8. DOCUMENTATION

Good documentation is an essential component of the QMS and should encompass all aspects of product manufacturing. A document management system should be established and used from the beginning and continually improved upon. The establishment of a consistent set of SOPs is in itself a major task in setting up a facility, and constitutes also the foundation of any QMS. Furthermore, the documentation system should be tamperproof and assure that only the validated, current and approved versions of instructions, operating procedures and formulas are available for use. QC/QA is the responsible unit for these documents, from the beginning to the end. These aspects are described in detail in the section on GMP. To summarize, the types of documents that should be an integral component of the QMS include:

— Raw material specifications and test procedures;
— In-process material specifications and test procedures;
— Finished product specifications and test procedures;
— SOPs;
— Production batch records;
— Records and reports;
— Quality audit records;

— Validation data;
— Stability studies data;
— Equipment logs;
— Product distribution records;
— Product label issuance and usage;
— Staff responsibilities and authorizations;
— Staff training records.

7.9. QUALITY AUDITS

Having established and implemented the QMS is just the beginning; it needs to be monitored for its effectiveness and continued suitability for the purpose. Therefore, the system should be audited at a regular interval, preferably twice a year. The simplest description of an audit is "monitoring the compliance and effectiveness" of the manufacturer's QMS. Monitoring of the QMS should be a perpetual activity. Audit is the formal manner in which a specific plan is developed to evaluate the system. Audit is also an opportunity for staff involvement and for further improvements.

The audit may be performed through self-inspection (internal audit) and/or by an external agency (external audit). It should be understood by the staff that an audit is an opportunity to candidly review the current state of affairs, and attainment of objectives of the QMS. The purpose is to determine if the system is being applied as documented and if the processes/procedures are producing the optimum and desired results. If applied judiciously, an audit is the means through which the weak links are identified and improved upon (continuous quality improvement).

Also, an internal audit is an opportunity for everyone in the organization to get involved and expand ownership of the QMS. It could be suggested that the internal audit should be carried out by staff who does not have direct responsibility in the area being audited, but should preferably be familiar with or have an association with the area being audited. Moreover, an audit should be performed in a spirit of objectivity and with an aim for improvements. At the end of an audit, non-conformities as well as suggestions for improvements (corrective and preventive actions) are planned, responsibilities for implementation are assigned and time lines are established for completion of the planned activities. Audits should be recorded as 'official' documents and reported to the higher management. Implementation of actions arising from audits should be monitored for completion and further evaluated for their effectiveness.

For larger facilities and those operating under the guidelines of GMP or ISO regulations, audits may be conducted by external auditors. These exercises are more formal, and of greater implications.

7.10. PERSONNEL

People are the key for the establishment, effective implementation and satisfactory maintenance of the QMS, and for high quality product manufacturing. It is the people who will make or break the system. Therefore, it is necessary to have qualified and competent staff, in sufficient number, to carry out the various operations at the facility. Furthermore, the staff should take ownership of the QMS and be committed to the quality policy. For further information, see the section on GMP (Section 8).

7.11. CONCLUSION

It needs to be recognized by the manufacturer that two key factors in achieving quality in products are: GMP that impose the manner in which pharmaceutical products must be manufactured; and personal and professional commitment of the staff.

For any manufacturer, large or small, it is essential to establish some type of system for the control of product quality. Although tedious and demanding of resources, the establishment of a sound QMS is rewarded with consistent quality products, which will instil confidence and trust by the end user.

Planning and implementing the QMS begins with establishing a quality policy which leads to the quality objectives and the philosophy of operation. The day to day operations entail control of a large number of variables: production; in-process testing; raw materials control; equipment calibrations; validations; testing and auditing. The competent and qualified staff who take ownership of the QMS are most vital in producing consistent and high quality products.

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8. GOOD MANUFACTURING PRACTICES

8.1. INTRODUCTION

Poor quality medical products are not only a health hazard, they also may contain little or none of the claimed ingredients and, therefore, may not have the intended therapeutic or diagnostic action. When the product is a radiopharmaceutical, the test using this material may not diagnose the disease correctly or may give a false indication when there is none. Moreover, the welfare of the patient undergoing a procedure demands that the care provider use radiopharmaceuticals conforming to the required specifications of identity, purity, efficacy and safety.

Only when production of every batch of pharmaceuticals is carried out in a controlled manner and with careful attention to detail can the manufacturer expect consistent quality in finished products. GMP is one such system of guidelines for controlled manufacturing of pharmaceuticals, ensuring that the products will consistently conform to the required quality. Moreover, GMP is the basis for designing processes and procedures which, when applied, should result in products conforming to the required specifications.

Although quality testing prior to release of a product batch for patient use is a major component of manufacturing, it is important to realize that QC alone does not constitute GMP. Testing product quality prior to releasing a product batch may identify a problem or non-conformity in a product, but only after the product is already made and, therefore, may not be correctable. Greater confidence in product quality can only be achieved through adherence to the GMP guidelines during batch manufacturing. Adherence to the GMP guidelines during manufacturing provides a reasonable assurance that every unit of a batch is of quality similar to the unit(s) tested in the laboratory.

Pharmaceutical manufacturing is a controlled process and generally regulated by national guidelines for medicinal products manufacturing. The individual country GMP guidelines are not very different from one country to another, and are largely derived from the international GMP guidelines such as those from the World Health Organization (WHO); International Conference on Harmonization (ICH); the European Union (EU); or Pharmaceutical Inspection Convention (PIC).

In essence, GMP encompasses everything that has a bearing on quality of the pharmaceutical product, and, therefore, is a comprehensive measure (the sum total of numerous elements) that includes: personnel; premises; equipment; starting materials; processes; QC/QA; documentation; packaging and shipping.

Being pharmaceutical products, radiopharmaceuticals must also be manufactured according to the basic principles of GMP. In contrast to the conventional pharmaceuticals, presence of the radioactive component in a radiopharmaceutical adds complications in manufacturing and controls requirements. Specific differences include radiation hazard to the operator, and relatively short shelf-life of several radiopharmaceutical products (in particular PET products) due to the short half-life of the radioisotope incorporated within the radiopharmaceutical. To complicate the matter further, radiopharmaceutical products are often used in a patient prior to full assessment of quality. Assurance of quality in these cases, therefore, is highly dependent upon strict adherence to GMP protocols and procedures.

It should be clear that the GMP guidelines do not address radiation related safety aspects of personnel, nor those of the environment during radiopharmaceutical manufacturing. The manufacturer must, therefore, address these issues separately and comply with the prevailing local, national, and international regulations in this matter, and develop appropriate procedures to be followed.

Akin to pharmaceutical manufacturing, several regulatory and international organizations, including WHO, FDA and EU, have formulated GMP and quality guidelines applicable to manufacturing radiopharmaceuticals. Furthermore, specific guidelines have emerged for manufacturing PET radiopharmaceuticals as the applications of PET are growing worldwide. It must be mentioned that even for a small facility manufacturing perhaps only PET products, GMP guidelines must be developed and applied in the production of radiopharmaceuticals of consistently acceptable quality.

This section discusses basic concepts and key elements of GMP pertaining to radiopharmaceutical manufacturing. The information provided herein, while being comprehensive, is not necessarily all-inclusive. The manufacturer should develop appropriate protocols and procedures which should be adapted and evaluated within the framework of the applicable GMP guidelines. Furthermore, these processes must be experimentally validated for suitability, ensuring product conformity to the required quality specifications. The net result should be that the products are manufactured in a controlled manner, and are released for patient use only upon conformation to the pre-established specifications. Development and application of a sound QMS as detailed in the pervious section is highly recommended.

8.2. ORGANIZATION AND PERSONNEL

The success of a GMP system and consistent quality in a product is predominantly operator dependent. The best procedures and guidelines are of no value if everyone involved in manufacturing does not adhere to the protocols, and does not use utmost care during the manufacturing process. Concurrently, it is of paramount importance that the staff possesses optimum qualifications in relation to education, job knowledge, training, and experience appropriate to their assigned duties and responsibilities.

The range of activities within the facility will vary according to the scope and objectives, and may even be influenced by the range of available technical expertise. Consequently, the manufacturer should ensure that the organizational arrangements, particularly staff proficiency and the number, truly reflect the nature of procedures to be performed (whether manufacturing or R&D or both). A manufacturer must employ an adequate number of people to perform the various tasks of manufacturing the radiopharmaceutical products, and also ensure that these employees possess adequate and appropriate qualifications and practical experience for the task assigned to them. For example, for a full scale radiopharmaceutical production facility planning to perform R&D work, the staff requirements will be much higher than those for a facility dedicated to manufacturing only the PET radiopharmaceuticals. In either case, it is necessary to define clearly the individual responsibilities and document these in each employee's job description to reduce ambiguity.

In addition to the appropriate technical background, all staff should be provided adequate training in GMP aspects pertaining to manufacturing of radiopharmaceuticals. Additional training should include aseptic technology and good radiation practice (radiation safety). It should be taken into account that radiopharmaceuticals are continuously being improved, along with development of new technologies, necessitating continued training of staff. Furthermore, staff should be made fully aware of their role and responsibility, and the potential impact of their actions (or inactions) on the product and consequently the welfare of the patient.

The key staff members in a supervisory position should ideally possess advanced technical and scientific education, pertinent experience, and in-depth understanding of GMP to match with their job responsibility. Furthermore, staff in these leadership positions should also take responsibility for development and maintenance of the manufacturer's quality policy and QMS for effective planning, implementation and monitoring. Collectively, it is the entire team which is ultimately responsible for establishment, implementation and maintenance of GMP regulations, and overall QA of the entire facility.

One of the requirements of GMP is the adequate separation of responsibilities without ambiguity. Accordingly, the production and the quality control functions must be independent of each other. The organizational chart, in addition to indicating the staff assignments, should clearly identify a designated person (or a position) authorized to release the finished product for patient use. Such separation of responsibilities could become a concern in a small facility (e.g. PET centre) with limited staff. Most of the GMP regulations make a concession that allows switching of the production and QC personnel as long as employees are adequately trained in both areas. However, the person manufacturing the batch must not qualify that specific batch for human use.

Clearly, at the core of successful implementation and continued practice of GMP are staff members who understand and support the manufacturer's quality policy, and are committed and motivated to maintain high quality standards within the organization.

8.3. HYGIENE

Humans are the most likely source of microbial and particle contamination during manufacture of a pharmaceutical batch. Therefore, a high standard of personal hygiene must be practiced at all times. Radiopharmaceuticals are a special case because of the short half-life of the accompanying radioisotope and/or stability considerations, and also because quite often the radiopharmaceuticals are not terminally sterilized. Therefore, aseptic processing applied during radiopharmaceutical manufacturing further necessitates good hygiene practice by the operators. Additional product protection is achieved through protective gowning and the clean room environment. The staff must adhere to proper protective clothing requirements (gowns, gloves, head and shoe covers, etc.) and acceptable conduct in the clean room. Manufacturer should establish a protocol for monitoring employee health and also work habits of the individuals. At the end of an aseptic operation, for example, the hygienic state may be monitored through sampling the gowns and gloves (finger) with rodec plates, and the work area by exposing the settling plates throughout the operation for monitoring microbiological contamination. The result of such monitoring reflects the prevailing work conditions and appropriate remedial and preventive actions in case of an observed breach.

8.4. BUILDINGS AND FACILITY

The size of the facility will depend largely upon the volume and variety of the radiopharmaceutical manufacturing programme and R&D activities, if any. A PET only facility will obviously be much smaller than a national accelerator facility engaged in manufacturing products for the entire country. As a general principle, the manufacturing facility should be designed to ensure adequate space availability and suitability for pharmaceutical manufacturing. An additional requirement in case of radiopharmaceutical manufacturing is radiation protection and radiation level monitoring (discussed in detail in Section 9). It is suggested that even in a small facility, operations should be performed within specifically designated areas to avoid mix-ups and cross-contamination (for example, segregation of incoming raw materials from the tested and approved materials). The flow of materials in a logical pattern generally achieves good results.

The most critical factor in aseptic processing is the microbial cleanliness and particulate quality of the air in production areas. At the most vulnerable points where sterilized containers and closures are exposed (critical areas), the air should be of Class 100. The layout of the facility should be designed to ensure that the required air classification in the critical areas can be kept by maintaining the surrounding areas with specific air classification. All clean areas should be carefully and frequently monitored for assurance of conformity to the required specifications.

In general, the facility should be maintained in a clean and sanitary condition through an effective cleaning routine and monitoring. Some additional considerations for a radiopharmaceutical manufacturing facility are highlighted below:

— Space planning and utilization should take into consideration radiation protection of the worker, along with protection of the product quality. Radiation protection dictates negative pressure in the area where the product is in relation to the area occupied by the operator, while the product protection (microbial contamination) necessitates the opposite. Careful designing of air flow patterns and the pressure differentials are the challenges in radiopharmaceutical handling as both requirements must be accommodated in the same location.
— Some of the other areas with specific designation include: quality control lab; sterility testing lab; aseptic processing areas; and raw materials receipt, testing, and storage areas. Furthermore, these areas should be separated from one another to avoid cross-contamination and to facilitate smooth work and materials flow.

— In production areas, attention should be given to the nature of the interior surfaces (walls, floors, and ceiling), ensuring smooth and hard composition allowing easy cleaning and disinfection. This is particularly applicable to the aseptic areas.
— For aseptic processing, isolation rooms (clean rooms) should be made available, where room air is filtered through HEPA filters under positive pressure. Access to the aseptic areas should be through personnel airlocks and material airlocks with interlocking doors. HEPA filters should be monitored and replaced at regular intervals.
— One often neglected subject is the storage area. This area should be of sufficient size for orderly storage of components, both radioactive as well as non-radioactive materials.

8.5. EQUIPMENT

A manufacturing facility will have a wide range of equipment with designated purpose. Unlike conventional pharmaceuticals manufacturing, radiopharmaceuticals manufacturing is often achieved using specialized and dedicated equipment. Whether the equipment is used in preparation of glassware (e.g., pyrogen oven, glassware washer) or in manufacturing (for example autosynthesizers, dispensing machines) or in the QC laboratory (dose calibrators, HPLC), selection should be based upon key performance attributes such as suitability for the intended use, reliability and ease of operation and serviceability.

Consistent production and the product quality depend upon consistent and reliable performance of the equipment. Therefore, all equipment having a bearing on product quality should be validated for performance at the time of installation and at a regular interval thereafter. Furthermore, equipment should be well maintained and in general should be in good working order at any given time. Defective equipment should be kept from inadvertent use.

Currently, several autosynthesizers have become available for production of PET radiopharmaceuticals. GMP compliance manufacturing and product quality require careful practice in aseptic handling, in addition to reliable performance of the equipment.

8.5.1. Validation and calibration

Equipment should be selected for its suitability for the intended use. New equipment must not be used until it has been properly installed, evaluated for its performance, and validated for suitability of its application. Furthermore, all equipment, in particular the critical equipment, should be continuously monitored and revalidated at a regular interval ensuring continued suitability and reliability.

It is necessary to have written procedures for validations, revalidations, and calibrations. Calibration procedures should define how often it is to be done, by whom, and the exact methodology to be used. Equipment used in measurements may need to be calibrated prior to use or at a regular interval for confidence in results. The frequency of calibration is usually determined by type of equipment and criticality of the measurement.

Accurate data of validations and calibrations should be maintained, and should be readily available for data analysis.

