

Cyclotron Produced Radionuclides: Guidance on Facility Design and Production of [¹⁸F]Fluorodeoxyglucose (FDG)



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FOREWORD

Positron emission tomography (PET) has advanced rapidly in recent years and is becoming an indispensable imaging modality for the evaluation and staging of cancer patients. A key component of the successful operation of a PET centre is the on-demand availability of radiotracers (radiopharmaceuticals) labelled with suitable positron emitting radioisotopes. Of the hundreds of positron labelled radiotracers, 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (FDG) is the most successful and widely used imaging agent in PET today. While FDG is utilized largely in oncology for the management of cancer patients, its applications in neurology and cardiology are also steadily growing.

A large number of PET facilities have been established in Member States over the past few years, and more are being planned. The design and operation of a facility for the production of FDG requires attention to detail, in particular the application of good manufacturing practices (GMP) guidelines and quality assurance. The product must conform to the required quality specifications and must be safe for human use.

This book is intended to be a resource manual with practical information for planning and operating an FDG production facility, including design and implementation of the laboratories, facility layout, equipment, personnel and FDG quality assessment. GMP and quality management are discussed only briefly, since these topics are covered extensively in the IAEA publication *Cyclotron Produced Radionuclides: Guidelines for Setting up a Facility* (Technical Reports Series No. 471). It should be noted that manufacturing processes and quality specifications for FDG are not currently globally harmonized, and these do vary to some extent. However, there is no disagreement over the need to ensure that the product is manufactured in a controlled manner, that it conforms to applicable quality specifications and that it is safe for human use.

Administrators, managers, radiopharmaceutical scientists, production technologists and regulators of radiopharmaceutical manufacturing, especially those required for the establishment of new FDG production facilities, are expected to benefit from this publication.

The IAEA thanks the consultants who prepared this publication and the reviewers for their valuable time and contributions, including M. Vora (Saudi Arabia), who edited this manuscript. The IAEA officers responsible for this publication were M. Haji-Saeid and M.R.A. Pillai of the Division of Physical and Chemical Sciences.

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1. INTRODUCTION

1.1. BACKGROUND

Positron emission tomography (PET) is an imaging modality in nuclear medicine that uses the principle of coincidence detection of the two annihilation photons resulting from the decay of a positron emitting radionuclide to measure radiotracer distribution within tissues. This information, when combined with assumptions based on physiology or biochemical models, can be used to assess biological processes in vivo. Diseases are biological processes, and since positron emitting radionuclides can be readily incorporated into biological molecules with minimum disruption of their biological activity, imaging with PET is a sensitive tool in diagnosing disease and evaluating its treatment. PET may be used alone or with other imaging modalities, such as radiography, computed tomography (CT), or magnetic resonance imaging (MRI), which rely on predominantly anatomical definitions of disease. In recent years, PET has found its widest applications in oncology [1.1, 1.2], and the field is growing. The recent modality of PET/CT, in which metabolic PET information is directly correlated with morphological CT registration, has particularly accelerated the application and demand for FDG worldwide.

The most widely used radiopharmaceutical in PET imaging is by far 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG) (also referred to as fludeoxyglucose or fluoro-deoxyglucose). The outstanding success of FDG is based on the principle of ‘metabolic trapping’; it is the unique concept of using a radiotracer to allow assessment of metabolic functions directly in vivo. Whole body PET imaging with FDG measures glucose metabolism in all organ systems with a single examination, thus improving detection and staging of cancer, selection of therapy, and assessment of therapeutic response. Although it begins within a specific organ, cancer is a systemic disease, the most devastating consequences of which result from metastases. The FDG–PET method often allows for the early detection and quantification of metastasis; thus FDG–PET has found applications in the diagnosis, staging, and restaging of several clinical conditions including lung cancer, colorectal cancer, lymphoma, melanoma, head and neck cancer, and oesophageal cancer. Similarly, clinical applications in the fields of neurology, cardiology as well as inflammation/infection are on the rise.

An FDG monograph is included in the International Pharmacopoeia (Ph.Int.), the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph. Eur.), and is beginning to appear in other pharmacopoeias. Although subjected to the manufacturing requirements of good manufacturing practices (GMP) akin to conventional pharmaceuticals in earlier times, it is now recognized that

radiopharmaceuticals, particularly PET radiopharmaceuticals with a relatively short half-life, necessitate special consideration in manufacturing. Consequently, competent authorities worldwide have established guidelines for radiopharmaceutical manufacturing, ensuring that products are manufactured in a controlled manner and that they meet the safety and quality characteristics they are represented to possess. It must be noted, however, that although FDG is manufactured in several Member States across the globe, no harmonization exists in GMP protocols at this time. For example, according to World Health Organization (WHO) guidelines, FDG manufacturing is subject to GMP requirements for radiopharmaceuticals [1.3]. On the other hand, in the USA, where PET imaging is most widely used, FDG production is subject to compliance with PET specific current good manufacturing practices (cGMP) guidelines [1.4]. (It is to be noted that a different set of rules may apply for the dispensing of FDG after it is manufactured.) In the European Union, manufacturing and production of FDG is subject to compliance with GMP guidelines as described in EudraLex [1.5]. In summary, regulations applicable to the production of FDG, whether for in-house use or for commercial purposes, are subject to national interpretation and are, therefore, a responsibility of national regulatory bodies.

Regardless of the differences, however, the ultimate aim of all the various guidelines and regulations is to manufacture an FDG radiopharmaceutical with the required attributes of quality and safety for human use.

The material presented in this book is based upon WHO GMP guidelines and quality specifications contained within the FDG monograph in Ph.Int. Considering the historical developments and maximum utilization of FDG in the United States of America and Europe, the corresponding pharmacopoeias, USP and Ph. Eur., are used as valuable reference sources for discussing FDG quality specifications and methodologies in planning new FDG production facilities [1.6–1.8].

1.2. OBJECTIVE

This book is intended to provide insight into the various requirements for establishing and operating an FDG production facility and to serve as a guidance document and a valuable reference tool. Topics include: overall facility planning, layout design, resource requirements (equipment, materials and personnel), FDG production and quality control, and a brief discussion pertaining to GMP and quality assurance applicable to FDG. Several of these subjects and the regulatory aspects pertaining to radiation protection are not discussed in this book as these are covered in other IAEA publications [1.9–1.16].

1.3. SCOPE

Every FDG facility is unique as per available resources and may face specific challenges. The information provided in this book covers the most important elements of an FDG facility and should be useful as an indicative guideline or as the basis for designing an FDG facility. Furthermore, the information will be useful in assessing resource requirements, planning, and aspects necessary for compliance with the applicable national regulatory drug manufacturing requirements.

1.4. STRUCTURE

This book is divided into six sections. The basic and necessary requirements discussed in these sections only pertain to the setting up of a facility for the production of the FDG radiopharmaceutical. With some foresight and additional provisions, however, a planned facility can be extended to enable the manufacturing of additional PET radiopharmaceuticals that may emerge in the future.

Section 1 encompasses the basic information pertaining to FDG production and discusses the scope of the book.

Section 2 discusses facility layout and design (environmental and structural aspects) with particular attention to compliance with GMP requirements. A facility is divided into ‘controlled’ and ‘non-controlled’ areas according to the functions being performed. A model layout based upon WHO guidelines is included in the discussion of key facility elements.

Section 3 pertains to staffing of an FDG production facility. Personnel are broadly categorized as production staff, quality control/quality assurance (QC/QA) staff and administrative staff. For various job functions, details are provided regarding necessary qualifications and staff experience.

Section 4 discusses the equipment essential for production of the [¹⁸F]fluoride, production of FDG, quality control, and general laboratory functions. Equipment selection criteria, validation and maintenance are also discussed.

Section 5 explains the chemistry involved in the production of FDG, followed by an explanation of the processes. Discussion also encompasses the setting up of the FDG synthesizer, raw materials control, pharmaceutical cleanliness and dose dispensing.

Section 6 is devoted to FDG quality control. Discussion pertains to necessary quality attributes, test methods, and product acceptance criteria. The need for overall quality assurance and how to achieve it is also briefly discussed.

Suggestions are made regarding the writing of a validation master plan to achieve consistent results.

Section 7 provides guidance on the transport of FDG from the manufacturing site to users.

A large amount of documentation must be generated and maintained by an FDG manufacturing facility in order to comply with GMP requirements. Examples of the documentation to be maintained by FDG manufacturers, as well as examples of a number of standard operating procedures, are provided in the Annex to this publication.

DISCLAIMER

This book is essentially a compendium of current practices in FDG production, and is written as a resource tool designed to promote efficient and high quality FDG production facilities. Content has been reviewed by the contributing authors as well as by reviewers spread across the globe who are experienced in FDG production and quality assurance. It is quite clear that there is no global harmonization at this time with respect to applicable GMP protocols for the production of FDG, product specifications, or processes. Therefore, responsibility for compliance with the applicable standard (national or international) for producing FDG suitable for human use belongs to the producer. In this book, the WHO GMP and the FDG monograph in the International Pharmacopoeia are used for discussion. Endorsement of one particular standard is neither intended nor implied.

The guidelines presented in this book should not be deemed as being inclusive of all suitable and applicable procedures or exclusive of other procedures producing similar results. Moreover, these guidelines are neither the rules nor the requirements of practice to establish a legal standard of operation.

Planners must take into consideration the circumstances particular to their own situation. Therefore, approaches that differ from those presented in this book may be acceptable. These should be evaluated carefully, however, in relation to the quality of the final product. It is hoped that planners will follow a reasonable course of action based on current knowledge, available resources, risk level assessment and the needs of a facility, to deliver a product that is safe for patient use and which possesses the required attributes of quality, purity and efficacy. The purpose of this book is to assist planners in achieving the above objectives.

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2. FACILITY LAYOUT

2.1. INTRODUCTION

The appropriate design and layout of a manufacturing facility is an essential requirement in achieving the desired product quality and safety. Also, it must be understood that every facility will be unique in itself depending upon a number of factors, including applicable national or international regulations and guidelines, availability of resources, and project scope. Moreover, aspects of facility design and layout vary significantly among Member States. Inter-facility variation is partly due to the fact that there is currently no global harmonization of FDG quality specifications, or methodologies to achieve GMP compliance.

Facility design is largely derived from applicable national (or international) regulations/guidelines pertaining to radiopharmaceutical manufacturing and radiation protection. For example, WHO and European Union (EU) regulations require compliance with guidelines applicable to conventional pharmaceutical manufacturing in addition to specific requirements for radiopharmaceuticals, necessitating these production activities be performed in environmentally controlled cleanrooms [2.1, 2.2]. In the USA, on the other hand, production of FDG is governed by the cGMP regulation designed specifically for PET radiopharmaceuticals [2.3], which does not necessarily enforce cleanrooms to control the production environment. The required control of cleanliness is achieved through the use of laminar flow cabinets, segregation of areas and operational controls. However, dispensing of the finished FDG product is governed by rules different to those for production. Regardless of differences in the nature and scope of production among facilities, certain production standards and controls are necessary to ensure the production of products conforming to the required level of quality and safety for human use. These controls include: flow of materials and people to avoid mix-ups, segregation of areas with radioactivity, and control of the environment to avoid the likelihood of product contamination. Furthermore, facility planning should also be based upon risk level assessment.