8.5.2. Maintenance and cleaning

A sound preventive maintenance schedule, as opposed to reactive and remedial maintenance, not only reduces the down-time, but also improves the production output. Spare parts availability may become an issue in some Member States; hence, it is recommended that an inventory of critical components and consumables be identified and stocked at the facility to reduce down-time. Following a major repair or maintenance, revalidation of the equipment is necessary to ensure equipment performance and suitability. General cleanliness in laboratories and specific cleaning of the equipment utilized in product manufacturing require careful planning and implementation. Documentation of equipment usage and a maintenance log are a useful exercise for reliable service.

8.5.3. Computers and software

Modern equipment (for example, PET autosynthesizers) is often operated and controlled with PCs. The computer systems and the software running the automated equipment require control and safeguarding, ensuring that no inadvertent or even deliberate changes have occurred.

8.6. COMPONENTS, CONTAINERS AND CLOSURES

Control of product quality entails control of materials that are either incorporated into the product or may come into contact with it. These materials generally include the active ingredients, vehicles (for example, water for injection, saline), containers and stoppers. GMP protocol for controlling the materials necessitates written procedures detailing specifications, procurement, acceptance testing, storage and usage in manufacturing. Procedures should cover the life cycle of a material, from time of receipt, to consumption or disposal.

8.6.1. Specifications

Control of product quality begins with the control of raw materials. All raw materials (chemicals, containers, closures) should have defined specifications of the quality. This is essential in order to attain repeatedly and consistently the required specifications in the finished product. It is this attribute that determines the specifications required in procured raw materials, which may be established in a number of ways. A good place to start is to adopt standards which are already established at another GMP compliant facility. Alternately, one may use reputed reference source such as pharmacopoeia, Merck Index, Chemical Abstracts, etc. Specifications of high purity material from a reputed supplier may also be considered. Lastly, one may establish specifications based on experience, which is often the case with new product development. Regardless of the source of specifications, the ultimate specification is the attainment of radiopharmaceutical product conformity and consistent quality.

8.6.2. Procurement and qualification

To ensure consistent product quality, raw materials should be purchased only from suppliers who are approved by the manufacturer based on validation of the material received in the past, and consistency of the quality. Procurement of raw materials should be carefully planned, ensuring adequate stock at all times. Upon receipt, each material must be quarantined, and the representative sample(s) tested according to the written SOPs for conformity of the procured material to identity, purity, strength, and overall quality.

Test procedures should be written in sufficient detail, describing receipt, handling, testing methodology, and storage conditions. In lieu of full testing of an incoming raw material, a certificate of analysis from a reliable supplier may be acceptable, provided that an identity test is conducted, and that the supplier

has been validated by the manufacturer for that material. It is essential to qualify raw materials from more than one supplier, providing an alternate source in case of necessity.

8.6.3. In-process materials

In a typical cyclotron facility, a radiochemical is produced through irradiation of a target material, followed by radiochemical separation, and then manufacture of the radiopharmaceutical batch. For continuation of the manufacturing process, it is necessary to test the in-process material at key stages during manufacturing for evaluating the material conformity with the required specifications. Two of these key points are: (1) at the end of target processing (radiochemical bulk); and (2) after formulation of the radiopharmaceutical bulk, prior to dispensing. The manufacturing process should be on-hold until the in-process material has been qualified and approved by the QC unit. The pre-established quality parameters must be achieved prior to continuation of the manufacturing process.

8.6.4. Disposition

Procured materials are either accepted or rejected based upon conformation to the required specifications. Accepted materials are stored appropriately, and the rejected materials must be removed from the area to avoid mix-ups. A written record should be maintained of such occurrences to continually assess the supplier. Also, a written record should be maintained of the disposition of each lot, and should be fully traceable to the original source. One way to remove any ambiguity between the approved and the not-yet-approved materials is to use colour coded labels: for example, green for the approved and released raw material; and red for quarantined material. For an effective control of raw material, each container or group of containers should be identified with a distinctive lot number which is unique for that batch of material only. This is the lot number that will be entered in the production batch record for full traceability of the materials being used in production. Similar control methods can be derived for the in-process materials.

In-process materials during the production cycle not conforming to the required specifications may be salvageable through rework in the interest of continuation of radiopharmaceutical batch production. However, such action should only be applied through pre-validated and approved written procedures.

8.6.5. Labelling and storage

The label affixed on the raw material container should include such information as receipt, test and expiration dates, and the number of containers in the lot. Everyone in the facility must be made aware that only the approved (for exampe, 'green' sticker) material must be used in manufacturing a radiopharmaceutical batch. Approved material should be stored according to the required storage conditions (temperature, light). Furthermore, an inventory system should be developed such that the oldest approved stock is utilized first; using the accounting method of first in, first out (FIFO).

8.6.6. Containers and closures

Product containers and closures require special mention. Radiopharmaceuticals are typically no-carrier-added and, consequently, contain extremely minute mass of the radioactive ingredient. It is not unusual that stored product may lose its potency through absorption of radioactivity on the surfaces or undergo radiochemical purity degradation. The manufacturer should assure that the containers and closures are not reactive, additive, or adsorptive so as to alter the safety, strength, identity, quality, or purity of the radiopharmaceutical throughout its shelf-life. All new products should be subjected to a stability study using the specified containers and closures prior to approval for use.

8.7. PRODUCTION AND PROCESS CONTROL

The ultimate goal of a manufacturer is to manufacture products that conform to the required specifications, and also with high level of quality assurance. Products of consistent quality can only be realized through consistent production procedures that have been developed, tried-out, and validated for the purpose.

Two basic components of a robust GMP are: SOPs that have been validated for their performance output; and that these procedures are adhered to during manufacturing. This concept of controlled application of procedures applies to every production and test procedure.

8.7.1. Product specifications

The manufacturer, having identified the products that will be manufactured, must begin with defining the product specifications. These are

generally derived from the national or international pharmacopoeias. While setting the product quality standards, it is also important to specify the allowed variance for each of the quality parameters. Procedures for manufacturing and testing are then developed and the product is evaluated against the established specifications. Zeroing-in on methodologies with consistent output is typically an interactive process, where several modifications and/or fine tuning are required. The validated procedure is then written as a SOP in simple and clear language, and with sufficient detail as to how things are to be done to ultimately achieve the desired product specifications.

8.7.2. Standard operating procedures

SOPs are the road maps derived from the procedures developed for product realization. For effective control of these official documents, manufacturer should establish a clear policy for initiation, review and approval of the SOPs. Furthermore, a mechanism must be developed and practiced for controlled issuance and usage of the approved SOPs.

The most important SOP in manufacturing is the production master batch record, or in short, a batch record (BR). The BR should describe in sufficient detail the tasks to be performed and the multiple steps involved in manufacturing the product to ensure that even when used by different individuals, results would be the same. An advantage of such a detailed procedure is that it allows easy investigation of a cause in case of a failure. A typical BR contains all the necessary information as to the date of manufacture, product lot number, calibration and expiration dates, identification and quantities of all the raw materials, equipment, and how things are to be done during the manufacturing process. It must be noted that only the approved raw materials must be used in manufacturing the product; the raw material lot numbers and quantity are entered in the BR at the time of manufacturing. All entries in the BR are initiated by the operator, and all critical steps and calculations are independently checked by another operator or supervisor, and concurrently initialled by both the operator and the checker. A typical batch record and SOPs are shown in Appendix IV.

Developing a production BR requires substantial effort even if 'borrowed' from a reliable source. During development stage, which should be in coordination with the QC/QA unit, the production process is performed repeatedly until it yields the desired results with a high degree of consistency. Additional time spent in developing a sound process is worth the effort, as it will result in a product that repeatedly conforms to the required specifications, affording a very low failure rate. It must be emphasized that the goal of any production process should be to design quality into the product and its

production process. When coupled with the supporting validation data, the potential for consistently achieving quality standards is substantially increased. To demonstrate clearly whether a process is in control, manufacturer should evaluate achieved product specifications in correlation with processing parameters (trending).

It must be noted that the product is qualified as being manufactured under GMP conditions only if the production processes are performed according to the approved and documented batch record (BR) and the applicable SOPs. Any deviation, inadvertent or intended, must be recorded and justified. The product batch must not be released for patient use if quality of product is in doubt or there is evidence of deviation from the established procedures.

Procedure modification is always a possibility for continuous improvements. In fact, such initiatives should be encouraged. However, caution is advised. Whenever a change is to be introduced in an existing procedure, the modified procedure must have been evaluated with respect to the impact on product quality. Furthermore, prior to implementation, the modified procedure must be validated and the staff must be informed of the change and also must be trained in use of modified procedure. Controls should be developed for avoidance of inadvertent use of the 'retired' procedures by removing it from circulation.

8.7.3. Finished products

The finished product is held in quarantine until the time that a representative sample has been tested for conformity to the pre-established quality specifications. For a small batch, which is usually the case in radiopharmaceuticals manufacturing, sampling is not necessarily based on a particular statistical method. Facilities engaged in production of PET radiopharmaceuticals are faced with situations arising from short half-life of the PET isotopes. Explicit arrangements are required to coordinate delivery time (to the user) and the time spent on quality assessment of the batch.

8.7.4. Product release

The finished product should be held in quarantine while it is being tested for conformity to pre-determined specifications. When all the necessary requirements of quality assurance for adherence to GMP are demonstrated, the batch is released for patient use. The manufacturer should designate clearly the finished product release authorization (either a designated person or a position).

A product failing to meet the established specifications or other quality criteria (for example, non-compliance with GMP) must be rejected. Circumstances leading to a failed product should be carefully evaluated. The cause of failure should be investigated, and procedures should be established for systematic evaluation of a failed product (a written and approved SOP should be available). Reprocessing may be performed in some instances, but only as per previously written and approved procedures. The reprocessed product must conform to all the specifications prior to approval for release. Frequency of reprocessing must be absolutely minimal. Excessive reprocessing represents a poorly validated process and loss of control in the system.

8.7.5. Reserve sample

A representative sample(s) of the batch must be set aside for retrospective testing in case of a customer complaint or query related to the product quality. Reserve sample consists of at least twice the quantity necessary to perform all the tests required to determine product quality. The duration of reserve sample retention varies among various GMP guidelines but most require 1 year.

8.7.6. Stability testing

Product stability data are required to determine the appropriate storage conditions and expiration time. For every product, it is necessary to perform stability studies to predict and confirm the product shelf-life under the climatic conditions expected, during product shipping and storage, and to establish storage conditions and expiration times. The test product should be held in the same container and closure system in which the product will be finally packaged.

8.7.7. Processes

The process of radiopharmaceuticals manufacturing is a combination of a number of subprocesses and procedures. The terms ‘process’ and ‘procedure’ are often used interchangeably; but in general, a process is of higher level than a procedure, and that a process may be composed of a number of procedures. For example, the manufacturing of a ^{201}Tl radiopharmaceutical begins with the process of isotope production, which consists of a number of procedures, including irradiation of ^{203}Tl target material in the cyclotron, followed by isolation of the ^{201}Pb radiochemical, growth of ^{201}Pb into ^{201}Tl, separation of ^{201}Tl bulk radiochemical, in-process testing of the ^{201}Tl bulk, formulation,

sterilization, and the finished product testing. In fact, there are a number of additional procedures that also come into use before a radiopharmaceutical batch is approved for release. Well developed processes are such that, when applied as written they are most likely to have consistent output every time.

Control and monitoring of processes is part and parcel of the GMP, and should be the responsibility of not just the supervisors, but also that of the operators. It is essential to verify that the operators have comprehended and indeed followed the procedures during production of every batch of the product. Therefore, it is important for supervisors to continue the education and training of the operators at regular intervals, and to monitor all procedures and implementation thereof.

8.7.8. Deviations

In spite of the application of validated procedures, there are likely to be occasions when processes do fail. There may also be either an accidental, inadvertent or intentional deviation in the process. As an operations policy and philosophy, intentional deviations from the written procedures must not be allowed. If a deviation has occurred during production of a batch, for whatever the reason, it should be fully investigated. Product may or may not be released depending upon severity of deviation. Further evaluation and analysis of the deviation should ensue to uncover root cause of the problem such that a recurrence is eliminated. Clear policies should be established for investigation, recording, and disposition of the affected product batch.

8.7.9. Reprocessing

A batch of the radiochemical bulk or radiopharmaceutical that fails to conform to the pre-determined specifications should be considered rejected. In some simple circumstances (for example, pH and concentration adjustment), the batch may be reprocessed with consent of all the concerned parties such that the reprocessed batch is made to conform to the specifications. Procedures for reprocessing should be carefully evaluated, validated and written as SOPs. Because of the radiation protection considerations, it should be ensured that reprocessing does not cause undue radiation burden to the operator.

8.7.10. Aseptic processing

Radiopharmaceuticals must conform to the acceptable level of microbial contamination. Certain radiopharmaceuticals with a very short shelf-life or being heat labile may not be subjected to steam sterilization in the final sealed

container. In such cases, assurance of microbial quality can only be achieved through application of aseptic processing and handling, and clean air environment. For aseptic processing, controlled environment of Class 100 conditions, with additional requirements for the surrounding buffer zone (normally Class 10.000) is required. Furthermore, a typical aseptic processing may entail assembly of product components sterilized in different ways: dry heat sterilization for glass vials; steam sterilization for stoppers; and sterile filtration of the liquid dosage form. Each of the individual procedure should be validated and carefully controlled. It should be understood that the risk of product contamination is proportionately higher in aseptic processing, necessitating much greater control of the process.

8.7.11. Radiation exposure

High energy emissions and relatively large quantities of radioactivity are integral components of radiopharmaceutical manufacturing. The manufacturing facility must comply with the required radiation protection measures (see Section 9). Furthermore, in the light of potentially high radiation exposure of the production staff, the manufacturer should consider investing in automated and/or remote operation equipment. Reducing operator intervention will often reduce radiation exposure and further enhance product quality.

8.8. DOCUMENTS AND RECORDS

Evidence of compliance with GMP, control of product manufacturing, product quality, and in general, control of processes can only be demonstrated through good documentation. Hence, records and reports pertaining to all aspects of manufacturing are essential components of product realization and QA. A record of data during execution of processes provides evidence of products being manufactured and tested according to the validated procedures. Moreover, good documentation should be viewed beyond fulfilment of GMP requirements. Such practices augment staff understanding and implementation of the organization's philosophy of operation in unambiguous terms. Furthermore, documentation provides all the necessary evidence for an audit in general and traceability of product manufacturing in particular.

In addition to detailing the step by step performance of SOPs, the manufacturer should describe in clear terms how the various documents are to be initiated, reviewed, approved and implemented. A well defined process of good documentation necessitates drafting of documents from various sections

of the manufacturing organization, usually in coordination with the QC/QA unit, with the final approval coming from the latter. There should be a master SOP which, in fact, describes the format of SOPs and how these are to be initiated, drafted, reviewed, validated and approved for use. There should be clear procedures on who must approve the SOPs, how often these need to be reviewed, how modifications are to be incorporated and how the old SOPs are to be archived.

For evidence of implementation and conformity, several records are also generated during manufacturing. These records are not only a requirement for evidence, but can also provide excellent collection of data that should be utilized for monitoring the processes and for continuous improvements.

Some additional aspects of good documentation include:

- Only the currently approved documents should be in use at any given time.
- Copying of approved documents should be controlled; for example, only the QC/QA unit should have the copying and issuing authority.
- Approved copied documents should remain in custody of the individuals or the units these are distributed to.
- Document change should be a controlled process: changes should occur only through proper validation, approval and authorization.
- Documents should be reviewed at regular intervals (e.g., yearly or more often) for continued applicability.
- Where documents require data entry (for example, batch records, raw materials testing), the entries should be clear and legible. No white-outs should be allowed to make the documents look 'neat'.
- Superseded documents should be removed from point of use and retained by the QC/QA unit for a defined duration.