The FDG production facility presented herein is based upon GMP guidelines prescribed by WHO. A US FDG facility model is also discussed for comparison purposes (Section 2.5). Furthermore, discussion of the general principles and concepts presented in this section refers to a Type 1 facility (FDG production for use within a facility and for distribution to other PET centres) as defined in IAEA Technical Reports Series No. 471 [2.4]. It must be emphasized that discussion is primarily meant to highlight the important design elements of an FDG production facility. It is also understood that not all Member States require adherence to the WHO guidelines for pharmaceutical manufacturing, and

that not all facilities may be able to encompass the recommendations presented in this section, especially existing facilities which are being modified, as opposed to greenfield constructions. Nevertheless, an FDG facility should be designed such that products complying with required quality and safety levels can be produced consistently and reliably without compromise, and in compliance with applicable GMP guidelines.

When laying out a new manufacturing facility for PET radiopharmaceuticals, it is important to keep in mind that it must comply with national or international codes for GMP and radiation protection regulations. The GMP rules and guidelines are usually described rather broadly using language such as “Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out” or something similar. A physical layout of a facility which establishes smooth workflow patterns through the thoughtful arrangement of space is one of the most critical aspects of planning a facility. The aim of this section is to discuss the essential components of an FDG production facility, bearing in mind that such a facility must comply with both radiation protection and pharmaceutical regulations. Moreover, the information contained herein may be used for guidance when planning a facility.

2.2. FACILITY LAYOUT PLANNING BASED ON WHO GMP

Facility layout planning and implementation will not only encompass the primary requirements of GMP and radiation protection associated with product manufacturing and handling, but will also enhance the flow of materials and people, and integrate the structural elements necessary to achieve these objectives. In this respect, application of controlled access in certain areas, interlocks, segregation, and pass-through boxes should be integrated in a building’s design, along with the type of structural materials appropriate to meet a facility’s objectives.

A WHO GMP based hypothetical facility for production and distribution of FDG that encompasses these features is presented in Fig. 2.1, and will serve as the basis for discussion of various elements of a radiopharmaceutical manufacturing facility. This discussion includes the basic requirements for all rooms and their interrelation within a GMP compliant facility manufacturing FDG using aseptic processing (most facilities employ filtration for sterilization of the FDG, necessitating a certain requirement for environmental classification surrounding manufacturing operations).

The FDG production facility can be divided into controlled and non-controlled areas. The controlled areas encompass provisions for product protection (GMP) as well as radiation protection associated with radioactive

product manufacturing and handling. In this regard, the controlled areas include: a cyclotron and its infrastructure, cleanroom(s) with hot cells for production and dispensing of FDG, a laboratory for quality control of FDG, and a packaging and temporary storage space for batch samples, recalled products and radioactive waste.

The non-controlled areas, on the other hand, encompass non-production areas from a GMP perspective and public areas with reference to radiation protection. These include: administrative offices, storage rooms, restrooms, technical rooms, and heating ventilation and air-conditioning (HVAC). The HVAC technical room, which may make a heavy demand on space, is often on the roof of a facility for optimal placement of ventilation ducts. The whole ventilation system must be leak free in order to avoid any inadvertent release of radioactive gases, and this is made easier if the ducts are short, straight and accessible. In some Member States, it is mandatory to include waste gas compression systems to collect and hold exhaust from hot cells and release it after it has decayed.

2.2.1. Non-controlled area

The offices, janitorial areas, restrooms and material storage areas, as well as the access restricted entrance into a facility, should be in a non-controlled but supervised area. It is preferable that the building entrance for personnel be separated from the entrance for supplies in order to avoid congestion and for personnel safety. In the layout presented in Fig. 2.1, the main entrance for personnel is designated as EN-01, which leads to the main corridor CO-01. From this corridor one can access offices OF-01, OF-02 and OF-03. Materials, on the other hand, enter through the access controlled EN-02. All received materials are temporarily stored (quarantined) in room ST-01 until they are identified, qualified, entered into the material database, appropriately labelled and finally released for use in production. Returned reusable transport containers are stored in room ST-03 where they are inspected and cleaned prior to transfer into the controlled area through airlock MB-02.

Released raw materials (chemicals, kits, vials, etc.) are stored in storage room ST-02, which should be equipped with a sufficient number of closets, ventilated safety storage cabinets for acids, bases and flammable chemicals, refrigerators and work benches. Temperatures within the refrigerators are constantly monitored and recorded for storing temperature sensitive precursors. Raw materials and chemicals needed for the production of FDG batches are transferred into the controlled area through the material transfer airlock (MAL) MB-01.

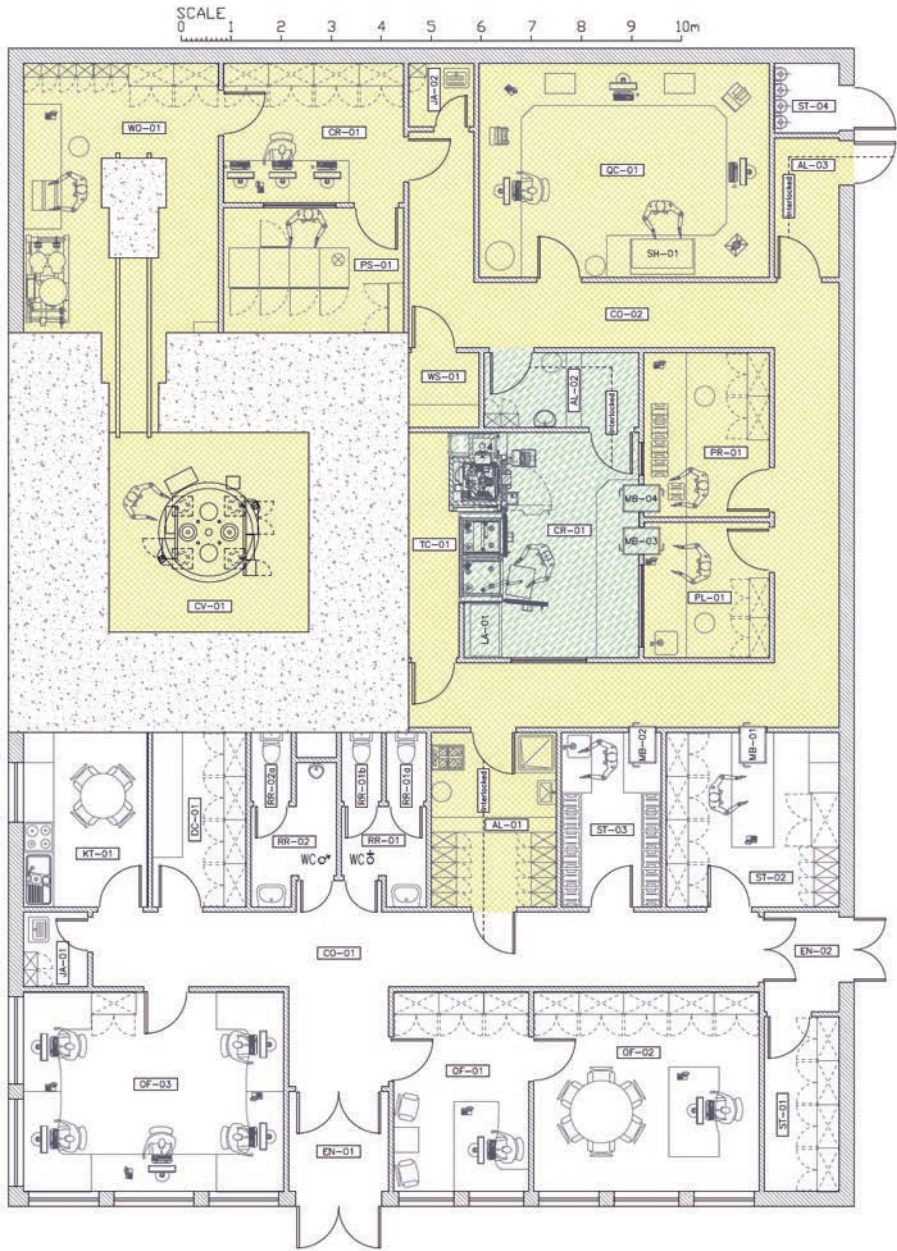


FIG. 2.1. Layout of a hypothetical FDG production facility fulfilling the requirements of WHO GMP.

The janitorial room JA-01 is used for storage of housekeeping and cleaning supplies, the kitchen KT-01 is a place for short breaks, while RR-01 and RR-02 are women's and men's toilets, respectively. There is a data centre, DC-01, which houses the network printers, a scanner, a telefax, a photocopier and cabinets for storing batch records and other GMP and QA related documents.

In most countries, safety regulations require that cylinders with compressed gases be stored in rooms with separate ventilation. For easy replacement of empty cylinders, it is useful to foresee a cylinder storage room that is directly accessible using a transport vehicle, as is room ST-04, which has an access point to the outside of the building. Typically, FDG production facilities require compressed helium (for the cooling of target windows and for the transfer of enriched water), hydrogen (for the ion source of the cyclotron and for the operation of the flame ionization detector (FID), of gas chromatographs), an argon/methane mixture (for the operation of certain types of radiation detectors), nitrogen (for liquid transport within synthesis modules), etc. These cylinders should be connected to a fixed network of tubing delivering these gases to the equipment requiring them. The process gas (normally nitrogen) used by the FDG synthesis module(s) may be regarded as a raw material and should as such be of good ('pharmaceutical' or 'medical') quality and have unique batch identification.

Storage of hydrogen and the corresponding plumbing typically requires additional safety measures. Such installations must be designed according to the particular fire protection and safety regulations of a site.

The flow of materials and people is designed so that there are minimum crossovers, in order to avoid potential mix-ups and to achieve the desired level of protection for both the people and the product.

2.2.2. Controlled area

The controlled area includes zones which need to be controlled in order to ensure GMP and/or radiation protection. Hence, the controlled area should be designed and built in such a way as to provide radiation protection and GMP compliance. The controlled area encompasses radiation protection zones as well as all production areas which are used for work with open radioactive sources. Both requirements are achieved through administrative controls such as controlled access, segregation of work spaces and protocols written as standard operating procedures (SOPs), and through engineering controls such as interlocked doors, appropriate pressure gradients, an appropriate number of air changes and pass-through boxes.

The radiation protection controlled area should only be accessible through the personnel airlock AL-01. This room should be equipped with lockers for street garments, smocks, boots and overshoes. It should have a step-over bench

separating the clean area from the potentially contaminated area. The personnel airlock should be equipped with a hand-foot contamination monitor and it should have at least one wash basin and one shower for decontamination purposes. Due to the small number of operators working in the controlled area of an FDG production facility, in most cases one personnel airlock for entering the controlled area is sufficient. However, in some countries it may be obligatory to have separate male and female personnel airlocks.

According to accepted radiation protection practices, the pressure at which radioactivity is handled should be maintained below atmospheric pressure. Moreover, there should be a regulated pressure gradient within an area, maintaining the lowest pressure at places (such as in rooms and/or isolators) with the highest risk of radiation contamination. On the other hand, GMP requirements favour a pressure cascade which maintains higher pressure in areas where aseptic manufacturing takes place with a decrease in pressure towards areas with a non-controlled 'dirty' environment. There are several possibilities to overcoming these contradictory requirements; one is provided in this section as an example (see Table 2.1). For a more detailed discussion of a pressure cascade, see Section 2.3.4.

AL-03 is a material airlock used for moving transport containers carrying product out of the controlled area to a transport vehicle. This route also serves as an emergency exit from the controlled area for personnel; however, it should never be used for entering the controlled area. The doors of these airlocks (AL-01 and AL-03) should be interlocked and equipped with audio or visual alarms warning personnel in case both of the airlock doors are open or if any of the doors is open for a long period of time. Table 2.1 shows the various pressure cascades and room classifications for the controlled areas discussed in these sections. The suggested numbers are not absolute, but rather indicative in terms of relative pressure differentials between rooms and numbers of air exchanges per hour and room size, depending upon function.

2.2.2.1. Cyclotron block

The cyclotron block typically has four rooms: the shielding vault housing the cyclotron (CV-01), the service room (WO-01), the control room (CC-01) and the power supply room (PS-01). For a self-shielded cyclotron, space requirements should be adjusted accordingly.

The cyclotron vault should provide protection from ionizing radiation created by cyclotron operation and irradiation of the targets typically installed directly on the cyclotron. The vault is usually made of ordinary steel reinforced concrete (with a density of $\sim 2350 \text{ kg/m}^3$) and depending on the performance of the cyclotron (proton beam energy and maximum current on target or targets if

TABLE 2.1. DESCRIPTION OF ROOMS OF A TYPE I FACILITY AS PRESENTED IN FIG. 2.1 (*numbers in table are for guidance only*)

Room designation	Function	Classification	Area (m ²)	No. of air changes (per hour)	Room pressure (Pa; relative to atmospheric)
EN-01	Personnel entrance	Uncontrolled area	4	—	—
OF-01 OF-01 OF-01	Staff offices	Uncontrolled area	50 (total)	—	—
ST-01	Quarantine storage room	Uncontrolled area	5	5–10	+10
EN-02	Material entrance	Uncontrolled area	3	—	—
CO-01	Corridor	Uncontrolled area	24	—	—
JA-01	Janitorial room	Uncontrolled area	2	—	—
KT-01	Kitchen	Uncontrolled area	9	—	—
DC-01	Data centre (archive)	Uncontrolled area	7	—	—
RR-01 RR-02	Toilets	Uncontrolled area	12 (total)	—	—
ST-03	Storage room for transport containers	Uncontrolled area	7	—	—
ST-02	Storage room for released raw materials	Uncontrolled area	12	—	—
ST-04	Storage room for technical gases	Uncontrolled area	2	—	—
AL-01	Personnel airlock for entering the controlled area	Controlled area	9	5–10	–5
CO-02	Corridor	Controlled area	34	5–10	–10
PL-01	Preparatory laboratory	Controlled area	7	5–10	+10
PR-01	Packing room	Controlled area	8	5–10	–10
AL-02	Personnel airlock for entering the cleanroom	Controlled area, GMP minimum class D	5	10–20	+5
CR-01	Radiopharmaceutical production laboratory	Controlled area, GMP minimum class D	16	10–20	+20

TABLE 2.1. DESCRIPTION OF ROOMS OF A TYPE I FACILITY AS PRESENTED IN FIG. 2.1 (*numbers in table are for guidance only*) (cont.)

Room designation	Function	Classification	Area (m ²)	No. of air changes (per hour)	Room pressure (Pa; relative to atmospheric)
WS-01	Storage for radioactive waste, recalled products and retention samples	Controlled area	3	5–10	–25
TC-01	Service corridor for hot cells	Controlled area	5	5–10	–25
CV-01	Cyclotron shielding vault	Controlled area	64 (16 internal)	10–20	–60
WO-01	Service room	Controlled area	21	10–20	–30
PS-01	Power supply room	Controlled area	9	10–20	–30
CC-01	Cyclotron control room	Controlled area	10	5–10	–10
JA-02	Janitorial room	Controlled area	2	5–10	–10
QC-01	QC laboratory	Controlled area	25	5–10	–10
AL-03	Material airlock/ emergency exit	Controlled area	4	5–10	–5

run in dual beam mode) it has 1.5–2.2 m thick walls. Depending upon the cyclotron’s energy, it is common practice to make the inner 20–40 cm of the shielding walls easily removable and to treat them as radioactive waste. Thus, the cost of decommissioning the facility and the amount of concrete treated as radioactive waste will be significantly reduced. The use of boronated concrete will also reduce neutron activation of the vault walls.

If a facility uses a self-shielded cyclotron, the vault will have significantly thinner walls, however the footprint of the vault will be practically the same as in the case of unshielded cyclotrons, since a large space must be left available within the vault to accommodate the self-shielding and its partial removal during service operations. A number of service penetrations should be made through these thick walls: for ventilation ducts, cables, cooling water and compressed air pipes, vacuum pump exhausts, capillaries for irradiated target transport, etc. These penetrations should be carefully designed without compromising the shielding properties of the walls; the use of ‘S shaped’ penetrations has been shown to work well [2.4].

The size of the vault and its infrastructure should be adapted to the requirements of a particular cyclotron, taking care that sufficient space is left around the cyclotron for service and maintenance. The vault should be located such that the cyclotron (typically weighing 11–25 t without self-shielding) can be taken into it. This is usually done through an opening in the roof and by using a heavy crane. This opening is closed by a concrete plug and hermetically sealed after cyclotron installation. Alternatively, if a vault is located on the perimeter of a building, an opening in the wall can be left to roll in a cyclotron, and later closed with concrete blocks and sealed.

The HVAC system servicing the cyclotron vault should remove the heat dissipated by the cyclotron which is not taken away by the water cooling system (typically 2–3 kW) and provide ample underpressure against adjacent, occupied areas. In most cases, a single HVAC system is sufficient for air handling in the whole facility.

A cyclotron cooling system should be installed in the service room, and it should provide space for the vault shielding door (usually made from concrete and moved on rails) and for a workbench and several cabinets. The vault shielding door can also be designed to open parallel to the entrance, thereby saving space in the service room. The workbench should have a stainless steel top (for easier decontamination) and be equipped with a lead window working station for servicing activated cyclotron parts, particularly for targets that require regular cleaning and maintenance. This is where most critical parts of the cyclotron can be repaired or serviced. A set of common tools (wrenches, screwdrivers, tweezers, pliers, crimping tools, soldering iron, etc.) and a selection of spare parts (window foils, stripping foils, O-rings, cathodes for the ion source, different fittings and tubing, etc.) should be stored in closets located in this room. There should be a control panel to operate the shielding door.

The control room (CC-01) should have an appropriate workbench and several cabinets. It is convenient if the control room is located next to the power supply room (PS-01), since a cyclotron operator can visually observe and monitor the power supply through a conveniently placed window. The control room typically houses three computer working stations: one for controlling the cyclotron and the targets, one for controlling and monitoring the radiation protection and safety system and one for controlling the HVAC system of the facility. The cabinets can be conveniently used to store operating manuals and other technical documentation. If a facility is equipped with a video surveillance system, this is the right place to install corresponding monitors and a video recording facility.

The power supply room is used for the installation of power supplies for the cyclotron, which includes the magnetic coils, radiofrequency (RF) system, safety and control system, etc. It should be located close to the cyclotron; the distance is

very often limited by the maximum permitted length of the RF cables. The HVAC system should remove the heat dissipated by the power supplies, typically amounting to 5–10 kW. Due to the fact that penetrations through the cyclotron vault's walls are usually located below ground level (in order to fulfil the radiation protection requirements), it is common to have a false floor in the power supply room for easy installation of a large number of cables.

If a self-shielded cyclotron is to be installed, the power supply will usually be installed in the same room with the cyclotron. Even though the vault housing a self-shielded cyclotron does not require heavy doors, the service room should be kept in order to provide a working place for servicing the targets while the cyclotron is in operation.

2.2.2.2. Radiopharmaceutical production block

In the referenced example, four rooms make up the block: the personnel airlock for entering the cleanroom (AL-02), the cleanroom for the production of FDG (CR-01), the preparatory laboratory (PL-01) and the packing room (PR-01). The personnel airlock AL-02 should be equipped for common gowning required to enter cleanrooms. It should have cabinets for storing cleanroom garments, a waste bin, a mirror and a step-over bench. A wash basin should be avoided in the cleanroom. The clean side of the airlock should be designed to be of the same class as the adjacent laboratory. In the interest of pharmaceutical quality, the cleanroom should be maintained at a positive pressure in comparison to the adjacent room. The apparent conflict with radiation protection necessitating relative negative pressure is solved by having overall negative pressure within the hot cells, where radioactivity is handled.

The facility should be designed to ensure the orderly handling of materials and equipment to prevent mix-ups and contamination of equipment and product, whether due to personnel or environmental conditions. This can be most readily achieved by employing the cleanroom concept. See Section 2.3 for more detail.

The cleanroom for FDG production should be designed to be minimum class D (a more detailed description can be found in the following section). It should house the hot cells for the synthesis modules, as well as a dispenser, a laminar flow cabinet (LA-01) and a workbench. The production room should be connected to the preparatory room through a material airlock, MB-03, from where raw materials, kits, vials, shielding containers and consumables are transported into the cleanroom. It should also be connected to the packing room through a material airlock, MB-04, through which the shielding containers are taken out of the cleanroom for packaging.

The FDG production cleanroom should be located as close as possible to the cyclotron, and the hot cells should be installed along the wall that is closest to

the cyclotron in order to reduce the losses of ^{18}F in the narrow bore tubing used for the transfer of irradiated enriched water. The hot cells should be located in the cleanroom, so that the doors can be fully opened in order to take advantage of drawers that are installed in them for taking the modules out for preparation or service. The inner containment enclosure and the air quality inside the hot cells housing the FDG production modules should be class C, and the pressure inside the containment should be well below the pressure in the cleanroom (FDG production in automated modules involves only closed system transfers and a sterilizing filtration at the end of production). The hot cell for the dispenser should provide a class B environment, which serves as the background for a class A environment, created locally where the vials are filled. The dispensing hot cell should be equipped with an airlock (class B) for inserting sterile vials and a sterile dispensing kit into the hot cell.