Below is a representative list of documents that should be developed. The manufacturer may find it necessary to have additional documents:

- Specifications of raw materials, in-process materials and finished products;
- Raw materials receipt, testing, disposition and storage records;
- Approved vendors list;
- Materials inventory records;
- Product labels control including labels release authorization and reconciliation (issued; used; rejected; and returned);
- Equipment installation, qualification, validation, usage and maintenance logs;

— Production batch records (the master formula);
— Evidence of product conformity (finished product certificates of analysis) and release authorization;
— Dispensing records;
— Staff duties descriptions and training records;
— Process validation and revalidation records;
— Deviations and corrective actions records;
— Records of archived documents;
— Radiation protection related records;
— Clean room air monitoring records.

8.9. PROCESS VALIDATION

A prerequisite for achieving consistently superior results in a production facility is to develop processes/procedures that perform consistently as planned. This confidence can only be achieved through validation of the processes, which means attaining sufficient experimental evidence to give reasonable assurance that the process/procedure under consideration does and indeed will continue to do what it is intended to do when applied as written. Each step of the manufacturing process must be controlled to maximize the probability of the finished product meeting all quality specifications. Process/procedure validation, therefore, is a systematic effort to demonstrate that the process will repeatedly produce the expected results. It must be understood that the validation of a process does not eliminate the requirement for testing of the finished product, nor the testing of the raw materials and the in-process samples prior to approval.

Process validation should be viewed as a component of designing quality into the product, such that the quality testing becomes largely a process of confirmation of quality. In an event when radiopharmaceuticals (for example, PET products) are exempted from sterility prior to use, it is essential that the production process is thoroughly validated and controlled to minimize the occurrence of a sterility failure.

In practical terms, when developing processes for manufacturing a specific product, the steps involved may be listed as: design, application, evaluation, fine-tuning, and acceptance. In addition to the process development, validation applies also to the equipment used in production or quality assessment. Equipment should be validated at the time of installation, after major maintenance or repair, and at a regular interval during its life cycle.

These steps are illustrated in the flow chart in Fig. 8.1.

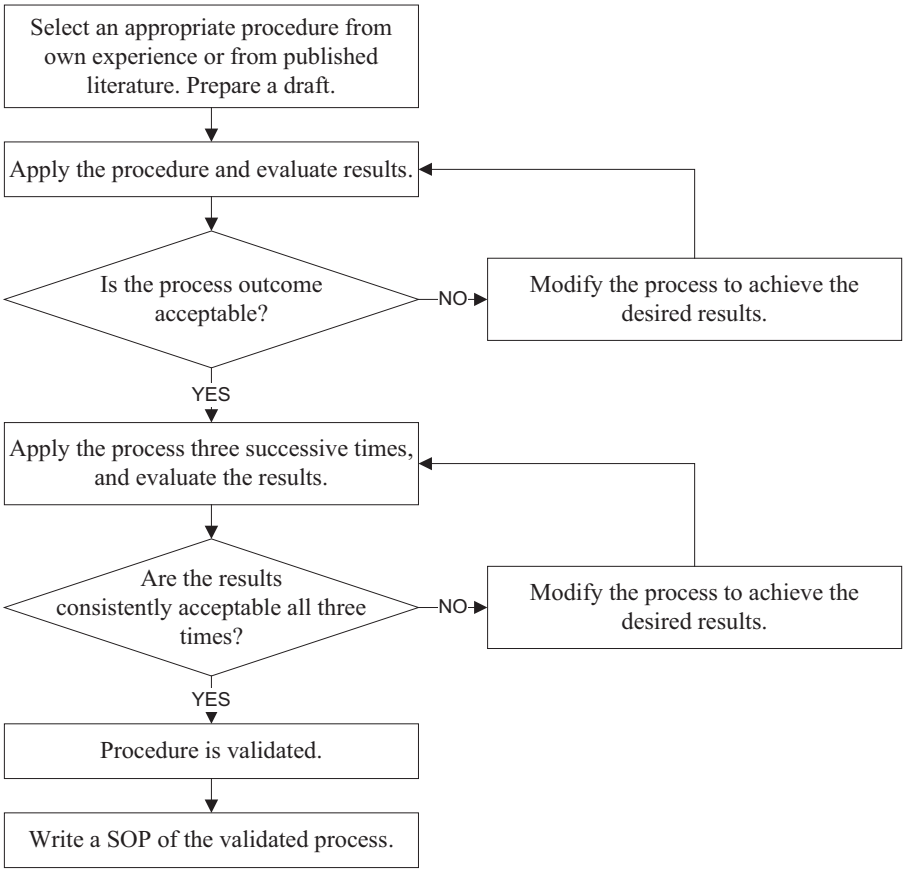

FIG. 8.1. Flow diagram of the steps in process validation.

8.10. LABORATORY CONTROLS

In a broad sense, laboratory control may be viewed as having two elements: (1) establishing the appropriate specifications, operation standards and procedures; and (2) implementing these specifications, standards and procedures to raw materials, in-process samples, and the finished radiopharmaceutical products. The manufacturer, therefore, should establish acceptable criteria for these elements and providing evidence of control.

For several radiopharmaceuticals, test methods are specified by the official compendia. The manufacturer may develop scientifically sound and validated methodologies, and demonstrate that the results are comparable with

the official compendia. In an event of a dispute or query, official methods should be applied.

Each batch of radiopharmaceutical must be tested for conformity to the pre-established specifications of radionuclidic purity, radiochemical purity, chemical purity, and a host of other quality parameters. Due to the short shelf-life (for example, PET radiopharmaceuticals), release of a radiopharmaceutical batch prior to testing for absence of objectionable microorganisms (sterility and pyrogen tests) may be an accepted practice, provided that such testing is initiated as soon as practicable (radiation considerations). Sound application of GMP protocols is of paramount importance for confidence in product quality.

Prior to approval of the batch for release, the QC/QA unit should review the production batch records, evidence of adherence to the written procedures and GMP, analysis of the raw test data, and all elements having a bearing on quality of the product batch for satisfactory conformance to requirements.

8.11. CONCLUSION

The foregoing is a general discussion of GMP as may be applied in manufacturing radiopharmaceuticals. For exact definitions and guidelines, the manufacturer must consult and conform to the applicable GMP regulations.

GMP guidelines represent control of multiple aspects of manufacturing that singly or collectively have a bearing on product quality. Adherence to GMP guidelines for products manufacturing not only enhances assurance of quality, but may in fact be a regulatory requirement, depending upon applicable national regulation, as is the case in most developed countries and many developing countries.

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9. RADIATION PROTECTION

9.1. INTRODUCTION

Facilities operating even small accelerators have radiological hazards that necessitate the implementation of an integrated radiation safety programme. The goal of this section is to provide some guidelines for a protection programme in a new accelerator facility being set up. The basis for many of these guidelines is the International Basic Safety Standards (BSS) which can be found at the IAEA web site (http://www-pub.iaea.org/MTCD/publications/PDF/SS-115-Web/Start.pdf and http://www-pub.iaea.org/MTCD/publications/PDF/Pub1117_scr.pdf.

The first step in the development of a radiation protection programme is an evaluation of all the situations where there is a potential for radiation exposure. The level of effort, formality, and detail of the radiation protection programme must be linked to the magnitude of both routine and accidental exposures, and to the probabilities of these exposures. This preliminary radiological evaluation should cover all aspects of operations and should include:

— An identification of the sources of routine and reasonably foreseeable potential exposures.
— A realistic estimate of the relevant doses and probabilities.
— Assessment of safety.
— Licensing process.

9.1.1. Definitions

There are several definitions and abbreviations which will be used in this section which may not be familiar to everyone. There are two definitions that are essential.

Gray: The SI unit of kerma and absorbed dose, equal to 1 J/kg. It is a unit of concentration.

Sievert: The SI unit of equivalent dose and effective dose, equal to 1 J/kg.

A complete list of definitions is given in the IAEA Safety Glossary, which is available at: http://www-ns.iaea.org/standards/safety-glossary.htm

9.1.2. Activated materials

All materials located within an accelerator enclosure have the potential to become 'activated' if they interact with the primary or secondary beams. Among those items that have the highest probability for activation are the targets, beam lines, collimators, and beam stops.

9.1.3. Contaminated versus activated material

Contaminated materials are items with fixed or removable surface contamination. Activated material is material with radioactivity dispersed throughout the item and cannot be removed except through some type of destructive means.

Activated materials normally do not present a potential loose contamination hazard, except during operations such as grinding, burning and machining. Everything inside the accelerator facility should be considered as contaminated until it can be shown to be free from contamination by performing a survey.

9.1.4. Types of controls

Once the hazards have been evaluated, controls are used to protect personnel and the general public from exposure to radiation hazards. The design of an effective safety programme incorporates a combination of:

— Engineered controls;
— Administrative controls;
— Personal protective equipment, e.g. respirators, protective clothing.

Some examples of engineering and administrative controls for radiation protection are shown in Table 9.1.

In addition to the overall evaluation mentioned above, a more thorough evaluation of the particular radiation hazards in a facility should include:

— The ways in which structures, systems, components and procedures related to radiation protection might fail, singly or in combination, and how such failures could lead to potential exposures, and the consequences of such exposures;
— The ways in which changes in the environment could affect protection or safety;

TABLE 9.1. EXAMPLES OF ENGINEERING AND ADMINISTRATIVE CONTROLS

Engineering controls	Administrative controls
— Shielding of the sources — Interlocks on operation of radiation producing devices when trying to access these areas — Using sealed enclosures to reduce exposure or contamination	— Remove the worker from the job if their dose is near the limits set for the job — Minimize exposure times by work planning — Use radionuclides only in designated areas using safe handling techniques — Limit personnel access to radiological areas

— The ways in which operating procedures related to protection or safety might contain errors, and the consequences of such errors; and
— The safety implications of any proposed modifications.

9.1.5. Radiation safety manual

A radiation safety manual (RSM) is one of the key elements of a sound radiation protection programme. This document defines the organization's operational philosophy, and provides mechanisms of control through various standard operating procedures and compliance requirements. This document should be written to specify programmatic and implementation requirements for the radiological control programme and provide associated guidance. Radiation workers should have easy access to this document for reference in all radiation areas. Furthermore, this document should be revised periodically with the most up to date radiation protection guidelines and the organization's policies.

9.1.6. Leadership role in radiation safety

Managers have certain responsibilities concerning radiation protection in their facilities, including:

— Establishing high standards of radiation safety;
— Providing the tools to achieve effective radiation protection;
— Holding workers and their supervisors accountable for radiation safety;
— Ensuring an open environment that encourages respect for the radiological requirements of the RSM;
— Resolving issues that inhibit performance of radiation safety.

In addition, workers also have certain responsibilities with respect to working with radiation. All personnel subject to these requirements should:

— Follow any applicable rules and procedures for protection and safety specified by the facility.
— Use the monitoring devices and the proper personal protective equipment provided.
— Cooperate with the radiation safety personnel with respect to protection and safety, the operation of radiological health surveillance, and dose assessment programmes.
— Abstain from any wilful action that could put themselves or others in situations that violate the requirements.
— Comply with all radiological postings encountered in the work place.
— Maintain training qualifications necessary to conduct assigned radiological work.
— Immediately report all radiological incidents that occur in the work place to their supervisor.
— Ask questions if uncertain of the radiological requirements for work.

All proposals for new installations, research work, and maintenance in radiological areas should be evaluated for radiological impact before the beginning of work through some formal procedure.

9.1.7. Improving radiological performance

The main elements of radiation protection are justification, optimization and individual dose limitation as set out in the BSS. Personal radiation exposure should be maintained ALARA. Radiation exposure of the work force and public should be controlled such that any exposures are well below regulatory limits, and that the benefits to the programme which are derived from these exposures, exceed the risks and the exposure does not exceed the dose constraints. A good way to ensure the radiological safety of each organization is to set up a radiation safety committee. This committee should meet as needed to review the current and proposed future radiological projects within the facility. It should have members who are working with radioactivity routinely, as well as members who are knowledgeable, concerning radiation safety practices. The committee should:

— Make recommendations to management to minimize radiation exposure and radiological releases;
— Evaluate items such as construction and design of facilities and systems, and plan major modifications;
— Evaluate work activities for radiation exposure and waste minimization;
— Pass on experience and advice through a lessons learned programme.

9.1.8. Radiation protection officer

A radiation protection officer (RPO) should be appointed for the organization. The RPO should serve as the senior radiological person for determining the adequacy of radiological performance and the interpretation of radiological requirements. The RPO and staff should also be available to the facility manager to help the work force with radiological concerns and planning. This resource should be involved as early as possible in any project that involves potential radiological exposures.

9.2. RADIOLOGICAL STANDARDS

The following are suggestions for radiological control limits for exposure of workers and the public based on accepted standards.

9.2.1. System of dose limitation

Dose limits for radiological workers and the public are provided in Table 9.2. It should be noted that these limits are subject to jurisdictional control, and it is the responsibility of the user to be informed as to the limits set by the institution and/or government agency.

More detailed information can be found at (http://www-pub.iaea.org/MTCD/publications/PDF/SS-115-Web/Start.pdf and http://www-pub.iaea.org/MTCD/publications/PDF/Pub1117_scr.pdf

Exposures due to background radiation, therapeutic and diagnostic medical procedures, and voluntary participation as a subject in medical research programmes should not be included in either personnel radiation dose records, or assessment of dose against the limits in Table 9.2. All occupational exposure received during the current calendar year should be included when demonstrating compliance with Table 9.2 dose limits.

TABLE 9.2. IAEA RECOMMENDED DOSE LIMITS FOR RADIOLOGICAL WORKERS AND MEMBERS OF THE PUBLIC

Type of exposure	SI units (per year)
Radiological worker: effective dose (internal + external), averaged over five years[a]	20 mSv
Radiological worker: equivalent dose to the lens of the eye	150 mSv
Radiological worker: equivalent dose to extremity (hands and arms below the elbow, feet and legs below the knees) and skin	500 mSv
Visitors and public: effective dose (internal + external)	1 mSv

[a] With the caveat that effective dose in any single year shall not exceed 50 mSv/a.

For the purpose of monitoring individual exposures to external radiation, personnel dosimeters should be provided to and used by radiological workers who, under typical conditions are likely to receive more than the public dose limit from Table 9.2.

9.2.2. Contamination control and control levels

Personnel exiting contamination areas should check for contamination using equipment that, under normal laboratory conditions, can detect total contamination of, at least, 15 Bq per 100 cm^2 for beta and gamma emitting radionuclides.

Personnel found with detectable contamination on their skin or personal clothing, should be assessed and decontaminated as necessary. The use of automatic monitoring units, such as portal monitors that meet the above requirements, is encouraged where practical.

9.2.3. Posting requirements

Radiological postings should be used to alert personnel to the presence of radiation and radioactive materials, and to aid in minimizing exposures and preventing the spread of contamination.

Physical barriers should be placed so that they are clearly visible from all directions and at various elevations. Radiological postings should be displayed only to signify actual or potential radiological conditions and be updated if conditions change.

A radiological posting that signifies the presence of an intermittent radiological condition should include a statement specifying when the radiation

is present, such as ‘Caution: radiation area when red light is on.’ Posted areas should be as small as practicable for efficiency.