Certain manufacturing operations can be performed in specially adapted barrier isolators, which provide the required controlled environment within the confines of the isolator and minimize the extent of personnel contact with the product. It must, however, be ensured that radiation protection is not compromised when isolators are employed at any stage of the manufacturing process.

The preparatory laboratory should be equipped with cabinets and a workbench. This is to be used for unpacking kits and other consumables from the bulk packing boxes prior to taking them into the production room via the material airlock in order to prevent contamination of the cleanroom. This is where all raw materials receive final inspection prior to their application.

The packing room is used for labelling shielding containers, inserting them into adequately labelled transport packages, securing packages, checking transport documents against package contents and dispatching products.

2.2.2.3. *Quality control room*

The QC laboratory, QC-01, should be large enough to install the necessary QC equipment and a shielded laboratory hood. A room with about 10–12 m of workbench space in total should be sufficient for a typical FDG production facility. The laboratory hood should be integrated into the ventilation system of the facility. It is necessary to install additional flexible ventilation tubes for local suction. These can be positioned above equipment such as the detectors of gas chromatographs, which release potentially contaminated radioactive gases or aerosols.

It is common to subcontract a specialized laboratory for sterility testing of the final product. If this is not possible, or if local regulations require on-site sterility testing, a dedicated room should be allocated for this purpose.

2.2.2.4. Utility rooms

It is very useful to have a service corridor behind the hot cells, shown in the hypothetical layout as room TC-01. Having rear access to the hot cells allows for servicing of the hot cells' ventilation system and for replacing filters outside of the cleanroom. Moreover, the target transfer line and corresponding valves can be easily accessed for service and maintenance without compromising the atmosphere of the cleanroom.

There should be a room for temporary storage of radioactive waste and activated parts of the cyclotron, as well as for the storage of recalled products. In this layout, this is the room WS-01.

Finally, there should be a janitorial room, JA-02, used for storage of cleaning utensils needed for cleaning rooms in the controlled area, including the cleanrooms.

2.3. CLEANROOMS

Control of product quality and compliance with GMP regulations for pharmaceuticals manufacturing require the production of FDG to be performed in a controlled environment, which can be achieved in an appropriately designed cleanroom. The specific structural requirements of a cleanroom include controlled access (of both materials and people) and air quality within a room. Both attributes are achieved through properly designed layout and air handling systems (HVAC). Furthermore, the planned arrangements must be evaluated and validated prior to implementation. The required grade of cleanroom air quality for FDG manufacturing is described in Section 2.2.2.2. A general discussion pertaining to cleanrooms and HVAC for advanced understanding of the subject is detailed below.

2.3.1. Definitions

A cleanroom is a controlled environment in which products (such as pharmaceuticals) sensitive to contamination are manufactured. It is an enclosure in which the concentration of airborne particles of a certain size and origin are maintained within specified limits [2.5, 2.6]. Eliminating sub-micron airborne contamination generated by personnel, processes, facilities and equipment is achievable only through careful design and construction of a cleanroom and by applying strict rules and procedures for occupancy, movement and proactive maintenance [2.6–2.14].

Cleanrooms are classified according to the number of particles per unit volume of air and air flow pattern. Table 2.2 provides a comparison of cleanroom classifications according to common standards.

TABLE 2.2. COMPARISON OF CLEANROOM CLASSIFICATIONS
(*maximum concentration limits (particles/m³ of air) for particles equal to or larger than the indicated sizes*)

ISO 14644-1:1999 [2.7]										EU GMP (2008) [2.15]			
ISO class	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1 µm	5 µm	GMP class	At rest		In operation			
								0.5 µm	5 µm	0.5 µm	5 µm		
1	10	2											
2	100	24	10	4									
3	1 000	237	102	35	8								
4	10 000	2 370	1 020	352	83								
5	100 000	23 700	10 200	3 520	832	29	A	3 520	20	3 520	20		
6	1 000 000	237 000	35 200	35 200	8 320	293	B	3 520	29	352 000	2 900		
7							C						
8							D						
9													

^a Not defined.

According to the European Economic Community (EEC) GMP definition, class A cleanrooms shall provide a unidirectional laminar air flow within the containment with a homogeneous air speed in the range of 0.36–0.54 m/s. These conditions should be maintained for the most critical operations, such as aseptic filling of vials or sterility testing of products. The air flow pattern in cleanrooms of class B, C and D can be turbulent or mixed.

Apart from controlling particulate contamination, cleanrooms used for radiopharmaceutical manufacturing should also be controlled and monitored for microbiological contamination. Table 2.3 presents the maximum allowed microbial contamination in cleanrooms of different classes.

2.3.2. HVAC systems for cleanrooms

The most important part of the HVAC system of a facility is that the air handling unit (AHU) maintains the required air quality in cleanrooms. A representative scheme is shown in Fig. 2.2. Cleanrooms used for the production of radiopharmaceuticals must be supplied with 100% fresh air in order to comply with radiation protection regulations (no recirculation of air is permitted in radiation protection controlled areas). The air quality of cleanrooms (temperature, humidity, differential pressure between rooms, differential pressure before and after the filters, etc.) should be monitored and recorded.

TABLE 2.3. RECOMMENDED LIMITS FOR MICROBIOLOGICAL MONITORING OF CLEAN AREAS DURING OPERATION
(recommended limits for microbial contamination^a by EEC GMP (2003) [2.12])

GMP Class	Air sample (cfu/m ³)	Settle plates (diam. 90 mm; cfu/4 h) ^b	Contact plates (diam. 55 mm; cfu/plate)	Glove print 5 fingers (cfu/glove)
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	n.d. ^c
D	200	100	50	n.d.

^a Average values.

^b Individual settle plates may be exposed for less than four hours.

^c Not defined.

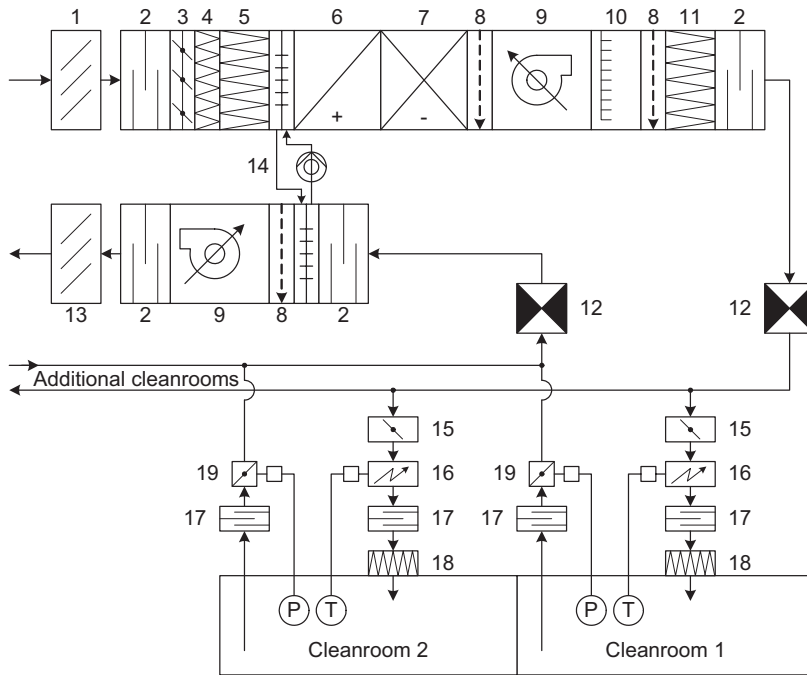


FIG. 2.2. Basic elements of a HVAC system for cleanrooms to be used for production of radiopharmaceuticals (filters are classified according to standard EN 779 [2.16]): 1 — air inlet grill, 2 — silencer, 3 — motorized damper, 4 — panel filter type G4, 5 — bag filter type F8, 6 — air heating unit, 7 — air cooling unit, 8 — drain, 9 — variable speed fan section, 10 — steam humidifier, 11 — filter type H10, 12 — motorized fire damper, 13 — air outlet grill, 14 — heat pump with heat exchangers, 15 — constant air flow regulator, 16 — electric heater, 17 — sound absorber, 18 — terminal absolute filter type U15, 19 — variable air flow regulator; T — temperature sensor, P — pressure sensor.

2.3.3. Cleanroom design

Although the air quality in a cleanroom is essential, it is not the only element that makes a cleanroom ‘clean’. The design, construction, maintenance and particularly the operations performed within a cleanroom are also very important.

Some common engineering guidelines that can help in designing cleanrooms are summarized in Table 2.4.

TABLE 2.4. BASIC DESIGN AND OPERATION CONSIDERATIONS OF CLEANROOMS

	EU GMP class		
	A, B	C	D
Area per occupant (m ²)	30	10	5
Room overpressure (Pa)	15	10–15	5–10
Air changes per hour	500	20–40	10–20
Clean air inlet as % of ceiling (wall) area	90	10–20	5–10
Clean air inlet locations	Ceiling (wall)	Ceiling	Ceiling or high sidewall
Return air location	Low level or floor (opposite wall)	Low sidewall	Sidewall
Terminal velocity at clean air inlet (m/s)	0.36–0.54	0.15–0.45	0.15–0.45
Airlock entrance needed	Yes	Yes	Yes
Occupants properly attired	Full gowns	Coverall	Smocks
Occupant activity	Minimum	Occasional movement	Constant activity
Traffic in/out per hour	Minimum	2–6	>6
Equipment in room	Minimum	≤30% floor	≤50% floor
Housekeeping	Meticulous	Good	Mediocre
Routine particle count interval	Weekly	Monthly	Quarterly

Note: These suggestions are based on best practices; national regulations may dictate other practices.

2.3.4. Pressure cascades

Design of pressure cascades in a radiopharmaceutical production laboratory must take into consideration both radiation protection and GMP requirements. Radiation protection tends to protect the environment from hazardous radioactive products, while GMP tends to protect pharmaceutical products from potential bacterial contamination emanating from the environment.

Careful design of pressure cascades is needed to fulfil requirements of both regulations. As a general rule, one should consider a minimum 10 Pa difference in adjacent rooms which are designed to have a pressure differential. This is because once pressure differentials are set they must be measured, and it is extremely difficult in real conditions to measure less than 10 Pa.

A cyclotron vault represents the highest risk of radiation contamination, thus the room must be designed to have the most negative pressure in the facility. Hot cells pose the next highest risk of radioactive contamination of the air and they are always designed to maintain a substantial negative pressure relative to the room they are built in.

It is much easier to protect cleanrooms from the dirty air entering from the outside when they have a pressure higher than the adjacent rooms; clean air from the cleanroom is pushed out, thus preventing penetration of dirt particles from outside. Therefore, in the layout presented positive air in the FDG production room is considered. In countries where radiation protection rules prevail, negative pressure might be maintained in the production room, where care should be taken to create ventilated airlocks surrounding the cleanroom to prevent penetration of ‘dirty’ air from outside.

Generally, to protect the controlled area from outside air, a so-called ‘envelope’ of positive pressure airlocks is recommended. When positive air pressure is applied in an FDG manufacturing room, care must be taken not to propagate eventually radioactively contaminated air through the whole facility. Design of the so-called ‘radioactive sink’ helps this task (as well as avoiding any recirculation of clean air by designing air handling systems to provide a 100% feed of fresh air, single pass). In the example facility, corridor CO-02 serves this purpose.

2.3.5. Validation of cleanrooms

Validation is defined as the establishment of documented evidence which provides a high degree of assurance that a planned process will consistently perform according to intended specified outcomes [2.17]. A considerable amount of information specific to PET radiotracer manufacturing is available in a recent IAEA publication [2.18]. Once a system or process has been validated, it is expected that it remains under control, provided no changes are made. In the event that modifications are made, or if problems occur or equipment is replaced or relocated, revalidation may become necessary. It is very helpful to prepare a validation master plan. This document will guide the validation of all equipment and spaces. Validation of cleanrooms should be performed according to a validation master plan.

Validation of cleanrooms is performed in three phases: installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). These qualification procedures are closely linked to the design of cleanrooms, as shown in Fig. 2.3, and their aim is to show that a cleanroom has been built according to design requirements and that it provides the necessary environment for the safe production of pharmaceuticals.

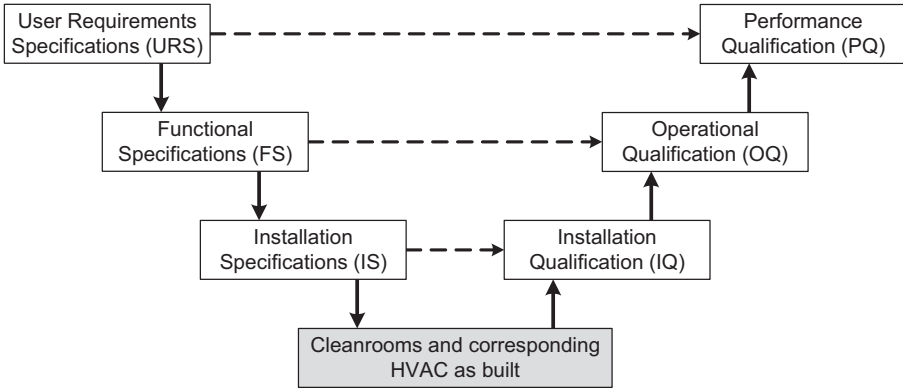


FIG. 2.3. Relations between the validation and design of cleanrooms (V model).

IQ documents that the equipment and auxiliary systems of a cleanroom have been correctly specified to meet user requirements, that they have been correctly installed, and that they conform to required specifications. Furthermore, installation qualifications should be documented and reviewed to confirm compliance. Part of the installation qualification of cleanrooms should be the following:

- Description of the cleanroom facility with appropriate schematic diagrams;
- Specifications of the elements of cleanrooms;
- Description of pressure cascades;
- Identification of cleanroom classes;
- Description of auxiliary systems and connections;
- Identification of critical instruments and devices;
- Installation checklist (compliance with design);
- List of spare parts, particularly high efficiency particulate air (HEPA) filters;
- Standard operating procedures (SOPs) for preventive maintenance;
- SOPs for the cleaning or sanitation of equipment, systems, and the environment.

An OQ documents cleanroom performance against designed specifications repeatedly and reliably within the operational scope framework. Operation qualifications should be documented together with a validation protocol and a report. Operation qualification is carried out in the ‘at rest’ condition of cleanrooms. Within the framework of operational qualification, the following should be done:

- Specification of acceptability criteria.
- Writing of SOPs for the operation of cleanrooms.

- Writing of SOPs for air sampling and testing procedures.
- Performance of an analysis of test results and validation of them for acceptability.
- For GMP classes D, C and B, the operation of cleanrooms should be approved according to the following criteria:
 - Pressure differences between individual rooms;
 - Quantity of air coming out of the HEPA filters;
 - Temperature and relative humidity;
 - Integrity and tightness of the installed HEPA filters;
 - Particle count;
 - Recovery test;
 - Smoke test;
 - Speed of air flow in the outgoing zone of the filter.
- For the GMP class A environment (required for sterile preparation, fractionating or dispensing FDG), operation should comply with the criteria for classes D, C and B already listed, plus the following additional criteria:
 - Average air speed and uniformity;
 - Parallelism of the air flow;
 - Leak test (only for closed environments).

Performance qualification is carried out in the working zone, where production takes place, particularly where the open dosage form is in contact with the environment (such as during dispensing). The following qualification tests are carried out in the ‘in operation’ condition of cleanrooms:

- Pressure conditions between rooms and containments (enclosures);
- Particle count;
- Smoke test;
- Microbiological control of the atmosphere.

2.4. OTHER CONSIDERATIONS

In addition to the primary considerations already discussed, there are additional structural and supporting components that require equal attention to detail. Some general requirements include surfaces that are impervious, easy to clean and resistant to contamination (microbial and radioactive), facilitating good hygiene and radiation safety. Sharp corners and crevasses where dust can gather are to be avoided in cleanroom areas. Furthermore, the controlled areas should be built with attention to radiation protection [2.4, 2.19, 2.20] and pharmaceutical manufacturing requirements [2.6, 2.15, 2.21, 2.22]. Viewing glass windows are

recommended for personnel comfort. Commonly accepted practices are detailed in the following sections.

2.4.1. Floors

The floor should be covered with an easily cleanable surface such as a continuous sheet of PVC or linoleum at least 2.5 mm thick. The covering should continue (extending up the wall) to a height of about 15 cm contiguous with the floor surface. All edges at the walls and between sheets should be sealed or welded to prevent seepage of spilled materials. As an alternative, an epoxy resin coating may provide an acceptable finish on smooth concrete, particularly in the cyclotron vault, due to its high radiation stability.

2.4.2. Walls and ceilings

The walls and ceilings should generally be smooth and painted with a hard gloss or high quality waterproof vinyl emulsion to facilitate cleaning. The use of stippled surfaces or a paint finish applied to unplastered concrete blocks is unacceptable. Paint coated aluminium based sandwich type plates used to build cleanrooms are ideal for building controlled areas as well. Joints between plates should be sealed with silicone type materials to facilitate cleaning. Service penetrations in walls and ceilings should be sealed and covered.

2.4.3. Doors and windows

Wooden surfaces should be covered with plastic laminate material or painted with a good quality polyurethane gloss paint or varnish. Doors should be lockable to ensure safe keeping or to restrict access. A high level of security for a building and/or an entire site is preferable to securing an individual laboratory within a building. Windows that can be opened to the outside are not permitted in controlled areas. Windows which do not open are acceptable.

2.4.4. Benches

Working surfaces should be smooth, hard and non-absorbent and have necessary heat and chemical resistant properties. All gaps and joints should be sealed with a silicone type material. The bench tops should be coved (upstanding) at the rear against the walls. Gaps should be sealed with a silicone type material. A raised front lip on a bench can help prevent a spillage from running off a bench onto the floor. Exposed wood, including that underneath benches and cupboards, should be painted with a good quality hard gloss paint or polyurethane varnish or

laminated. The use of wood surfaces should be avoided in laboratories. Dedicated areas of bench should be set aside for radioactive work and be clearly marked. It is a good practice to work in plastic or metal trays, thus providing a secondary containment on bench tops to minimize spills and the spread of radioactive contamination.

2.4.5. Waste disposal sinks and drainage pipes

Facilities producing FDG typically will not require special waste disposal sinks. If mandatory, sinks and drains should be constructed of suitable material: for most applications, stainless steel is preferred. Where possible, sinks combined with drainage boards should be used, with rounded front edges and coved (upstanding) at the rear against the walls. A rear splash plate should extend a reasonable distance up the wall behind the sink. Small diameter U-shaped or bottle traps should be used, instead of large traps or catch pots, to avoid accumulation of radioactive sediments. Holding tanks may be required for compliance with discharge consent conditions. Drainage pipes for radioactive effluents should be labelled with the ionizing radiation symbol.

2.4.6. Ventilation and containment

Dispensing or preparation of radioactive materials which may cause airborne contamination should be carried out under conditions which prevent dispersion of the substances. In particular, volatile radioactive materials should never be used in an open laboratory; they must be handled in appropriate containment, such as a fume cupboard, hot cell or isolator. Recirculating ventilation systems are inappropriate for controlled areas where open radioactive sources are handled. A guiding principle for effective control of contamination is that air movement should be maintained from less-contaminated areas to more-contaminated areas by means of pressure differences between rooms. Exhaust air from hot cells should be filtered (for example, with aerosol and charcoal filters) and monitored before release. Most synthesis procedures and equipment do release airborne activity during operation, and discharge should be controlled. Gas storage and delay line decay systems have been used in many installations, but are often expensive and space consuming. Often, radioactive gas phase effluents may be efficiently captured directly on the outlets of synthesis modules. Shielded activated charcoal filters on the gas outlet of hot cells are also useful as radioactive gas traps.

2.4.7. Radioactive storage facilities

Adequate storage space should be available to organize essential equipment in order to minimize clutter in working areas and reduce the risk of spreading contamination. Waste disposal bins in a laboratory (used for storing solid waste awaiting disposal) should be constructed of a material which is robust, and preferably should be foot operated. Lids should be closed when not in use and the contents in the waste bags sealed or secured before removing them from the bin. All sharps, bottles, tubes, etc. should be placed in special containers to ensure safe handling of the materials. Adequate storage space should be available for the temporary storage of radioactive waste within a controlled area. In general, there will be a very low volume of long-lived radioactive waste from a manufacturing lab. Most of the long-lived radioactive waste arises from the activation of cyclotron/target parts, particularly the Havar entrance foil used in the targets. The storage space must be kept locked and may need to be kept under surveillance.

2.4.8. Other facilities

Adequate decontamination facilities, including decontamination solutions, should be available. A designated hand wash basin and a shower cabin for decontamination should be provided: these must never be used for the disposal of radioactive substances (other than traces from the decontamination of personnel). Warning signs, clearly and legibly marked with the word 'Radioactive', with the ionizing radiation symbol, and any other information necessary (contact person, telephone number, etc.), should be placed as required by radiation protection guidelines.