9.3. CONDUCT OF RADIOLOGICAL WORK

There are several phases to the safe conduct of radiological work. Safety controls can be engineered into the facility while the buildings are still under construction. Once the facility has been completed, work involving radiological concerns needs to be planned and evaluated before, during, and after the work. Additional planning is necessary when the organization is faced with special cases, such as expansion into new work areas, or maintenance in radiological areas with potential contamination to the staff and the premises. A key part of this planning is to learn from the planning that has been done previously. The feedback from the worker and any unsafe conditions encountered while doing the work should be discussed and written up, so that they can serve as a resource to future work planning. A flow chart for overall work planning is shown in Fig. 9.1.

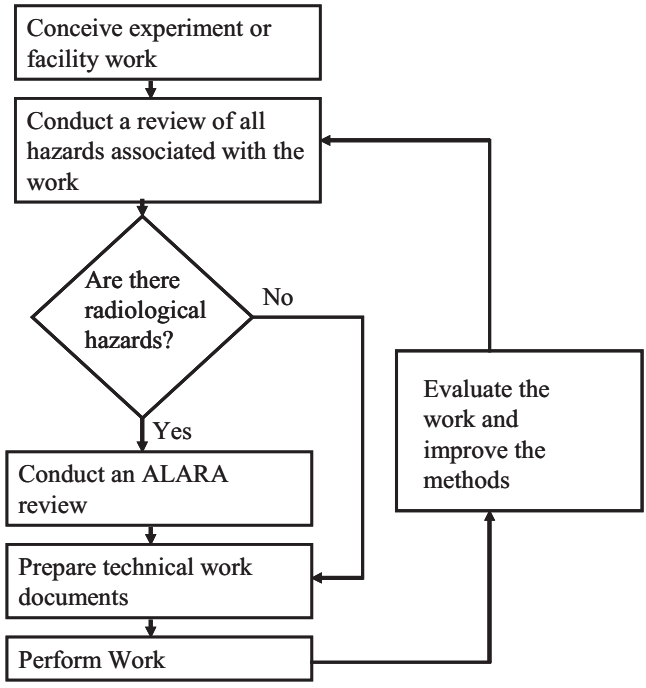

FIG. 9.1. Workflow diagram including both normal hazards and radiological hazards.

As a guiding principle, **the level of planning should be commensurate with the level of hazard**. An assessment should be made as to the potential dose and the planning done accordingly. A procedure where the maximum dose that could be received is 1 mSv does not need the same level of planning as a procedure which could result in a dose of 20 mSv.

9.3.1. Planning for maintenance, operations and modifications

Plans and procedures should be prepared for maintenance and modifications in radiological controlled areas with potential for radiation exposure. Tasks with the potential to exceed some trigger levels set by the radiation safety officer should undergo a formal, documented safety review. Each protocol and procedure should be reviewed at least annually for effectiveness and to incorporate any necessary modifications.

9.3.2. Preparation of work planning documents

Technical work in radiological areas must be thoroughly evaluated to achieve the maximum radiation protection, and these evaluations should be well documented. One mechanism for documenting the work planning is the radiological work permit (RWP). The RWP is an administrative mechanism which can be used to establish radiological controls for intended work activities. It should inform workers of radiological conditions in an area, and the entry requirements for that area. The permit provides a way to relate worker radiation exposure to specific work activities.

A general RWP or job specific RWP should be used to control activities such as entry into radiation or contamination areas; handling of materials with removable contamination that exceed 15 Bq per 100 cm^2 above background. Preparation of technical work planning documents should consider the following:

— Information from similar work completed previously.
— Time for starting the work, its estimated duration, and the human resources involved.
— Maps of estimated dose rates.
— Other activities in the same area which may interfere with the work.
— Protective clothing and tools to be used.
— The possibility of using special tools, including robots.
— Communication necessary to ensure supervisory control and coordination.
— Handling of waste arising from the job.

— Conventional safety.
— Special radiological control requirements to be included in technical work documents.
— Access to and exit from the work area.
— Service lines (air, welding, ventilation).
— Removal or shielding of sources of radiation.
— Planning for installation of temporary shielding.
— Decontaminating where possible and covering any remaining contaminated areas.
— Working in lowest radiation levels.
— Performing as much work as practicable outside radiation areas.
— Incorporating points in the procedure where the radiological situation should be assessed before proceeding to the next step, radiological control hold points (RCHPs).
— Minimizing discomfort of workers, for example by adjusting the environmental conditions (such as air temperature) for the protective clothing to the extent possible.

In addition to the RWP, the following information may be posted or transmitted to the workers:

— A detailed dose rate map of the work area and possible hot spots, produced from a survey made prior to the work, or otherwise estimated;
— An estimate of contamination levels and how they may change during the course of the work;
— An estimate of individual and collective exposure for each work step;
— Specification of any additional dosimeters to be used by the workers;
— Specification of protective equipment to be used in different phases of the work;
— Details of any time or dose restrictions;
— Instructions on when to contact the RSO.

9.3.3. Work preparation

Tools and equipment. Tools and equipment should be inspected to verify that they are operating properly before being brought into contamination areas. The use of radiological clean tools or equipment in contamination areas should be minimized by the implementation of a contaminated tool crib.

Temporary shielding. The installation, use, and removal of temporary shielding should be controlled by a facility or department procedure. Shielding used as a part of benchtop activities or hoods should be exempted. The effects

of the additional weight of temporary shielding on systems and components should be evaluated and established to be within the design basis prior to installation. The installed temporary shielding should be periodically inspected and surveyed to verify the effectiveness and the integrity of the installation.

Personal protective equipment and clothing. Protective clothing designated for radiological control use should be specifically identified by colour, symbol, or appropriate labelling; and should not be used for non-radiological work. Personal protective equipment and clothing should not be stored with personal street clothing. An example of a person ready for radiological work is shown in Fig. 9.2.

Eating and drinking. To minimize intake of radioactive material by personnel, eating or drinking, including chewing gum or smoking, should not be permitted in contamination areas. When a potential for personnel heat stress exists, drinking may be permitted within a contamination area under certain conditions and controls.

FIG. 9.2. Chemist wearing personal protective equipment and clothing including marked laboratory coat, safety glasses, gauntlets (arm protectors) and double gloves.

Monitoring workers for personnel contamination. Personnel should check for contamination with a large area proportional counter or a thin window GM counter under the following conditions:

— Personnel exiting a contamination, high contamination, or airborne radioactivity area to an uncontaminated area should perform a whole body scan.
— Personnel exiting a radiological buffer area containing contamination, airborne radioactivity or radioactive material area where dispersible materials are in use should at least, perform a hand and foot scan, although a whole body scan is recommended.

When monitoring equipment cannot be established close to the step-off pad due to high background radiation levels, and checking cannot be performed at the exit from contamination areas, or airborne radioactivity areas, the egress path to the monitoring station should be controlled and personnel should proceed directly to it. Personnel checking should be performed after removal of protective clothing and prior to washing or showering. Personnel checking should be performed using instruments that can easily detect 15 Bq above background. An example of such an instrument is shown in Fig. 9.3.

The instrument is checked every day prior to the first use to ensure that it is reading correctly. This is noted in the log and initialled by the person checking the instrument.

Personal items carried by a worker, such as notebooks, papers, and flashlights, should be subject to the same checking requirements. The use of automated personnel contamination monitors is encouraged. Instructions for personnel checking should be posted adjacent to personnel checking

FIG. 9.3. Example of instrument used for an exit scan. Note the calibration source and daily log on the top of the instrument.

instruments or monitors. These instructions should include directions for action when contamination is discovered on skin or personal clothing. An example of a whole body checking station is given in Fig. 9.4.

Cleanup: Requirements for area cleanup should be included in the work planning documents. Work activities should not be considered complete until support material and equipment have been removed, and the area has been returned to at least pre-work status.

9.3.4. Controls for benchtop work, laboratory fume hoods and gloveboxes

Radiological work which has the potential to generate radioactive contamination in a localized benchtop area, laboratory fume hood, or glove-box should be conducted in accordance with a written procedure. Protective clothing should, at a minimum, include laboratory coats and gloves for work at a localized benchtop and laboratory fume hood operations with dispersible radionuclides.

FIG. 9.4. Example of a whole body checking station inside a laboratory door way. Note the postings on the outside of the laboratory.

Upon completion of work or prior to leaving the area, workers should monitor those areas of their body that are potentially contaminated. At a minimum, this includes hands, arms, and front portions of the body and shoe soles. Gloves should be secured at the wrist as necessary or protective gauntlets worn. Shoe covers should be considered based on the potential for floor contamination. Workers should periodically monitor their hands during work; they should also monitor adjacent surfaces that might inadvertently become contaminated.

9.3.5. Waste minimization

A radioactive waste minimization programme should be in effect to reduce the amount of radioactive waste. Uncontaminated waste should be segregated from potentially contaminated material and radioactive waste following the concepts of exclusion, exemption and clearance. Waste reduction philosophies, techniques, and improved methods should be emphasized in training. The following practices should be instituted to support waste minimization:

— Restrict material entering controlled areas to those needed for performance of work.
— Restrict quantities of hazardous materials, such as paints, solvents, chemicals, cleaners, and fuels entering controlled areas, and take measures to prevent inadvertent radioactive contamination of these materials.
— Substitute recyclable items that can be decontaminated in place of disposable ones and reuse equipment when practical.
— Select consumable materials such as protective coverings and clothing that are compatible with waste processing systems, volume reduction, and waste from acceptance criteria.
— Reserve an assortment of tools primarily for use in contamination or airborne radioactivity areas. Tools should be maintained in a designated storage or distribution area or a contaminated tool crib. Controls should be established for tool issuance and use.
— Segregate reusable items, such as protective clothing, respirators and tools, at the step-off pad.
— Minimize the number and size of radioactive material areas.

9.3.6. Changes in procedures

It is important to maintain control of radiological work, both to ensure that the work is done safely, and that procedures are followed over a long period of time. Often in routine practice, procedures may change gradually to expedite the work. Therefore, it is important that these changes be documented if they really improve performance, or eliminated if they impact negatively on the safety of the procedure.

9.4. RADIOLOGICAL HEALTH SUPPORT OPERATIONS

Dosimeters issued to personnel under the previous guidelines must be read frequently, as per norms established by the national authority and the results made available to the employee, and to the RPO or radiation safety committee. This monitoring programme should be conducted by utilizing an accredited service. Dosimeters should be issued only to personnel formally instructed in their use, and should be worn only by those to whom the dosimeters were issued. Permanent or temporary personnel monitoring equipment should not be issued prior to successful completion of the appropriate training. Trained personnel should wear their primary dosimeters so that they monitor the typical exposure to the body. The personnel monitoring badge should be protected from contamination. Personnel exposures to the skin, lens of the eye, and extremities should be reported separately if they are monitored. Dosimeters, when not in use, should not be left in the controlled or radiological areas.

9.4.1. Dose received from external sources

The dose received from external sources is typically measured using a thermoluminescent dosimeter (TLD). This type of dosimeter should be worn by:

— Personnel who under typical conditions are likely to receive an annual external whole body dose greater than 1 mSv, an annual dose to the extremities or organs in excess of 50 mSv, and other tissues (including lens of the eye and skin) greater than 15 mSv.
— Declared pregnant workers who are likely to receive, from external sources, a dose equivalent of 0.5 mSv or more to the embryo/foetus during the gestation period.

— Minors and members of the public entering a controlled area likely to receive a dose of 0.25 mSv or more in a year from external sources.

A typical TLD is shown in Fig. 9.5. In certain circumstances, a self-reading dosimeter (SRD) should be used to help ensure compliance with radiological dose limits. Self-reading dosimeters (pencil dosimeters, electronic dosimeters) should be issued to personnel when required by a RWP, or if they are working in a radiation area where a person could receive significant (10% of the annual limit) external radiation in one work day.

The SRD should be worn in addition to the primary dosimeter and in the same general area on the body. Only calibrated SRDs should be used. The dose recorded by the SRD should be attributed to the worker and counted towards the worker's dose until the results of the primary dosimeter are received. Dosimeters with alarms should be required for entry into areas where dose rates are greater than 10 mSv/h. SRDs should be read periodically while in use and should not be allowed to exceed 75% of full scale. The energy dependence of supplemental dosimeters, particularly to a low energy beta radiation, should be considered in determining their applicability. Use of electronic dosimeters with alarms is encouraged for entry into high radiation areas or when doses greater than 1 mSv in one working day are expected. An electronic dosimeter provides an early warning of elevated exposure through the use of alarm set points at specified dose rates or integrated doses.

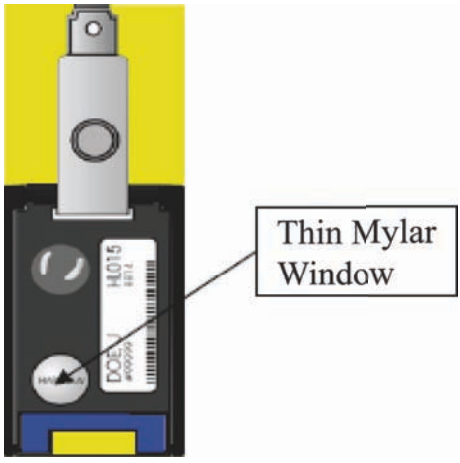

FIG. 9.5. Thermoluminescent dosimeter typically used to monitor external radiation dose.

9.4.2. Dose received from internal sources

Personnel should participate in an internal dose monitoring programme if they are likely to ingest or inhale radioactivity which could be absorbed by their body at a level where they might receive more than 1 mSv.

Routine bioassay monitoring methods and frequencies should be established for personnel who are likely to receive intakes resulting in a committed effective dose equivalent greater than 1 mSv.

9.5. TRAINING AND QUALIFICATION

Training is a critical part of conducting safe radiological work. It is the management's responsibility to ensure that workers, who may be occupationally exposed to radiation and persons with assigned responsibilities in the radiation protection programme, receive general radiation protection information and training. Basic information on radiation protection principles should also be provided to workers who may not be occupationally exposed, but whose work may have an impact on the level of exposure of other workers or of members of the public (for example, designers, engineers, planners). They should be trained to take account of radiation protection requirements in their activities so as to optimize the protection of other people.

Training of workers directly involved in work with radiation sources should include relevant information, presented in the form of documents, lectures, and applied training that emphasizes procedures specific to the worker's job assignment. Particular attention should be paid to contractors, to ensure that they are provided with necessary information and training. Training of workers considered occupationally exposed should address topics at a level of detail commensurate with the workers' job assignments and the potential hazard. The training should cover topics such as the following:

— The main risks associated with ionizing radiation.
— The basic quantities and units used in radiation protection.
— The radiation protection principles (optimization of protection, dose limits, etc.).
— The fundamentals of practical radiation protection, for example, use of protective equipment, shielding, behaviour in designated areas.
— The specific task related issues.
— The responsibility to advise a designated person immediately if any unforeseen occurrence involving increased radiation risk arises.

— Where appropriate, actions that may need to be taken in the event of an accident.
— Where work involving significant exposure to radiation is to be undertaken, consideration should be given to the use of training on mock-ups or simulators to ensure that the work will proceed as smoothly as possible, all unnecessary hazards will be avoided, and exposure times will be minimized.

Individuals whose job assignments are incidental to the use of radiation, such as caretakers/janitors or security staff, and others who may spend brief periods in areas where exposure is possible, should be given basic information on the hazards and any preventive actions to be taken. For such individuals, there needs to be a brief discussion of items such as the use of time and distance to limit exposure; a qualitative discussion of the trivial risk from the minimal exposure they may receive; and specific directives regarding actions that are prohibited, those that are required and those that are recommended.

9.5.1. Training and qualification programme

Trained personnel should: work safely in and around radiological areas; maintain their individual radiation exposure and the radiation exposures of others; be capable of recognizing unsafe radiological work practices; and heighten awareness of radiological hazards within the work environment. Where unique radiation protection requirements exist at facilities, additional facility specific training should be developed to supplement the basic information. Proficiency in dealing with radiological issues should be demonstrated at least every two years.

A very important point in the proper maintenance and safe operation of any radioisotope laboratory is daily cleaning. The staff members employed in this task actually have very important responsibilities, and the qualifications and site specific training and continuous education should be addressed in any facility, possibly through one or several SOPs on the subject. Cleaning staff should be approved for these tasks, should wear dosimeters, should where relevant be checked for internal contamination and should be encouraged to report any contamination found.

A training matrix is given in Table 9.3 to show the level of training recommended for each level of involvement with radiological environments.

TABLE 9.3. ACTIVITIES REQUIRING CORE RADIATION PROTECTION TRAINING

Activity	GET	Radwork	Bench-top	Sealed source	Contam	HiRad
Entering a controlled area	■					
Entering a radioactive material area	■					
Handling sealed radioactive sources	■	■				
Handling dispersible radioactive material	■	■	■			
Handling radioactivate material	■	■				
Excavating in a soil contamination area	■	■		■		
Evaluating and moving low level radioactivate material between posted areas	■	■	■			
Being assigned responsibility for control of sealed radioactive sources	■	■				
Entering a radiological buffer area	■	■				
Entering a radiation area	■	■				
Entering a high radiation area	■	■			■	■
Entering a contamination area	■	■		■		
Entering a high contamination area	■	■		■		■
Entering an airborne radioactivity area	■	■		■		

GET: General employee training.
RadWork: Radiological worker training.
Benchtop: Benchtop and dispersibles training.
Contam: Contamination training.
HiRad: High level radiological training.

9.5.2. Training requirements

Each project, procedure, or process should be assessed to determine the level of training required to carry it out. The training should be completed by the employee before work begins, and retraining should be repeated every two years.

9.5.3. Employee records

Employee records need to be kept to ensure that training is up to date, and that the employee is qualified to conduct any required work. Employees should be notified when their training needs to be refreshed, and given the opportunity to be retrained.

9.6. RADIATION WASTE MANAGEMENT

Radioactive waste is classified as:

- **Exempt waste (EW).** Waste that meets the criteria for clearance, exemption or exclusion from regulatory control for radiation protection purposes.
- **Very short lived waste (VSLW).** Waste that can be stored for decay over a limited period of up to a few years and subsequently cleared according to arrangements approved by the regulatory authority, for uncontrolled disposal, use or discharge. This would include radioactive waste containing primarily radionuclides with short half-lives often used for research and medical purposes.
- **Very low level waste (VLLW).** Waste which does not meet the criteria as EW, but which does not need a high level of containment and isolation and therefore is suitable for disposal in near surface landfill type facilities, with limited regulatory control. Such landfill type facilities may also contain other hazardous waste. Typical waste in this class would include soil and rubble with low activity concentration.
- **Low level waste (LLW).** Waste that contains material with radionuclide content above clearance levels, but with limited amounts of long lived radioactivity. It requires robust isolation and containment for periods of up to a few hundred years and is suitable for disposal in engineered near surface facilities. It covers a very broad range of materials that includes short lived radionuclides at high activity levels, but long lived radionuclides only at relatively low activity levels.
- **Intermediate level waste (ILW).** Waste which, because of its content, particularly of long lived radionuclides, requires a higher level of containment and isolation than is provided by near surface disposal. However, it needs no or only limited provision for heat dissipation during its storage and disposal. It may include long lived radionuclides, in particular alpha emitting radionuclides, that will not decay to an activity level acceptable for near surface disposal during the time which

institutional controls can be relied upon and therefore requires disposal at greater depths of the order of tens up to a few hundred metres.

— **High level waste (HLW):** Waste with radioactivity levels high enough to generate significant quantities of heat by the radioactive decay process or with large amounts of long lived activity which need to be considered in the design of a disposal facility for such waste. Disposal in deep (usually several hundred metres or more below the surface), stable geological formations is the generally recognized option for its long term management.

Most of the waste generated at an accelerator facility will fall into the categories of short lived, low level or intermediate level waste. The main sources of these wastes will be spent targets, chemicals used in the processing of targets and separation of radioisotopes from the target materials. Usually, this material can be collected on-site at a specific facility or in a designated area. The radioactive waste should then be transferred to an authorized or licensed handler for removal from the site.

9.6.1. Decay in storage

One aspect of the short-lived radioactive isotopes is 'decay in storage' where the materials are allowed to decay to a low level in a shielded area before they are removed for disposal. During this time the amount of radioactive material may significantly decrease depending on the half-lives of the radioisotopes present, and in some cases the material may be discarded as regular waste if certain conditions are met. Normally, a facility may hold by-product material with a physical half-life of less than 120 days for decay in storage before disposal without regard to its radioactivity if the facility:

— Monitors by-product material at the surface before disposal and determines that its radioactivity cannot be distinguished from the background radiation level with an appropriate radiation detection survey meter set on its most sensitive scale and with no interposed shielding.
— Removes or obliterates all radiation labels, except for radiation labels on materials that are within containers and that will be managed as biomedical waste after they have been released from the licensee.

9.6.2. Protection of the general public

One of the most serious concerns is the protection of the general public from releases of radioactivity. Therefore, concentrations of radioactive material which may be released to the general environment must be below certain levels, defined set by regulatory control of radioactive discharges to the environment. Any radioactivity released in ground water, surface water, air, soil, plants, or animals must not result in an annual dose exceeding an equivalent of 250 μSv to the whole body, 750 μSv to the thyroid, and 250 μSv to any other organ of any member of the public. A reasonable effort should be made to maintain releases of radioactivity in effluents to the general environment.

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10. SUMMARY

Establishment of a cyclotron based radionuclide and radiopharmaceutical production facility is a major undertaking regardless of the scope and size of the facility. Regulatory demands of radiation protection and pharmaceutical manufacturing only add to the need for meticulous attention to a large number of factors in overall planning and successful implementation. Also, a significant commitment of resources, not just during the onset of the project, but also for sustained continuity further adds to the already difficult decision making process.

In this publication, all these issues have been addressed and discussed conceptually for the benefit of planners and stakeholders of a new facility. The need for a clear vision and realistic scope of the programme has been repeatedly emphasized throughout this book as this aspect of project planning is absolutely vital for defining and achieving the mission and objectives of the facility.

The most critical aspects in conceptualization, planning and subsequent implementation have been discussed in detail and are highlighted below as necessary actions:

— Performing a feasibility study which balances wishful thinking with project viability;
— Forming a task force composed of the stakeholders to evaluate strategically the various aspects of project planning to ultimately recommend the scope and objectives of the facility, and also to formulate the project plan;
— Assessing the financial aspects of the project, including the set-up and operating costs of the facility through the development of business models and cost–benefit analyses;
— Designing a facility and layout that encompasses the scope of the project and also takes into consideration the regulatory requirements;
— Ensuring the availability of appropriately qualified and trained staff, critical for efficient and high quality operation of the facility;
— Applying GMP regulations for the production of radiopharmaceutical products which are consistently safe for human use;
— Integrating the radiation protection regulations in building design and formulating procedures to ensure personnel radiation safety.

Finally, the central theme of this publication is to develop a realistic scope for the facility based upon rational vision of the stakeholders, and in line with the available resources. It is aimed to provide information for an informed decision making process.

Appendix I

GENERAL FACILITY CONSIDERATIONS

The following are points to consider in the design of a radioisotope production facility. These are divided into general considerations and functional areas such as the laboratory, cyclotron vault, etc. They should serve as a starting point to ensure that the necessary utilities and amenities are present. The list is not comprehensive, but may serve as a starting point to think about what is needed in each room or area. Of course, not all the items will apply to all levels of facility, but thought should be given to how these needs could be met if the facility should expand in the future.

General facility considerations

— Utility shut-off controls should be located outside the laboratory.
— Laboratories should have an abundant number of electrical supply outlets to eliminate the need for extension cords and multiplug adapters.
— Electrical panels should be placed in an accessible area not likely to be obstructed.
— Ground fault circuit interrupters should be installed near sinks and wet areas.
— Environmental chambers where evacuation or other alarms cannot be heard should be equipped with strobe lighting or additional alarms.
— Central vacuum systems should not be used, since they are vulnerable to contamination. Local vacuum pumps are preferable.
— All vacuum lines should have cold traps or filters or both to prevent contamination.
— Chilled water loops should be available for equipment in need of cooling. Loops help to avoid excessive wastewater. Supply and returns should be insulated to minimize condensation.
— There should be a break or lunch room where the staff can meet.
— Functional areas: cyclotron.

Cyclotron vault

— Size: leave room for easy access and future expansion.
— Wall thickness: be sure the walls are thick enough to provide adequate shielding for present and potential future uses.
— Trenches: to supply present and potential access for cables and lines.

— Room for expansion: outside the vault.
— 208, 440 V electrical service for expanded electrical usage.
— Expanded normal voltage service (110 V or 220 V) — for equipment, tools.
— Possible addition of beam lines.
— Power supplies and electronics: easy access, adequate water and air conditioning services.
— Heat exchanger: easy access and sampling for testing of radioactivity levels.
— Cryogen storage: separate area if possible.
— Gas bottle storage.
— Control room: cable trenches, computer floor, adequate metering, extra normal voltage outlets (220 V or 110 V).
— Spare parts storage: one spare of most major components, stock of expendables.
— Shop space, electronic and mechanical: size and equipment.
— Radioactive parts storage: radioactive decay before disposal.
— RF shielding of the area around the cyclotron and power transmission.
— Magnetic field shielding if required.
— 'Tie-point' wiring, well documented, many extra cables and conduits.
— Target repair and maintenance area with radioactive waste disposal.
— Extensive communication equipment to PET and laboratory.
— Overhead electric cranes for equipment moving.
— Functional areas: laboratory.
— Chemistry laboratory: the size, number of sinks, utilities.
— Reagent storage, refrigerators: number and type.
— Synthesis module room: separate if possible, shielded from other areas.
— Quality assurance: space for test equipment, low background.
— Radionuclide generator storage: separate if possible.
— Office space: sufficient for employees, outside laboratory.
— Lavatories: easily accessible.
— Janitorial storage: sufficient size, floor drain.
— Gas cylinder storage: near laboratory and loading dock.
— Conference area: sufficient for the entire radiopharmaceutical production group.
— Eating areas outside the laboratory: amenities (microwave, toaster oven, hot water, sink, etc.).
— Hazardous waste storage: outside laboratory.
— Supply storage: gloves, laboratory coats.
— Record storage: fire resistant room if possible, computer records.
— Instrument-to-computer links.
— Communication to PET and cyclotron.

— Emergency/safety exits.
— Safety shower: decontamination area and supplies.
— Area for sterile set up for radiopharmaceuticals.
— Construction and access considerations.
— Equipment transportation, unloading and installation area.
— Floor loading (including access routes).
— Ensure that the floor is level.
— Ceiling heights: sufficient for all equipment and cranes.
— Access for cryogens.
— Controlled access to areas of possible radioactivity.
— Radiation protection considerations.
— Air turnover in vault areas and laboratories.
— Pressure gradients in the facility.
— Shielding in the accelerator vault.
— Shielding around the synthesis modules.
— Monitoring equipment in the facility (portal).
— Stack monitoring and location of monitors.
— Electronics in high radiation areas should be radiation resistant.
— Robotics for synthesis, target manipulation.
— Decontamination facilities and supplies.
— Facility environment.
— Electrical supplies: voltage, currents and phases.
— Air conditioning: general area, computer areas, humidity, filtration.
— Water supply and floor drains, sinks with holding tanks.
— Chilled water supply.
— Establish controlled areas.
— Fire detection and safety.
— Telephone, fax service.
— Housekeeping.

Appendix II

EXAMPLE OF RADIOLOGICAL WORK PERMIT (RWP) AND ASSOCIATED FORMS[1]

ALARA REVIEW CHECKLIST

Respond Yes/No/NA (not applicable) to the following issues. If there is a 'No' response, additional description is required; include an attachment. Technical work documents and the RWP may need to be revised following the ALARA review.

Topic	Yes	No	NA
Are radiological control hold points in the technical work documents and RWP at appropriate places?			
Has radioactivity been eliminated or reduced through source removal (e.g. line flushing, de-sludging) or decontamination techniques?			
Have work processes and special tooling been used to reduce time/exposure in the work area?			
Have engineered controls been used to minimize the spread of contamination and generation of airborne radioactivity?			
Are there special radiological training or monitoring requirements and are they identified in the work plan or RWP?			
Would the use of mock-ups for high exposure or complex tasks help reduce the dose in a cost effective manner?			
Have engineering, design and temporary shielding to reduce radiation levels been considered?			
Have walk-downs and/or or dry runs of the activity using applicable procedures been conducted?			
Have staging and preparation of necessary materials and special tools taken place in low dose rate areas?			

[1] Adapted from documents in use at Brookhaven National Laboratories, USA.

Topic	Yes	No	NA
Have prefabrication and shop work outside the radiation area been maximized?			
Have abnormal and emergency procedures and plans been reviewed?			
Has the line manager identified points where signatures and second party or independent verifications are required?			
Have success or completion criteria, with contingency plans to anticipate difficulties been established?			
Has there been a pre-job estimate of collective dose to be incurred for the job?			
If respiratory protection is required for the activity has an analysis been made to ensure that the total dose received is not increased to avoid an internal dose? If YES attach analysis that shows the total dose received with and without respiratory protection (Attachment 9.10).			
Have provisions for waste minimization and disposal been made?			

1. Radiological work anticipated to exceed the collective dose criteria of 7.5 man-mSv shall be reviewed and approved by the Department/Division ALARA Committee.

2. Optimization techniques, including cost–benefit analysis, represent a fundamental part of radiological design analysis and work review. For review of minor activities with low associated doses, a cost–benefit evaluation is an intrinsic part of the engineering review process and a detailed evaluation is not necessary. For review and planning of major tasks involving higher collective dose expenditures greater than 7.5 man-mSv, a detailed and documented evaluation shall be performed.

Radiological Management, ALARA Committee Chairman, Radiological Engineer or FS Representative:

Printed name/Signature: _____

DOSE ESTIMATE WORK SHEET

Job	Task	Number of persons	Task duration (h)	Dose rate (mSv/h)	Total dose for task (man-mSv)
Total	---------	-------	--------	-------	

PRE-JOB BRIEFING

RWP #_____

The topics to be covered are: (check all that apply)

Scope of work to be performed	Special dress requirements
Synopsis of work procedure to be followed	Any radiological hold points required during work
	Verify that workers' year to date dose has been determined
Radiation levels in the work area	Communication to be used during work
Low dose wait areas	Emergency communications available in area
Traverse routes to work area	Location of emergency exits in the work area
Supplemental dosimetry and its use	Emergency response provisions
Dose rate that will void RWP	Housekeeping requirements for the work area
Accumulated dose that will void RWP	Final cleanup responsibilities
Contamination levels in work area	Any additional special provisions of this RWP (list below)
Special contamination controls in effect for this RWP	
Contamination levels that will void RWP	
Minimum PCs required for work	
Location of entry and exit points including SOP	

Individual performing brief shall list all attendees

	Print name	Date:
1	_____	_____
2	_____	_____
3	_____	_____

Printed name/signature of facility support person conducting the pre-job briefing

PRE-JOB REVIEW FORM

Pre-job review check-off area

Issue reviewed	Date Completed
Scope of work to be performed	
Radiological conditions of the workplace	
Procedural and RWP requirements	
Validate that selected workers have current bioassay (If bioassay is required by RWP)	
Special radiological control requirements	
Radiologically limiting conditions, such as contamination or radiation levels that may void RWP	
Radiological control hold points	
Communications and coordination with other groups	
Provisions for housekeeping and final clean-up	
Emergency response provisions	

Determination if a department/division ALARA review is required:

1. Estimated individual dose is greater than the department limit (~1.0 mSv per day as at C-A) or the collective dose is greater than 7.5 person-mSv (the collective dose should be considered over a project, or work evolution, rather than an isolated phase of the project or work evolution).