2.5. FACILITY LAYOUT PLANNING BASED ON THE US cGMP

In contrast to the WHO GMP, US cGMP requirements related to PET radiopharmaceutical production are formulated specifically for PET products, and are relatively less restrictive and less demanding on resources. There are several significant differences between the two sets of regulations, which has an influence on facility layout planning and construction costs. The US cGMP for PET radiopharmaceuticals, for example, allows for multiple operations in the same area, and the requirements for aseptic processes are relatively less demanding.

In addition to differences in GMP requirements, radiation protection standards are also less restrictive in the USA (and some other Member States) compared to EU and IAEA requirements: the widely accepted annual radiation

dose limit for occupational workers is 20 mSv (as recommended by the IAEA [2.19]); while in the USA the annual limit is 50 mSv.

Figure 2.4 presents a hypothetical FDG production facility layout based on a self-shielded cyclotron, which fulfils US radiation protection and cGMP requirements. The facility has two entrances: EN-01 for personnel and the inlet of raw materials and EN-02 for the exit of products. Similar to the WHO model facility, in the non-controlled area there is a corridor (CO-01), there are offices for staff (OF-01 and OF-02), a kitchen/meeting room (KT-01), a data centre (DC-01), a janitorial room (JA-01), toilets (RR-01 and RR-02), storage for unreleased materials (ST-01), storage for released materials (ST-02), storage for compressed gases (ST-03), an electrical room for the switching boxes, computer servers, etc., and a technical room for cooling and HVAC systems (PS-01).

The self-shielded cyclotron is placed in a lightly shielded vault (CV-01), which is directly accessible from the radiochemical laboratory (PL-01). In this laboratory, one can find hot cells housing modules for FDG production and in the same room one can prepare reagents and kits for production as well as perform quality control procedures (a laminar flow cabinet is required). There is a small separate room for a laminar flow cabinet, needed for sterile operations (QC-01). Finally, the dispensing, packing and dispatch of final products is performed in room PR-01.

The production area may be accessed through several doors. Due to the presence of radioactivity in the production areas, however, a hand/foot contamination monitor (frisking station) is placed at each entrance for radioactive contamination monitoring and control.

2.6. SUMMARY

Establishing an FDG manufacturing facility requires due consideration to two applicable regulatory aspects: radiopharmaceutical manufacturing and radiation protection. Currently, there are no specific globally harmonized requirements for the design and specifications of an FDG production facility. The WHO and US facility models differ significantly from each other. It can be noted that European facility requirements are almost identical to those specified in the WHO model. An important consideration is that structural design, work flow and environmental control should be integrated into the planning of a facility such that product manufacturing conforms to necessary requirements and control. More importantly, a facility must be conducive to manufacturing FDG conforming to required quality attributes and which is safe for human use.

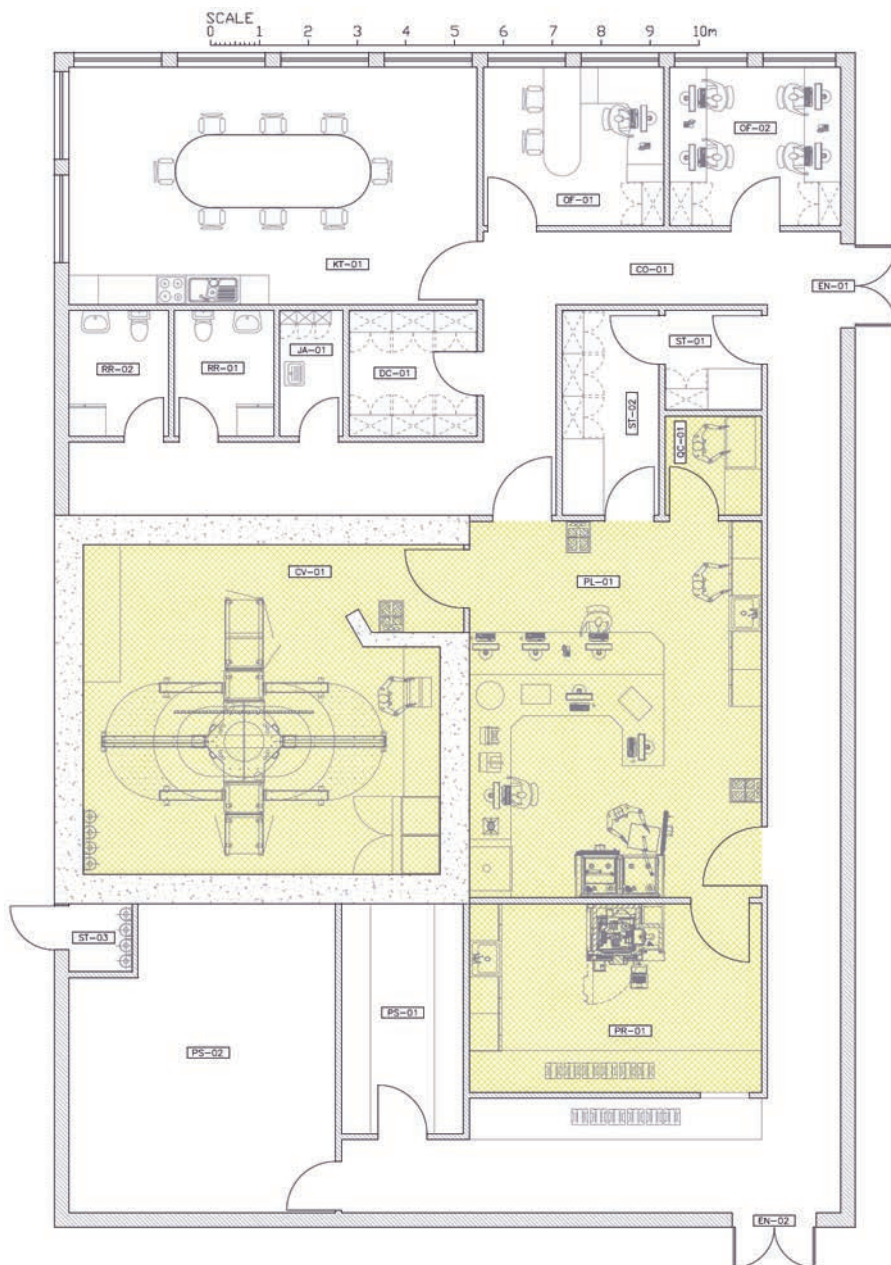


FIG. 2.4. Layout of a hypothetical FDG production facility that fulfils the requirements of the US cGMP.

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3. PERSONNEL

3.1. INTRODUCTION

A facility for FDG production requires staff with the appropriate education, background, experience and training necessary to carry out diverse functions for the production of a radiopharmaceutical safe for human use, and in compliance with the various regulations. The manufacturing of FDG entails three processes: cyclotron production of [^{18}F]fluoride, radiochemical synthesis and dispensing of FDG, and quality assessment. Qualified and trained technical staff who are experienced in carrying out specified functions and who are also competent in radiation protection are essential. In addition to technical staff, administrative and support staff complete the personnel requirements of a facility.

Representative job functions, along with associated duties, are described in this section. It must be emphasized that not all job positions described herein are required at all facilities, but the job functions definitely are. The aim is to provide information and guidance to facility planners in developing a staffing plan essential for an FDG production facility. Ultimately, it is the planned size and scope of a facility that will determine the number of staff and qualification levels required for implementing and maintaining efficient operations. A smaller facility manufacturing FDG for on-site clinical use only with limited distribution to other PET centres will require fewer staff members compared to a facility with larger capability and scope for distribution to multiple external PET centres. Furthermore, staff experience and training will have a significant effect on the number of people required at a facility.

With the explosive growth of PET imaging, experienced people are simply not readily available on the 'market'. The situation varies depending upon the geography, local requirements, financial resources, and scope of a facility. Creating a team at a new FDG centre with the limited availability of experienced people can be a major challenge. It is, therefore, essential that a comprehensive training programme be implemented, including cross-training, such that one individual can perform multiple tasks which will ensure that all job functions are covered regardless of illness or other absences.

3.1.1. Overview of staffing plan

A facility should ideally have individuals who can carry out diverse technical functions for the efficient production of FDG, including:

- (1) Operating a cyclotron for production of [^{18}F]fluoride and performing cyclotron maintenance and repairs (cyclotron operator/engineer);

- (2) Manufacturing and dispensing of FDG according to the prescribed standard operating procedures (radiochemist/technologist);
- (3) Assessing FDG quality parameters prior to release for patient use (QC person);
- (4) Overseeing operations and providing overall quality assurance (manager);
- (5) Managing the radiation protection aspects of a facility.

Collectively, staff will have the responsibility of making FDG available for patient use, as well as ensuring that manufacturing is performed in a controlled manner and that a product conforming to required quality specifications is produced.

In addition to staff members performing the primary functions noted above, a second staff group will be required in various functional capacities to support the reliable and efficient operation of a facility. These functions include equipment maintenance, engineering, radiation protection and administration. Support staff may not be employed directly in the FDG production facility, but should be available through institutional channels or may be contracted as needed from external sources. Furthermore, primary staff performing some of the support functions should reduce dependency on external sources as well as overall staffing requirements.

It is essential that a facility has at least one person (often referred to as the qualified person, responsible person or authorized person) with a proven record of expertise together with a high level of practical experience in FDG production, and who is qualified and experienced in GMP and quality management. (National regulations will determine the required qualifications of this designated individual.) This person will be designated to have facility oversight, and will have the authority to release a product for patient use. Furthermore, this person will provide the technical guidance and leadership needed for the coordination of efforts to manufacture FDG reliably and consistently.

How many staff members does an FDG production facility need? The answer depends largely upon the size and scope of the facility, staff competence and the prevailing GMP regulations. This is a subject of discussion without a specific answer. On the one hand, it can be argued that a smaller facility producing only one or two batches of FDG per day requires fewer personnel with less stringent organizational delineation. In other words, duties such as production and QC can be performed by the same person as long as protocols are developed and implemented for appropriate checks and oversight prior to the release of finished product. On the other hand, conventional GMP protocol may require a clear separation of duties and no overlap of staff responsibilities.

In reality, staff may (and often do) perform multiple functions at a smaller facility. Even in such cases, a separation of functions is recommended in order to

enhance quality assurance and to avoid a potential conflict of interest. In other words, for a given batch of FDG, the production staff make the product, and the staff performing quality control test the product. However, roles may be switched for another batch of FDG production. It is important to note that various guidelines for producing radiopharmaceuticals require the overall responsibility for product release belong only to the QP (qualified person). Also, one person within a facility must have the dedicated responsibility of controlling SOPs.