❑ Yes ❑ No

2. Predicted airborne radioactivity exposures are in excess of 40 DAC-hours.

❑ Yes ❑ No

3. Work area removable contamination is greater than 100 times the values in Radcon Manual.

❑ Yes ❑ No

4. Entry into areas where dose rates exceed 10 mSv/hour ❑ Yes ❑ No

5. Potential radioactive releases to the environment that would result in an off site exposure of ≥1 mSv. ❑ Yes ❑ No

Completion of an ALARA review is required if a positive response is given to any of the above conditions.

The requirements for an ALARA review are found in the Radcon Manual, Chapter 3, Part 1, Section 312.A or in Attachment 9.4 of this procedure.

Comments

Person Performing the Review

Printed name _____ Signature _____ Date _____

POST-JOB REVIEW FORM

Date: _____ Time: _____ Work location: _____

Reason for post-job review (check applicable reason):

- An indicated collective dose of ≥7.5 person-mSv based on supplemental dosimetry has been accrued _____
- An indicated collective dose of >1.0 man-mSv based on supplemental dosimetry has been accrued and exceeds the estimated collective dose by ≥50% _____
- Stop radiological work authority was implemented _____
- A radiological awareness report was issued _____
- Significant lessons learned were identified _____
- Requested by the facility radiological representative _____
- Requested by the line manager _____
- Request made by any individual that performed work under the RWP

Discuss the following items as well as any other relevant topics. Attach additional notes/minutes to this form as applicable.

Review pre-job determinations. Were all aspects of the job properly considered? Explain.

Were there any lessons learned during this job that would help keep radiation exposures ALARA for future work activities? Explain.

Were there any other lessons learned during this job that would benefit future jobs? Explain.

Review conducted by: _____ _____

FS representative (printed name & signature) Date

Appendix III

QUALITY MANAGEMENT SYSTEM CHECKLIST

The following is a list of key questions that should be asked for establishing a sound quality management system. This is only a partial list of questions that should be asked; the organization may add more questions specific for own situation. The questions are divided into various sections for reconciliation with an applicable (national or international) quality standard (including GMP). A few comments are added for further clarification.

SECTION 1: GENERAL

Item	Question	Comments	Yes/No/NA
1.1	Has the organization defined its quality policy?	It is essential that the Organization management lays down the explicit quality policy that is to be followed by the staff. The policy should be communicated to the staff in unambiguous terms and resources provided to achieve the desired quality management system.	
1.2	Are the scope and objectives of the organization defined?	Resources allocation (building, staff, equipment, etc.) will be linked directly to the mission of the organization and its scope and objectives. For example, distribution of the radiopharmaceuticals to other facilities will entail additional equipment and arrangement for packaging and shipping.	
1.3	Are the products to be manufactured identified?	Production requirements for SPECT and PET radiopharmaceutical manufacturing are quite different.	
1.4	Have provisions been made for expansion of manufacturing to other products in the future?	Pre-planning will reduce many headaches in the future for expansion.	

Item	Question	Comments	Yes/No/NA
1.5	Is the applicable GMP standard (national or international) reviewed?	Radiopharmaceutical manufacturing should be performed under the guidelines of GMP with an aim to manufacture products conforming to the required quality and safety.	
1.6	Is the applicable radiation protection standard (national or international) reviewed?	Radioisotope handling must be performed under the guidelines of radiation protection practice with an aim to ensure radiation safety of the staff as well as the public.	

SECTION 2: ORGANIZATION AND PERSONNEL

Item	Question	Comments	Yes/No/NA
2.1	Is the organizational chart prepared?	There should be an organizational chart so that it is clear as to lines of authority and responsibilities.	
2.2	Are the staff qualifications defined for each position within the organization?	Qualifications include: education, training, and experience among other attributes. Supervisors should possess advanced education, training and experience.	
2.3	Are employees trained in GMP practices?	Training in applicable GMP should be made mandatory for all staff involved in production, as well as QC/QA.	
2.4	Is the job specific training and continuing education planned?	The organization should have an adequate ongoing programme for training employees in new procedures and operations and in the areas where deficiencies have been identified.	

Item	Question	Comments	Yes/No/NA
2.5	Are there adequate number of employees and supervisors assigned to perform various tasks?	Staffing levels should correspond to the size and complexity of the operations. Also, GMP regulations normally require second-person checks at various stages of production as well as test verification. Consultation services of experts should be available.	
2.6	Is the QC (or QA) unit established as an entity separate from the production unit?	Separation of the QC/QA unit from the production unit is required by most GMP guidelines. However, for a smaller production facility (such as, PET), a clear distinction may not be possible. The facility should define these functions within the framework of applicable GMP guidelines.	
2.7	Are the responsibilities and authorities of the QC unit defined and well communicated throughout the organization?	GMP necessitates defining the QC unit responsibilities and authority.	
2.8	Is a qualified person (QP) or the position identified to release the finished product for patient use?	It should be made very clear as to who is qualified and authorized to release the finished product.	

SECTION 3: FACILITY AND EQUIPMENT

Item	Question	Comments	Yes/No/NA
3.1	Is the facility size and functionality compatible with the scope and objectives of the organization?	The variety and volume of production will determine the size of the facility requirement. Space planning and utilization should take into consideration radiation protection of the worker along with protection of the product quality.	
3.2	Are the production areas compatible with pharmaceutical manufacturing?	Critical factor in aseptic manufacturing is the microbial and particulate control of the environment in production areas.	
3.3	Is the clean room environment adequate for the purpose? Is the air class status monitored?	Pharmaceuticals that are not terminally sterilized necessitate Class 100 air environment in the immediate vicinity of the open product. Air quality and clean room classification needs to be regularly evaluated.	
3.4	Is the facility conducive to safe radiation practice?	Shielding of high radiation areas is required. Use of remote or automated equipment for handling radioactive sources is recommended.	
3.5	Does the facility have an effective cleaning and sanitization routine?	Aseptic processing is helped by proper cleaning of the production areas. Neat and clean appearance breeds discipline and enhancement of quality operations.	
3.6	Is there a provision for controlled storage of the raw materials?	Inventory should be maintained to avoid unpleasant surprises.	
3.7	Is the equipment appropriate for intended application?	Equipment used in the production, processing, or packaging would have to be appropriate for the performance of its intended function.	

Item	Question	Comments	Yes/No/NA
3.8	Is the production equipment compatible with planned products to be manufactured? Is there a sufficient number of production equipment?	Radiopharmaceuticals production necessitates production equipment that takes into account not only the product realization and quality, but also radiation protection. Some duplication is desirable and even unavoidable.	
3.9	Is the QC equipment appropriate for analytical work to be performed?	QC equipment should deliver the expected results with required accuracy and precision.	
3.10	Is the equipment maintained regularly? Is it in a good state of repair?	All equipment should be maintained regularly and be in good working order at time of use.	
3.11	Is sufficient technical support available for equipment repair?	People qualified to repair the equipment should either be available on-site or on call from the manufacturer.	
3.12	Is there a log or record for usage, cleaning, repair and calibration?	Logs need to be kept which include an entry every time the equipment is used, repaired and/or calibrated.	
3.13	Is there an overall system to report mechanical or equipment failures and are repairs tracked to completion?	There needs to be a tracking system that ensures that repairs are carried out in a timely manner and raises a flag if they are not completed in a reasonable time. ‘out of order’ equipment must be clearly identified to avoid inadvertent use.	

Item	Question	Comments	Yes/No/NA
3.14	Is the equipment validated at the time of installation? Is the equipment validated after major repair?	Newly installed equipment should be qualified (validated) before first use to verify that it was installed correctly and is capable of operating as intended. When operated under actual production parameters or selected method, the equipment should produce consistent results within established specifications.	
3.15	Are controls established for equipment calibration?	Where needed, calibration should be performed prior to the use of the equipment for the intended task. Facilities should follow calibration checks.	

SECTION 4: MANUFACTURING

Item	Question	Comment	Yes/No/NA
4.1	Has the organization identified the applicable national or international GMP standard?	Pharmaceutical manufacturing is controlled by the national standard of GMP. In the absence of a national standard, international guidelines such as those of WHO should be adopted.	
4.2	Has the organization identified products it will manufacture?	Protocols and procedures, and resources allotment will be linked directly with the variety and volume of production.	
4.3	Are the product specifications defined?	Product specifications are derived from national or international pharmacopoeia. These pre-established specifications are to be achieved prior to release of a product batch for patient use.	

Item	Question	Comment	Yes/No/NA
4.4	Are production processes defined?	Processes are designed to achieve the required product attributes. These are documented in the production batch records and SOPs.	
4.5	Are the production processes validated?	Prior to implementation, the defined processes and procedures should be validated for performance.	
4.6	Is provision made to monitor the processes?	Processes should also be monitored for performance and for continued suitability.	
4.7	Are the staff adhering to the GMP and SOPs during manufacturing?	Adherence to GMP during manufacturing should be monitored and assured. Deviation from the SOPs and breach of GMP protocols should not be allowed. Product should be rejected if it is evident that there have been deviations. All deviations should be investigated and corrective actions applied for non-recurrence in the future.	
4.8	Do employees wear proper protective clothing in designated areas?	Product protection and operations in the clean areas necessitate proper gowning and gloving to reduce microbiological contamination and to enhance product quality.	
4.9	Are labels attached to all products and raw materials?	An unambiguous labelling must be practiced.	
4.10	Is the current SOP available at the job site?	All SOPs should be readily available to the people working in the area without the necessity of leaving the area.	

Item	Question	Comment	Yes/No/NA
4.11	Are procedures established for raw materials procurement?	Raw materials procurement and storage should be controlled. Vendors should be qualified.	
4.12	Are procedures established for qualification of the raw materials prior to use in production?	Only accepted raw materials should be used in production.	
4.13	Are raw materials and components stored appropriately?	Raw materials should be controlled to avoid mix ups and deterioration because of poor storage conditions.	
4.14	Are procedures established for in-process sample specifications and testing?	In order to continue with production, it is sometimes necessary to evaluate the in-process materials (e.g., radiochemical bulk).	
4.15	Are controls in place to avoid cross-contamination?	Manufacturer should ensure that possibility of contamination of a product from another one is eliminated. Single product per hot cell, for example, is a possible answer.	

SECTION 5: QUALITY CONTROL

Item	Question	Comment	Yes/No/NA
5.1	Does the QC/QA unit exist as a separate organizational entity?	To the extent possible, the QC/QA unit should exist as a separate entity. In some situations such as a small PET production facility, this may not be possible. Arrangements should be made within the scope of the GMP regulation (refer to Section 2.6).	
5.2	Does the QC/QA unit alone have both the authority and responsibility to approve or reject all components, drug product containers and closures, in-process materials, packaging materials, labelling and the finished products?	The QC/QA unit should have final authority for the release of a product and may not be overridden by any other authority such as facility management.	
5.3	Does the QC/QA unit routinely review production records to ensure that procedures were followed and properly documented?	This review is required. Records should reflect the specifications being achieved for each product batch, including identity, strength, quality, purity, and, if appropriate, sterility.	
5.4	Is adequate laboratory space, equipment, and qualified personnel available for required testing?	The laboratory space and equipment should be sufficient to ensure that all testing may be carried out easily and without the possibility of contamination from other testing.	

Item	Question	Comment	Yes/No/NA
5.5	Are all the laboratory procedures validated?	Confidence in results obtained from the applied test procedures will be high when all procedures have been thoroughly validated for the intended application. It is essential to know the accuracy, precision and limitations of the procedures being applied.	
5.6	Is there an adequate system of sampling and testing?	The analyte (raw material, in-process material, or the finished product) being tested should be a representative sample of the bulk. The test material should not be released until appropriate laboratory testing is completed, reviewed, and approved by an appropriate releasing authority.	
5.7	Is there an adequate system of reporting test results and documentation?	The product batch record should include test results in raw form, as well as the reported results after review.	
5.8	Is the procedure established for handling a product batch that does not conform to the required specifications?	A non-conforming product batch is to be rejected. Remedial actions, if applicable, to correct the non-conformity should be formally evaluated by the production and the QC/QA units.	
5.9	Are all reagents and standards appropriately handled and stored?	Standards should be traceable and carefully handled to avoid adulteration and contamination.	
5.10	Is there a schedule established for quality audits?	Regular audits of the QA/QC unit should be done to ensure proper procedures are in place and are being followed.	

SECTION 6: DOCUMENTATION

Item	Question	Comment	Yes/No/NA
6.1	Are controls established for good documentation?	Documentation is the primary feature of a sound QMS. If it is not documented, it did not happen! Therefore, the organization should ensure a good documentation practice.	
6.2	Are procedures formulated for documents preparation, review and approval?	Written procedures should be established for how the documentation will be done.	
6.3	Are the SOPs and BRs prepared according to the GMP guidelines?	Batch records and SOPs are the road maps that are to be followed to achieve the planned results. Therefore, these documents should be derived from validated procedures.	
6.4	Are the procedures established for issuance of current SOPs and BRs?	QC/QA should be given the responsibility and authority of document control.	
6.5	Are the procedures established for removal of the obsolete documents?	There should be a written procedure on how to replace old records with newer versions as modifications are made.	
6.6	Are procedures formally controlled so that only one version is available at any given time?	Only the current version of SOPs and batch records should be available at any given time. The QA unit should take custody of the replaced documents.	

Item	Question	Comment	Yes/No/NA
6.7	Is there a revision history maintained for all documents?	Each document should be identified with a revision number to maintain the history of the changes made.	
6.8	Is there a formal documentation change control procedure?	Modification of documents must be controlled. There should be a written procedure for changing documents.	
6.9	How often are procedures reviewed and revised?	There needs to be a set schedule for review.	
6.10	How are the changes made in processes incorporated into documents?	There should be a formal procedure for changing a process or procedure. Once the process or procedure has been validated, the modifications should be incorporated into new working documents (SOPs and BRs).	
6.11	Has the organization identified the records it should keep?	Records such as batch records, SOPs, equipment maintenance, calibrations, staff training should be kept for a period of time as defined by national regulations.	
6.12	Are the customer satisfaction surveys and complaints recorded?	For the organization distributing products to other users should maintain good customer relations through appointing a person or a unit to handle customer relations.	

Appendix IV

EXAMPLES OF PRODUCTION BATCH RECORDS AND SOPS: RAW MATERIAL CONTROL SPECIFICATIONS FOR THALLIUM CHLORIDE RADIOCHEMICAL BULK*

Batch records (BRs) and standard operating procedures (SOPs) pertaining to manufacturing and quality control of thallium chloride ^{201}Tl radiopharmaceuticals are given in the following sections. These are only representative examples of BRs and SOPs used at one particular radiopharmaceutical manufacturing facility. While reviewing these examples, attention should be focused on the style and flow of instructions rather than on technical details. Every production facility should develop their own protocols and procedures ensuring their applicability and suitability for the purpose.