Tables 3.1 and 3.2 list the primary and support functions required at a production facility. Invariably, FDG production facilities have a limited number

TABLE 3.1. SUMMARY OF PRIMARY TECHNICAL FUNCTIONS

Primary job function	Job title and minimum education requirement	Specialized training
Cyclotron operation ([¹⁸ F]-fluoride production)	Cyclotron operator Two year technical degree or equivalent (engineering degree preferred)	<ul style="list-style-type: none"> • Factory training • On the job training • Supervised training • Mechanical and electrical repairs • Radionuclide production • Radiation safety
FDG production and distribution	Radiochemist/technician Diploma or degree in chemistry, pharmacy or equivalent	<ul style="list-style-type: none"> • Synthesis of FDG • GMP • Quality management • Courses in laboratory operations • Equipment specific training • Radiation safety
Quality assessment	QC chemist/technician Diploma or degree in chemistry, pharmacy or equivalent	<ul style="list-style-type: none"> • Analytical chemistry and instrumentation • Quality testing of FDG • Quality assurance and management • GMP • Courses in laboratory operations • Radiation safety
Oversight and quality assurance	Qualified person Diploma or degree in chemistry, pharmacy or biological sciences Significant experience in FDG manufacturing and quality management	<ul style="list-style-type: none"> • Formal training in GMP • Synthesis of FDG • Analytical methodology • Quality assurance and management

Note: National regulations will determine the required qualifications of a qualified person.

TABLE 3.2. SUMMARY OF SUPPORT FUNCTIONS

Job function	Job title and minimum education requirement	Specialized training
Radiation protection	Radiation protection officer ^a Degree in medical physics, health physics, radiation physics or science	<ul style="list-style-type: none"> • National and international radiation safety regulations • Supervised training • Radiation protection officer certification
Maintenance and repairs	Engineer Experience in electronics, electromechanical engineering or equivalent	<ul style="list-style-type: none"> • Electro-mechanical diagnosis and repair • Cyclotron maintenance and repairs • Radiation protection
Management	Manager Advanced degree in physical or biological sciences	<ul style="list-style-type: none"> • FDG synthesis and QC/QA • Advanced quality management • GMP • Supervision and management • laboratory operations • Radiation protection

^a National regulations determine the required qualifications of a radiation protection officer.

of full time employees. It is, therefore, desirable that the people engaged in primary job functions (Table 3.1) are cross-trained in at least one additional function for backup in case the primary person is not available due to scheduled or unscheduled absences. Furthermore, cross-training should be kept current by carrying out alternate job functions at regular intervals.

3.2. PRODUCTION STAFF

Members of the production unit carry out routine operations for the production of [¹⁸F]fluoride, and the synthesis and dispensing of FDG. Important aspects of production include adherence to GMP and radiation protection. In addition, production staff should perform minor equipment repairs, oversee supplies, stock and most importantly, maintain proper documentation of production activities in order to fulfil GMP documentation requirements.

The job descriptions listed below are typical duties to be performed by people assigned to particular jobs. Some of the listed duties may be performed by another person in the organization as deemed appropriate. It is essential that duties to be performed by each individual are specified without ambiguity.

Individuals may need to perform other FDG related job duties, which may happen quite often in smaller production facilities, in addition to their primary job functions. Proficiency in more than one type of job function becomes a necessity in a facility with limited staff. This is achieved through proper cross-training and retraining at regular intervals.

3.2.1. Cyclotron operator

The typical duties of the cyclotron operator include the following:

- Liaising with a production chemist to schedule [^{18}F]fluoride production (beam current, duration, dual or single irradiation);
- Performing a preliminary cyclotron check to ready it for operation;
- Tuning and operating the cyclotron;
- Loading, irradiating and unloading ^{18}O enriched water;
- Monitoring cyclotron systems and detecting potential malfunctions;
- Performing first line cyclotron maintenance and possibly some repairs;
- Ordering, stocking parts and maintaining inventory;
- Performing target maintenance and periodic rebuilding;
- Maintaining records of repairs and production;
- If required, producing FDG (cross-training);
- Participating in training programmes.

Cyclotron operators should have at least a two year technical degree or the equivalent and some specialized training in the particular cyclotron being used. This may include training at the factory and/or training in another facility with a similar cyclotron and target system. The operator should have experience in target preparation, maintenance and troubleshooting. Practical knowledge of radiation protection related to cyclotron operation and radioactivity is also required. At most small facilities, a cyclotron operator can easily be the production chemist if support is available from the cyclotron manufacturer for maintenance and repairs. Cyclotron operation is usually fairly automated and, if required, the cyclotron operator can carry out other tasks, such as setting up an FDG synthesis module, while the target is being irradiated. In a facility producing several batches of FDG per day, a cyclotron operator is likely to be required full time.

3.2.2. Production radiochemist/technician

The radiochemist's primary duties entail manufacturing and dispensing FDG in compliance with GMP guidelines. FDG is produced in a synthesis module requiring proper set-up with the correct reagents. Furthermore, attention

to aseptic processing is essential in manufacturing FDG, since it is generally not steam sterilized.

Specific responsibilities of the production person include the following:

- Planning production (doses required) and liaising with cyclotron and QC staff about timely production and release;
- Preparing the synthesis and dispensing modules;
- Preparing reagents and loading modules in readiness for FDG synthesis and subsequent dispensing;
- Carrying out routine synthesis of FDG;
- Maintaining FDG synthesis equipment;
- Preparing sterile vials, stoppers and essential glassware;
- Performing all production related functions in compliance with standard operating procedures and aseptic methodology;
- Maintaining production documents;
- Ordering, stocking, and maintaining inventory of production supplies;
- Packaging radioactive shipments for customers;
- Preparing and updating SOPs and pertinent GMP documents;
- When required, operating the cyclotron for isotope production and/or performing quality control on FDG (cross-training);
- Participating in training programmes.

The production person should have a diploma or degree in chemistry, pharmacy or biological sciences. Training and experience in aseptic technology and GMP practices is essential for consistent and reliable production of FDG conforming to required quality specifications. Training in the operation and minor troubleshooting of specific synthesis and dispensing modules is necessary. Working knowledge of radiation safety practices is also essential. Regulatory requirements necessitate good documentation practices, which requires considerable time and attention to detail. A production chemist should be well versed with the preparation of production related documents. In a small facility, the production chemist may have to operate the cyclotron or perform quality testing, necessitating cross-training in both areas. Production staff must also possess working knowledge and have regular training in radiation protection.

3.3. QUALITY ASSURANCE/QUALITY CONTROL STAFF

The two facets of quality management are: quality control (QC) and quality assurance (QA). QC is concerned with measurements, analysis and evaluation of results, the purpose of which is to ensure that a product conforms to all quality

requirements. QA, on the other hand, is a wide ranging concept that covers all aspects that individually or collectively influence product quality. The members of the QA/QC staff are responsible for ensuring that the product is manufactured according to established SOPs, and they must maintain the documents associated with GMP. The IQ, OQ, PQ and validation documents for all equipment need to be generated and archived. It is recommended that only one person be made responsible for the security of all documents and that the chosen person be the only one authorised to make changes to these documents under usual circumstances. In a small facility, all these functions may become the responsibility of a single individual.

3.3.1. Quality control person

The quality control person's primary job is to test and qualify the FDG, and the materials and supplies used in FDG production. The quality assurance person, on the other hand, has the responsibility of assuring the overall quality of operations. However, in a small facility, all aspects of QC/QA described herein may become the responsibility of the QC person.

Specific responsibilities include the following:

- Performing various analyses using specific equipment to assess the quality of FDG;
- Recommending disposition (approved or rejected) of product batches based upon test results;
- Testing and qualifying (verification) of raw materials and supplies used in production;
- Performing calibration and standardization of equipment, and ensuring the good working order of equipment;
- Maintaining accurate records of tests performed and their results;
- Monitoring result trends for continuous improvement;
- Performing stability and validation studies;
- Understanding and promoting compliance with GMP;
- Preparing, updating, maintaining and taking custody of SOPs and pertinent GMP documents;
- When required, performing FDG synthesis (cross-training);
- Verifying that the premises and QC equipment are correctly maintained;
- Participation in training programmes.

The quality control person must have a diploma or a degree in chemistry, pharmacy or biological sciences with experience in analytical methodology (chemical and microbiological), GMP, and an understanding of FDG synthesis. It

is essential that the QC chemist possess an understanding of and familiarity with tests that need to be carried out, and with the associated potential problems accompanying each of the analytical tests. This especially includes the need for a good understanding of pharmacopeia monographs (Ph.Int., USP and Ph. Eur.). Courses in laboratory operations and a working knowledge of radiation protection practices are required. It is also essential that each facility has a person who is knowledgeable in the quality assurance aspects described earlier in this section.

3.3.2. Qualified person

An FDG production facility must have a designated person who is responsible for oversight and who has the authorization to release product for patient use. (This person may be known as the qualified person, the responsible person, or the authorized person. Moreover, national regulations will determine qualification and certification requirements.) This is the person who is ultimately responsible for ensuring that the product conforms to required quality specifications and is safe to use for patients. This person should have a degree in physical, chemical, pharmaceutical or biological sciences and more importantly, possess practical and preferably extensive knowledge regarding all aspects of GMP and quality management. In addition to technical proficiency, a qualified person usually needs to be ‘certified’ by national authorities. The qualified person ensures that manufacturing and testing are performed in compliance with GMP standards and national pharmaceutical manufacturing regulations. Facility management must have confidence that the qualified person will perform his/her duties responsibly. The qualified person may be required to perform other job functions (such as facility management, training, production, QC, etc.) and is not restricted exclusively to product release. In the absence of a person with extensive knowledge in GMP, quality management and FDG manufacturing, it is advisable to seek out a consultant with these attributes.

3.4. ADMINISTRATIVE AND MAINTENANCE STAFF

Every facility needs to have an administrative organization associated with it. There are management duties, secretarial tasks and engineering tasks associated with daily operations. The job titles listed below need not be full time employees of a facility. The duties may be shared by more than one person, and individuals may perform many aspects of these job duties in addition to other primary job functions. For example, the cyclotron operator in many facilities are physicists who could also function as radiation protection officers with proper

training. Below are some job duties that should be considered when planning staffing requirements. These need not be full time staff members of the cyclotron facility, but their services should be available when required.

3.4.1. Manager

A facility manager is the coordinator of a facility's day to day activities and a link with higher management. A manager should have sufficient insight into and in-depth understanding of the field to properly supervise and train technical staff. Production of radioisotopes may be primarily considered to be a technical task. While the production of radiopharmaceuticals using GMP protocols is technical as well, a culture must be developed within a facility by its management and senior staff. A manager should have sufficient experience and expertise to train staff in these subjects. Also, a manager should have the ability to detect and correct deficiencies in the overall operations of a facility. In a small facility, one of the primary employees mentioned in Sections 3.2 and 3.3 may be designated as the manager, if qualified.