In general, BRs and SOPs should be written as a set of simple instructions that can be easily followed by the operator. Some other features in such documents include: issuance dates; revision numbers; document number; production batch identification number; raw material numbers, etc. Such detail is essential for control of documents ensuring that only the approved and the most current procedures are being practiced. Furthermore, with this kind of accurate record-keeping, it is easy to trace all the raw materials and components that were incorporated into the product, facilitating trouble-shooting and investigations in the case of a product failure.

* Appendices IV–IX are adapted from documents in use at the Cyclotron and Radiopharmaceuticals Department, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.

Raw Material Control
Specifications for Thallium Chloride (Tl-201)

Quality Control Section
Raw Material Control

PRODUCT: **THALLIUM CHLORIDE Tl-201 RADIOCHEMICAL BULK**	Revision No.	Effective Date:	Page 1 of 1
	Prepared by:		Date:
ITEM CODE: **05-653**	Reviewed by:		Date:
	Approved by:		Date:

SPECIFICATIONS AND SAMPLING PLAN

TEST	SPECIFICATION	SAMPLING PLAN
1. Radionuclide Identification	The gamma-ray spectrum must reveal the presence of photo peak energies of 167 and 135 KeV.	0.002 ml of the Radiochemical Bulk.
2. Radionuclidic Purity. Tl-201 Tl-202 Pb-201&Pb-203 Tl-200	 Not Less Than 99.0% Not More Than 0.8% Not More Than 0.1% Not More Than 0.1%	 Determine from Item #1.
3. Specific Concentration as Tl-201 At Calibration Time and Date. Total Activity Volume	 Record Reading Record Reading Record Reading	Determine from Item #1.
4. pH.	5.0 – 7.5	0.005 ml.
5. Thallium Spot Test.	NMT 0.5 ug/mCi Tl-201	0.1 ml.
6. Copper Spot Test.	NMT 1.0 ug/mCi Tl-201	0.2 ml.
7. Iron Spot Test.	NMT 2.5 ug/mCi Tl-201	0.1 ml.

NMT: not more than.

Appendix V

SOP FOR THE QUALITY CONTROL OF THALLIUM CHLORIDE RADIOCHEMICAL BULK

Quality Control Section Raw Material Control			
PRODUCT: THALLIUM CHLORIDE Tl-201 RADIOCHEMICAL BULK	Revision No.	Effective Date:	Page 1 of 4
	Prepared by:		Date:
ITEM CODE: 05-653	Reviewed by:		Date:
	Approved by:		Date:

TEST METHOD

	METHOD
1. Radionuclide Identification , Radionuclidic Purity and Specific Concentration.	General 1. Radionuclidic purity and Identity test is a quantitative and qualitative analysis of a sample of radioactive material. 2. The volume of the sample must be accurately measured as the product dilution is dependent on this assay. Use capillary or calibrated pipets. If the pipets are calibrated to contain, rinse the pipet with diluent and add the rinses to the point source. 3. Dead time must be less than 10%. Sample size or counting geometry can be adjusted to meet the dead time criteria. 4. Use only calibrated MCA Ge(Li), NaI or any other counting system, calibrated for both energy vs. channel number and energy vs. efficiency. 5. The analyst must be familiar with MCA series Canberra Model 1510 or any equivalent MCA series operations. Procedure 1. Take a point source card which is a pre-cut cardboard 2x2 inches in size. 2. Fill a 1ul pipet with Tl-201 Chloride bulk sample. Carefully wipe off the excess sample on the outside wall of the pipet. 3. Place the filled pipet over the center of the point source card and cover with a piece of transparent tape. 4. Place the line source in the appropriate counting geometry. There are two calibrated counting geometries in the system; 10 and 20 cm. Note: The counting geometry or the sample size may be adjusted such that the dead time is less than 10%. 5. Set the counting time (live time) depending on the activity of the sample, usually 300 seconds. For **MCA Canberra Model 1510 Operation Procedure refer to SOP # 04-03-007.** 6. Count, analyze and take a plot of the spectrum.

Quality Control Section Raw Material Control			
PRODUCT: **THALLIUM CHLORIDE Tl-201 RADIOCHEMICAL BULK** **ITEM CODE:** **05-653**	Revision No.	Effective Date	Page 2 of 4
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

TEST METHOD

	Radionuclide Identification The gamma-ray spectrum of Tl-201 bulk sample must contain only photopeaks identifiable with the gamma-ray transition energies found in the decay scheme of the Tl-201. Identify all the photopeaks. If there are peaks in the Tl-201 Spectrum that are not in the standard spectrum, determine the source. If unable to resolve, notify the supervisor. Radionuclidic Purity and Specific concentration Radionuclidic purity of Tl-201 chloride refers to the proportion of radioactivity due to the Tl-201 in the total radioactivity measured. Radionuclidic impurities may arise from impurities in the target materials and excitation functions at the energies of the bombarding particles during production. The results printed out are in uCi/ml. Convert to mCi/ml. Calculate the specific concentration of Tl-201, the percentage of Tl-201and the percentages of the different radiocontaminants in the sample.
Volume	Volume of the Radiochemical Bulk Refer to the batch record and obtain the volume of the material.
Total Activity	Total Activity as Tl-201 Determine the total activity of the Radiochemical bulk as follows: Total Activity in mCi = Volume in ml x Specific concentration in mCi/ml
2. pH.	Determine the pH of the sample using pH paper with suitable range.
3. Thallium Spot Test.	1. Transfer 0.1 ml of sample, 0.1 ml of standards 1 & 2 ug Tl/ml and 0.1 ml of blank (De-ionized water) into separate 10 x 75 mm test tubes. 2. To each test tube add in the order given: 3 drops of bromine water 2 drops of 10% Sulfosalicylic acid. 2 drops of 12 M HCl. 3 drops of 0.05% rhodamine B 14 drops of benzene

Quality Control Section Raw Material Control			
PRODUCT: **THALLIUM CHLORIDE Tl-201 RADIOCHEMICAL BULK** **ITEM CODE:** **05-653**	Revision No.	Effective Date:	Page 3 of 4
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

TEST METHOD

	3. Vortex each tube vigorously for 10 seconds. 4. Let stand until the layers separate. The top layer or the benzene layer will appear red to violet pink, depending on the amount of thallium present. 5. Visually compare the color of the sample against the standards and the blank against a white background. 6. Report which standard the sample color comes closest. 7. Obtain the specific concentration of Tl-201 bulk solution at calibration time and date 8. Calculate the ugTl+/mCi Tl-201 as follows: $$\text{ug Tl/mCi Tl-201} = \frac{\text{Tl conc. (spl.) in ug/ml}}{\text{Specific Concentration of Tl-201 in mCi/ml}}$$
4. Copper Spot Test.	1. Transfer 0.2 ml of sample, 0.2 ml of standards 2 & 4 ug Cu/ml and 0.2 ml of blank (De-ionized water) into separate 10 x 75 mm test tubes. 2. Add 0.3 ml of Concentrated Hydrobromic Acid HBr (48 %) to each tube and observe the color change. The color will vary from violet to brown depending on the amount of copper present. 3. Visually compare the color of the sample against the standards and blank. 4. Obtain the specific concentration of the bulk material at calibration time and date. 6. Calculate the ug/ml Cu/mCi as follows: $$\text{ug Cu/mCi Tl-201} = \frac{\text{Cu conc. (spl) in ug/ml}}{\text{Specific Concentration in mCi/ml}}$$

Quality Control Section Raw Material Control			
PRODUCT: **THALLIUM CHLORIDE Tl-201 RADIOCHEMICAL BULK** **ITEM CODE:** **05-653**	Revision No.	Effective Date:	Page 4 of 4
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

TEST METHOD

5. Iron Spot Test.	1. Transfer 0.1 ml of sample, 0.1 ml of standards 1 & 5 ug Fe/ml and 0.1 ml of blank (De-ionized water) into separate 10 x 75 mm test tubes. 2. Add 0.1 ml of 6 N HCl to each tube. 3. Heat contents of each tube. 4. Allow to cool. 5. Add 0.1 ml 5% solution of Potassium thiocyanate KSCN to each tube and observe the color change. Depending on the amount of Fe+++ present, the color will vary from pink to red. 6. Visually compare the color of the sample against the standards and the bulk against white backgrounds. 7. Express results as a range between the two standards. 8. Obtain the specific concentration of the bulk material at calibration time and date. 9. Calculate the ug Fe+++/mCi as follows: $$\text{ug Fe/mCi Tl-201} = \frac{\text{Fe conc. (spl.) in ug/ml}}{\text{Specific concentration in mCi/ml At calibration Time and Date}}$$

Appendix VI

TEST RECORD OF
THALLIUM CHLORIDE RADIOCHEMICAL BULK

Quality Control Section
Raw Material Control Record

PRODUCT: **THALLIUM CHLORIDE Tl-201 RADIOCHEMICAL BULK**	Revision No.	Effective Date:	Page 1 of 2
	Prepared by:		Date:
	Reviewed by:		Date:
ITEM CODE: **05-653** **LOT NO. :** _____	Approved by:		Date:

Manufacturing Date: _____

Calibration Date/Time: _____12:00

Expiration Date/Time _____12:00

1. Radionuclide Identification.	The gamma-ray spectrum must reveal the presence of photo peak energies of 167 and 135 KeV.	_____	
2. Radionuclidic Purity.			
Tl-201	Not Less Than 99.0%	_____%	
Tl-202	Not More Than 0.8%	_____%	
Pb-201&Pb-203	Not More Than 0.1%	_____%	
Tl-200	Not More Than 0.1%	_____%	
3. Specific Concentration as Tl-201 At Calibration Time and Date.	Record Reading	_____mCi/ml	
Total Activity	Record Reading	_____mCi	
Volume	Record Reading	_____ml	
4. pH.	5.0 – 7.5	_____	
5. Thallium Spot Test.	NMT 0.5 ug/mCi Tl-201	_____ug/mCi Tl-201	
6. Copper Spot Test.	NMT 1.0 ug/mCi Tl-201	_____ug/mCi Tl-201	
7. Iron Spot Test.	NMT 2.5 ug/mCi Tl-201	_____ug/mCi Tl-201	

Production Record and Test Data:
Reviewed By: _____ Date: _____

Disposition : Released _____ Rejected _____

By : _____ Date : _____

Appendix VII

PRODUCTION BATCH RECORD FOR THALLOUS CHLORIDE INJECTION

RADIOPHARMACY BATCH RECORD

Product: Thallous Chloride Tl-201 Injection	REVISION NO.:	EFFECTIVE DATE:	Page 1 of 5
Description: Sterile, Apyrogenic, Isotonic Solution of Tl-201 in 0.9% Sodium Chloride, pH 4.5 - 7.5	PREPARED BY:		DATE
Item Code: 201.4	REVIEWED BY:		DATE
Lot No.: _____	APPROVED BY:		DATE

	Operator	Check
Batch Record Approved for Used:_____ Q.A. Signature _____ Date		
Date of Manufacture: _____ Total Activity: 5.0 mCi/vial Calibration Time/ Date: 12:00 / _____ Volume: 5.0 mL/vial Expiration Date: _____ Concentration: 1.0 mCi/mL (72 Hours Post Calibration) **PRODUCT LABEL SAMPLES** **VIAL LABEL**		
SHIELD LABEL		

Product: Thallous ChlorideTl-201 Injection	REVISION NO.:	EFFECTIVE DATE:	Page 2 of 5
Item Code: 201.4			
Lot No.: _____	APPROVED BY:		DATE

A. Materials:

	Description	Quantity	Item Code #	Lot #	Operator	Check
1.	Tl-201 Chloride Solution	_____mCi _____mL	05-653	_____		
2.	0.9% sodium Chloride Injection 100 mL Expiration Date:_____	_____mL	15-015	_____		
3.	Depyrogenated Serum Vials, 10 mL Expiration Date: _____	_____	25-062	_____		
4.	Sterile Stoppers, 20 mm, Grey Expiration Date: _____	_____	25-071	_____		
5.	Flip-off Seals, 20 mm, Yellow	_____	25-024	_____		
6.	Millex-GS Filters 0.22 µm Expiration Date: _____	_____	20-014	_____		

B. Preparation for Manufacturing:

1. Prepare materials for Radiopharmaceuticals formulation according to SOP-08-01-008.
2. Prepare aluminum seals according to SOP-08-01-005.
3. Perform cleaning and preparation of Laminar Flow Hood (LFH) according to SOP-04-06-002.
4. Perform aseptic processing according to SOP-02-04-001.
5. Assemble dispensing apparatus according to SOP-04-03-001.
6. Put label on vials to be filled and place in LFH in clean lead containers.
7. Perform environment and operators monitoring-aseptic handling according to SOP-02-04-002.
8. Prepare shields and vials for final packing according to SOP-08-01-009.

C. Manufacturing Procedure

1. Activity and Volume required for Production:

No. of Vials		Activity/ Vial		Total Activity
_____	X	5.0 mCi	=	_____mCi

Product: Thallous ChlorideTl-201 Injection **Item Code:** 201.4	REVISION NO.:	EFFECTIVE DATE:	Page 3 of 5
Lot No.: _____	APPROVED BY:		DATE

	Operator	Check
2. Radiochemical Data a. Volume Received _____ mL b. Activity Received _____ mCi c. Calibration Date _____ Time: _____		
3. Total Radiochemical Bulk Transfer : Yes _____ No _____ (If less than total transfer, show calculations below): **Calculations for Radiochemical Bulk Transfer:** Total Activity Required / Concentration / Bulk Volume Required _____mCi ÷ _____mCi/mL = _____mL		
4. Final Product Volume: _____mCi ÷ 1.0 mCi /mL (Final Volume of Product) = _____mL		
5. Volume of diluent needed: Final Volume / Rad. Chem Bulk Used / Total Diluent _____mL - _____ mL = _____ mL		
6. Add to the Tl-201 bulk the 0.9% Sodium Chloride diluent equivalent to the amount in Step #5: Diluent added _____ mL		
7. To the bulk vial attach a long drawing needle with 0.22 µm filter and needle vent. Connect vacuum line to vent needle. Re-circulate to mix for five minutes. 8. Connect bulk vial to dispensing machine and re-circulate to purge bubbles from lines. 9. Dispense 1 to 2 ml in a shielded vial and send to QC for "In-Process Testing"; wait for the results of analysis. Test No. _____ (In process test logbook). Attach results sheet to batch record.		
10. Radiopharmaceutical product filling and assay: (Note: Assay activity periodically at random and adjust the filling volume if needed.) a. Dispense 5.0 mL of diluted bulk in a vial and measure activity in dose calibrator. (Tl-201 Preset) b. Activity _____ Time _____ Hours to Decay _____ Activity _____ x {DF} _____ = _____mCi (Should be within 4.75 to 5.25 mCi i.e. within ± 5% of average). c. Dispense required number of vials. Place first and last filled vials in the appropriately marked shields.		

Product: Thallous ChlorideTl-201 Injection Item Code: 201.4 Lot No.: _____	REVISION NO.:	EFFECTIVE DATE:	Page 4 of 5
	APPROVED BY:		DATE

	Operator	Check
11. Bubble point test (Millipore filter); according to SOP-06-01-002. Results: _____		
12. Autoclave the vials together with biological and autoclave strip indicators. Refer to SOP-08-01-002).		
13. Allow vials to cool, then assay and transfer to labeled shields. Attach the sssay record and autoclaving record to the batch record. Save first and the last vials for Q.C.		
14. Transfer the settling plates and Autoclave Test (Biological Indicator) to Q.C. for incubation.		
D. Reconciliation Record:		
1. Radiochemical: Received: _____mL _____ mCi Retained : _____mL Used for Product: _____mL (Equivalent to step 4)		
2. Product Formulation: Sodium Chloride: _____mL Radiochemical Bulk: _____mL Total Volume: _____mL		
3. Vials Prepared: Vials Filled: _____ Vials Rejected _____ Vials to QC: _____ Vials for Distribution: _____		

Product: Thallous ChlorideTl-201 Injection **Item Code:** 201.4		REVISION NO.:	EFFECTIVE DATE:	Page 5 of 5
Lot No.: _____		APPROVED BY:		DATE

Operator | Check

4. Volume:

Used in Filling: _____ mL
Remaining in Line _____ mL
Quality Control _____ mL
Others _____ mL
Stored for Decay _____ mL
Total Volume _____ mL

	Issued	Rejected	U S E D				Return	Total
			Rec	Prod	Batch	Cust		
Vials								
Shields								

E. Labels:

Q.A.

Batch record is complete and accurate. Returned labels disposed.

Operator: _____ Date: _____ Initial:_____
Checker: _____ Date: _____ Initial:_____
Supervisor: _____ Date: _____ Initial:_____
QA: _____ Date: _____ Initial:_____

Appendix VIII

STANDARD OPERATING PROCEDURE FOR QUALITY CONTROL OF THALLOUS CHLORIDE INJECTION

Quality Control Section Finished Product Control			
PRODUCT: **THALLOUS CHLORIDE (TL-201) INJECTION**	Revision No.	Effective Date:	Page 1 of 5
	Prepared by:		Date:
ITEM CODE: **201.4**	Reviewed by:		Date:
	Approved by:		Date:

TEST METHOD	
1. Sterility Test.	**Note:** Because of the radioactive decay the product can be released prior to the completion of the test. The test is usually done in groups with other lot numbers and with other products. For the complete procedure refer to **Sterility Testing, Radiopharmaceuticals and Raw Materials SOP# 06-06-007.**
2. Pyrogenicity.	Note 1: Perform in duplicate. Note 2: Use the sample as it is without dilution. Note 3: Positive and Negative controls for both the one hour standard bacterial endotoxins test and the 20 minutes test must be done every saturday. 1. Dispense 0.1ml of the product into each 0.1ml reconstituted LAL tubes. (Sample). 2. Dispense 0.1ml of sterile water for injection USP or BP into each 0.1ml LAL tubes. (Negative Control) 3. Dispense 0.1ml of 0.25 EU/ml CSE in sterile water which is prepared monthly into each 0.1ml reconstituted LAL tubes. (Positive Control) 4. Mix each tube gently. 5. Incubate each tube undisturbed in dry block incubator for 60 minutes at 37 ±1º C. At the end of the incubation period, record the positive, negative and sample results. Report as "pass" if the negative controls and samples do not gel and the positive controls form a firm gel.
3. pH.	Determine the pH of the sample using pH paper with suitable range.
4. Radionuclide Identification & Radionuclidic Purity.	Transfer the results of the same test from Tl-201 Chloride Radiochemical Bulk used in the preparation of the finished product.
5. Radiochemical Purity.	Materials ITLC (SG) Gelman product No. 61886 Seprachrom chamber NaI (Tl)-detector coupled with SCA or Radiochromatogram Scanner. Micropipets 2 ul.

Quality Control Section Finished Product Control			
PRODUCT: THALLOUS CHLORIDE (TL-201) INJECTION **ITEM CODE:** 201.4	Revision No.	Effective Date:	Page 2 of 5
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

TEST METHOD

Chromatography Solvents
Primary solvent - 100% Acetone (HPLC grade)
Secondary solvent - 100% Methyl ethyl ketone
Development Time
3 minutes

Method

A. Sample application
1. Remove chromatogram chamber from base.
2. Make a pencil mark thru hole #2 and hole #3. This marks the origin.
3. Spot the required amount of sample,usually 2 ul with a micropipet thru hole #1 and hole #4.
4. Let spots dry. Visualize wet spots by back lighting the chamber.

B. Migration
1. Pour approximately 4.0 ml of solvent into camber base.
2. After spots are dry, insert chromatogram chamber into base until lower edge is about 2 mm above solvent level.
3. Equilibrate for 15 seconds.
4. Gently ease chamber evenly into solvent all the way to the bottom of base. When in position, do not move chamber.
5. Allow migration to continue until the solvent front just reaches the solvent frontline. The solvent front may be visualized by back lighting the chamber
6. Immediately separate chamber from base.
7. Immediately pull tabs in opposite directions to open chamber. With a pencil, mark the solvent front. Let ITLC dry thoroughly at room temperature.

C. Chromatography Analysis
I. Scanning Method: pass the ITLC under the scanner's radiation Detector.
Note: The ITLC strip should be wrapped in cellophane tape or

TEST METHOD

paper before passing through the scanner to allow for ease of handling and to prevent scanner contamination from loose radioactivity. For **Bioscan S200 Analyzer Operation Procedure refer to SOP# 04-03-08.**

II. Manual Strip Counting Method (Alternative Method)

1 Measure the distance from the origin to the solvent front. Record.
2 Prepare a TLC by cutting the strip in half between hole #2 and hole #3, then cut into two portions:
Cut 1 - Beginning of strip to R_f 0.50 (R_f 0.00 – 0.50)
Cut 2 - R_f 0.50 to end of strip (R_f 0.50 – 1.00)
3 Calculate the R_f value as follows:

$$R_f = \frac{\text{Distance travelled by the spot from origin}}{\text{Distance travelled by solvent front}}$$

4 Place each portion into a separate counting tube.
5 Using standard geometry and set count time, count the radioactivity In each counting tube. The counting tube must be at the same distance from the detector and in the upright position throughout the Counting time. (Gross count)
6 Take a background count.
7 Determine net counts(Gross counts-Background counts)
8 Calculate percentage in each cut. For example

$$\%\text{at } R_f\ 0.0 – 0.50 = \frac{\text{Net counts in Cut1}}{\text{Total net counts in Cuts 1 and 2}} \times 100$$

9 Not less than 95% of the activity must be contained in Cut 1 (R_f 0.0 – 0.50).
10 Record all data in the test record sheet.
11 R_f of interest
Cut 1 (R_f 0.0 - 0.5) - Tl-201 (Tl+)
Cut 2 (R_f 0.5 - 1.0) - Tl-201 (Tl+++)

Quality Control Section Finished Product Control			
PRODUCT: THALLOUS CHLORIDE (TL-201) INJECTION **ITEM CODE:** 201.4	Revision No.	Effective Date:	Page 4 of 5
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

TEST METHOD

6. Osmolality.	Determine in duplicate the Osmolality using 15 ul of the sample, for the **Fiske One-Ten Osmometer Operation refer to SOP# 04-03-011.**
7. Visual Inspection.	**Materials:** Spot light: intensity between 100-300 foot-candles. White and black background. Magnifying lens. **Procedure:** Note 1: The sample (the vial) to be tested must be free of attached labels. Note 2: The light source may be positioned above, below, or behind the sample being inspected. Note 3: The white background aids in the detection of dark colored particles, light or retractile particles will appear against the black background. 1. Hold the vial from the top and carefully swirl contents by rotating the wrist to start contents of the container moving in a circular motion. Note 2: Vigorous swirling will create air bubbles, which should be avoided Note 3: Air bubbles will rise to the surface of the liquid, this helps to differentiate them from particulate matter. 2. Hold the vial horizontally about 4 inches below the light source against a white and black background. Light should be directed away from the eyes of the inspector and hands should be kept from under the light source to prevent glare. 3. Inspect the color of the solution; it must be clear and colorless. If no particles are seen, invert the vial slowly and observe for heavy particles that may not have been suspended by swirling. Inspect the patient vial if the inspected QC vial has visible particles or if the solution is not clear or if it is colored. Reject the lot if the patient's vial does not pass the test.

Quality Control Section Finished Product Control			
PRODUCT: **THALLOUS CHLORIDE (TL-201) INJECTION**	Revision No.	Effective Date:	Page 5 of 5
	Prepared by:		Date:
ITEM CODE: **201.4**	Reviewed by:		Date:
	Approved by:		Date:

TEST METHOD

8. Specific Concentration.	Refer to test method for the same test of Tl-201 Thallous Chloride Radiochemical bulk.
9. Total Activity per vial.	Review the radioactivity assay record sheet; reject any low or high fill. Randomly, assay three vials in calibrated dose Calibrator using Tl-201 pot. Setting. Calculate the activity of each vial at CalibrationTime/Date. Take the average of the three readings and record the results.
10. Final Package Inspection.	Packaging and labeled vials must be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label information and proper packaging components. Procedure 1. Carefully examined the labels for identity and conformity to the labeling specified in the batch production record. 2. Inspect the crimping; any vials with loose or dented crimps must be rejected. 3. Inspect the labels; any vial or shield with damage or faded label must be rejected.
11. Reserve Sample.	Collect a representative sample of each lot as reserve. Log it in the reserve sample logbook and store in appropriate place. Samples must be retained for at least three months after the expiration date.

Appendix IX

QUALITY CONTROL RECORD FOR THALLOUS CHLORIDE INJECTION

Quality Control Section
Finished Product Control Record

PRODUCT: **THALLOUS CHLORIDE (TL-201) INJECTION**	Revision No.	Effective Date:	Page 1 of 6
	Prepared by:		Date:
	Reviewed by:		Date:
ITEM CODE: **201.4** **LOT NO. :** _____	Approved by:		Date:

Except for sterility test, each lot must meet all specifications prior to release.
Manufacturing Date: _____

Calibration Date/Time: _____ 12:00

Expiration Date/Time: _____12:00

Tl-201 Bulk used:
Item Code: 05-653

Lot No.:_____

1. Sterility.	Must be sterile.	Refer to Sterilitylogbook.	
2. Pyrogenicity.	Must be apyrogenic.	_____	
3. pH.	4.5 – 7.5	_____	
4. Radionuclide Identification.	The gamma-ray spectrum must reveal the presence of photopeak energies of 167 and135 KeV.	_____	
5. Radionuclidic Purity.			
Tl-201	Not less than 99.0 %	_____ %	
Tl-202	Not more than 0.8%	_____ %	
Pb-201 and Pb-203	Not more than 0.1%	_____ %	
Tl-200	Not more than 0.1%	_____ %	
6. Radiochemical Purity.	Not less than 95%	_____ %	
7. Osmolality.	250 – 350 mOsmo/Kg	_____ mOsm/Kg	
8. Visual Inspection.	Must be clear, colorless and free from visible particles.	_____	
9. Specific Concentraton.	0.9 – 1.1 mCi/ml	_____ mCi/ml	
10.Total Activity at Calib.Time/Date	4.50 – 5.50 mCi/vial	_____ mCi/vial	

Quality Control Section
Finished Product Control Record

PRODUCT: **THALLOUS CHLORIDE (TL-201) INJECTION**	Revision No.	Effective Date:	Page 2 of 6
	Prepared by:		Date:
ITEM CODE: **201.4**	Reviewed by:		Date:
LOT NO. : _____	Approved by:		Date:

Except for sterility test, each lot must meet all specifications prior to release.

Manufacturing Date: _____

Calibration Date/Time: _____ 12:00

Expiration Date/Time: _____12:00

Tl-201 Bulk used:
Item Code: 05-653

Lot No.:_____

11. Final Package Inspection	Conforms to packaging prescribed.	Sample: _____ Ac ____ Re ____ No. of Defectives: ___	
12. Reserve Sample.	Received, logged and stored.	_____	

Q.C. Status : Pass _____ Fail _____

By: _____ Date: _____

For Q.A. use only:

Production Record Review: Reviewed By: _____

Quality Control Record Review: Reviewed By: _____

Product Disposition : Released ____ Rejected _____

By : _____ Date : _____

Quality Control Section
Finished Product Control Record

PRODUCT: THALLOUS CHLORIDE (Tl-201) INJECTION	Revision No.	Effective Date:	Page 3of 6
ITEM CODE: 201.4	Prepared by:		Date:
LOT NO. : _____	Reviewed by:		Date:
CALIB. TIME/DATE: 12:00 _____	Approved by:		Date:

BACTERIAL ENDOTOXIN TEST

Time On : _____ Dry-Block Temp. : _____

Time Off : _____ Dry-Block Temp. : _____

Samples	**Results**
Sample	( ) ( )
Positive Control	( ) ( )
Negative Control	( ) ( )

LAL R&S # : _____

E. Coli Endotoxin R&S # : _____

Concentration of Positive Control : _____EU E. Coli/ml

_____ng E. Coli/ml

Legend: (+) firm gel (-) no firm gel

Disposition: Pass _____ Fail _____

By : _____ Date : _____

Checked by : _____ Date : _____

Quality Control Section
Finished Product Control Record

PRODUCT: **THALLOUS CHLORIDE (Tl-201) INJECTION**	Revision No.	Effective Date:	Page 4 of 6
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SPECIFIC CONCENTRATION

Sample #	Specific Concentration mCi/ml
1	
2	
3	
Average	

Disposition: Pass ____Fail ____

Operator: _____ Date: _____

Quality Control Section
Finished Product Control Record

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TOTAL ACTIVITY ASSAY

Assay Time/Date : _____/_____ Decay Time : _____Hrs.

Decay Factor: _____

$t_{1/2}$: 73.05 Hrs. Pot. Setting : Tl-201

Sample	**Assay at Assay Time**	**Assay Corrected to Calib. Time/Date**
1	_____	_____
2	_____	_____
3	_____	_____

Average: _____ mCi/vial

Disposition: Pass _____ Fail _____

Operator: _____ Date : _____

Quality Control Section
Finished Product Control Record

PRODUCT: **THALLOUS CHLORIDE (Tl-201) INJECTION**	Revision No.	Effective Date:	Page 6 of 6
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RADIOCHEMICAL PURITY
TLC METHOD

Distance from origin to solvent front: _____ Cm. Background Counts: _____

		Gross Count/Minute	**Net Count/Minute**	**% Activity**
	Cut2 Solvent Front	_____	_____	_____
	Cut1 Origin	_____	_____	_____
	Total		_____	

Operator: _____ Date: _____

ACRONYMS

ALARA	as low as reasonably achievable
BR	batch record
EW	exempt waste
FDG	2-[^{18}F]fluoro-2-deoxy-D-glucose (fluorodeoxyglucose, fludeoxyglucose)
FID	flame ionization detector
FIFO	first in, first out
GC	gas chromatography
HEPA	high efficiency particulate air filter
HDPE	high density polyethylene
HPGe	high purity germanium detector
HPLC	high performance liquid chromatography
HVAC	heating, ventilation and air conditioning
ICH	International Conference on Harmonization
ISO	International Organization for Standardization
LAL	Limulus amebocyte lysate (test for the presence of pyrogenic material)
PET	positron emission tomography
PET/CT	positron emission tomography/computed tomography
PIC	Pharmaceutical Inspection Convention
PIXE	particle induced X ray emission
PPE	personal protective equipment
PVA	polyvinyl alcohol
PVC	polyvinyl chloride
RSM	Radiological control manual
RCHP	radiological control hold points
RPO	Radiation protection officer
RWP	Radiological work permit
SPECT	single photon emission computed tomography
SRD	self-reading dosimeter
TCD	thermal conductivity detector
TLC	thin layer chromatography
TLD	thermoluminescent dosimeter
VSLW	very short lived waste
WHO	World Health Organization

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This report provides technical guidelines for planning new cyclotron facilities for manufacturing radionuclides and radiopharmaceuticals. It covers the most important design and technical aspects including, but not limited to, feasibility studies and strategic planning, facility requirements and design, staffing, radiation protection, good manufacturing practices and quality management.

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA
ISBN 978–92–0–103109–9
ISSN 0074–1914