3.4.2. Radiation protection officer

As radioactive materials are handled in an FDG production facility, it is essential to have the services of a radiation protection officer (RPO) available on-site or from an external source. An RPO evaluates the adequacy of radiation protection performance and interprets radiation protection requirements. When planning a facility, it is advisable to seek the services of an RPO for the layout design, thus ensuring both radiation protection and compliance with regulatory requirements. The RPO should develop standard operating procedures pertaining to the administrative and operational control of radiation within a facility, and should also be available to help the work force with radiation protection concerns and training in achieving ALARA (as low as reasonably achievable) radiation levels.

3.4.3. Engineer(s)

There are engineering functions which are typically required on a routine basis in an FDG facility. There are the first line maintenance and troubleshooting functions for the cyclotron, synthesis modules and laboratory equipment which must be performed immediately, and liaison with equipment manufacturers for complex remedial actions. The engineer in this position should have some experience in electronics, vacuum systems and cyclotrons.

3.5. TRAINING

One of the most important aspects of operating an FDG manufacturing facility is personnel training. GMP guidelines clearly state training requirements and the need to maintain records of such training. Basic training in GMP and quality assurance must be provided for all personnel at the time of initial hiring, and special training should be provided according to assigned duties. Furthermore, for all new employees hired, equipment specific and site specific training should be and can be provided by an experienced person or through the services of an external consultant. A system must be in place to ensure that all training remains current. Moreover, retraining should be a process of continuing education to ensure that staff performance continues to be at the highest level to guarantee the highest quality product and best safety standards in radiopharmaceutical production. This is particularly true when a new process or piece of equipment is to be brought into daily use. Each individual's training record should include the specifics of training provided. An example of a training log is shown in Section A-18 in the Annex to this publication. Some important training topics include:

- GMP (concept and application);
- Quality control (analytical applications);
- Quality assurance;
- Radiation protection;
- Equipment specific (production and QC) training;
- New processes and procedures;
- Aseptic operations.

3.5.1. Continuing education

Employees should be retrained on a regular basis. This time period varies based on the type of training required and local or national regulations, but a reasonable time is every two years, since training tends to decline after that period of time. Complacency also becomes a possibility over a period of time and should be guarded against.

Employees should periodically reread SOPs and other procedural documents to ensure that practices have not drifted from those specified. SOPs should be reviewed on at least an annual basis to ensure that they stay up to date.

An important aspect of GMP is the development of a 'quality culture' within a facility. Concurrently, good radiation protection practice and a strong safety culture are also essential components of an FDG production facility. Management should convey in unambiguous terms the expected operations practices and quality policies of their facility.

3.6. SUMMARY

An FDG manufacturing facility requires a relatively small number of primary employees, depending largely upon the size and scope of a facility. Staff is broadly divided into production, quality assurance and administration. In contrast to primary job functions, some job functions do not require full time employees; these functions may be fulfilled by available staff through other channels, or through the assignment of multiple responsibilities to primary staff. Due to a number of factors, including a shortage of experienced people, it is not unusual for a limited number of people to perform multiple tasks, particularly in a small FDG facility. Therefore, it is essential that every team member be able to perform at least one additional job in the production chain. This is achieved through cross-training at the onset, followed by continuous training through a formal programme. Single person production and QC should be avoided and must be undertaken only in extreme and rare cases. At least one person within a facility must have extensive knowledge of FDG manufacturing and practical knowledge of GMP and quality management, usually the qualified person with the authorization for product release.

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4. EQUIPMENT

4.1. INTRODUCTION

In addition to physical structure, as discussed in Section 2, an FDG production facility must have a wide range of equipment to carry out the production of FDG, analysis of the final product and reagents used in preparation, including shielded hot cells for radiation protection and laminar flow enclosures for sterile preparations. Furthermore, production equipment must include a cyclotron for the production of [^{18}F]fluoride, one or more FDG synthesizers, and perhaps a dispenser to fractionate the bulk radiopharmaceutical into unit doses. Analytical laboratory equipment is comprised of a variety of devices needed for various quality assessment activities pertaining to FDG and its components.

Equipment should be selected according to the expected level of performance, ease of operation, technical support for repairs and maintenance, and to facilitate compliance with GMP. Furthermore, all equipment should be validated prior to being put into service. This is accomplished by following the procedures for design, installation, operation and performance qualifications (DQ, IQ, OQ, PQ). Selection of equipment (DQ) conforming to these requirements is the responsibility of the facility planners. Installation and operation qualifications are usually provided by the equipment supplier, while performance assessment is usually the joint responsibility of the supplier and the user. Furthermore, all equipment used in production or quality control must have regular checks for performance and preventive maintenance, and some items may require frequent calibration. It is a good practice to maintain records of the initial validation of equipment, as well as subsequent usage, maintenance and repairs.

Production and QC equipment should be placed in controlled areas fulfilling GMP as well as radiation protection requirements in order to satisfy radiopharmaceutical regulatory compliance and staff safety. Access to these controlled areas should be restricted to facility personnel only. Sufficient bench space should be made available in the quality control laboratory to ensure freedom of movement and ease of operation. Some principles guiding the layout of laboratory equipment can be found in IAEA Technical Reports Series No. 471 [4.1].

In this section, the most common items of equipment used in the manufacturing and quality control of FDG are described.

4.2. CYCLOTRON AND TARGETRY

FDG manufacturing begins with the production of [^{18}F]fluoride in a cyclotron. The parameters of [^{18}F]fluoride production are explained briefly in this section. A more complete description of these processes can be found in Ref. [4.2].

Two important characteristics of cyclotrons pertaining to the production of [^{18}F]fluoride are the proton beam energy and the beam current being used. These two factors, along with the target volume, will determine how much [^{18}F]fluoride can be produced in a given amount of time. To some extent, the higher the energy and the beam current, the greater the fluoride production, as explained in Sections 4.2.2 and 4.2.3 below. For a facility making FDG solely for its own imaging needs, the production of [^{18}F]fluoride, and hence the amount of FDG produced is not at all limited. Even production for multiple PET centres is usually not limited, as longer and dual beam irradiations, and/or multiple productions per day are practically routine at many such facilities.

The ultimate choice of cyclotron type at a new facility, and its specific proton beam energy and current, will depend largely upon programme scope and available resources, in particular financial and spatial resources. Almost all currently available commercial cyclotrons are negative ion machines, and several makes and models are available to suit the needs of a facility. A proton beam is extracted by stripping the electrons off the H^- ion and creating an H^+ ion, which curves in the opposite direction within the magnetic field and is therefore pushed out of a machine. This type of extraction is very efficient, and there is little residual activation of the a machine's interior compared to older positive ion machines. This means that the targets are the main source of radiation dose in cyclotron operations.

4.2.1. Commercial cyclotrons

The characteristics of several commercial cyclotrons are provided in Ref. [4.3]. Table 4.1 shows the typical proton energy and beam current capabilities of several common PET cyclotrons.

4.2.2. Beam energy and [^{18}F]fluoride

The yield of [^{18}F]fluoride will depend upon the energy exerted by a proton beam on a target. Figure 4.1 represents the theoretical thick target yield, and is included here to show the relative dependence of [^{18}F]fluoride yield on proton beam energy.

TABLE 4.1. COMMERCIALY AVAILABLE PET CYCLOTRONS: PARTICLE ENERGIES AND CURRENTS

Cyclotron model	Manufacturer	Proton energy (MeV)	Proton beam current (μA)
TR14	ASCI	14	300
TR19	ACSI	13–19	300
Minitrace	GE	10	50
PETtrace	GE	16.5	100
Cyclone 10/5	IBA	10	100
Cyclone 18/9	IBA	18	150
Kotron 13	Sung Young	13	50
Eclipse HP	Siemens	11	120
Eclipse RD	Siemens	11	80
HM12	Sumitomo	12	100
Sumitomo HM18	Sumitomo	18	150
AIMA PN	Thales	14	100
RIC 18/9	NIIEFA	18	100

Note: Information available at the time of compilation (February 2010).

F-18 Yields

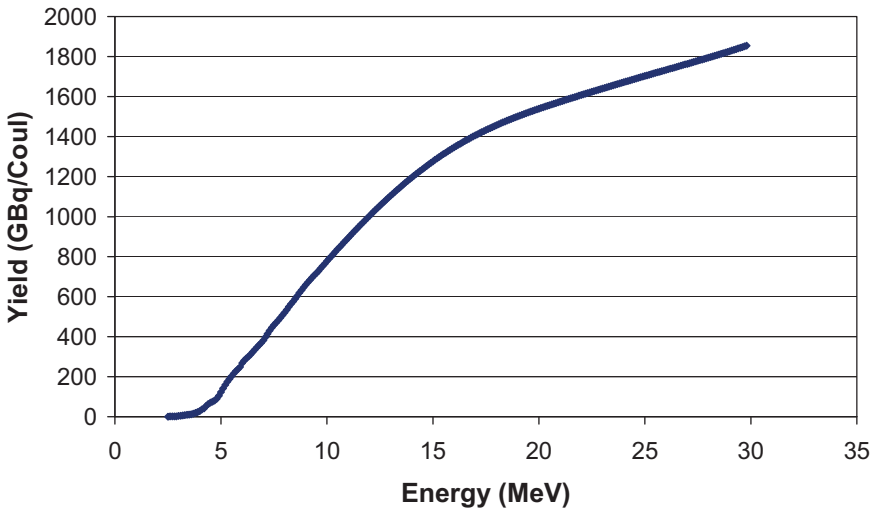


FIG 4.1. Variation in yield as a function of beam energy.

As can be seen from the chart, the yield of [¹⁸F]fluoride rises nearly linearly from 5 to 15 MeV and gradually, at a lower rate, above 15 MeV. Table 4.2 shows clearly that a 15+ MeV cyclotron will theoretically produce at least 50% more [¹⁸F]fluoride compared to a 10–11 MeV cyclotron for the same beam current (energies above 18 MeV are not really necessary for the practical production of [¹⁸F]fluoride).

4.2.3. Beam current

The beam current of a cyclotron determines how much radioisotope can be produced at a given energy. In theory, production yield is directly proportional to the beam current. In practice, beam current — which can be used on any target — is determined by the ability to remove the heat produced in a target by a beam. All of the cyclotrons listed in Table 4.1 are capable of generating a beam with a current of at least 50 μ A. The liquid targets used for ¹⁸F production are usually not run above 100 μ A because of the limitation imposed by the dissipation of heat generated during irradiation. Typically, a given target with a given operating pressure has an optimum current, at which the production rate is the highest. This need not be the highest possible current. Ideally, the current used should be optimised against the amount of FDG needed at the end of synthesis (EOS), as there is some coupling between the quality of the target water and irradiation conditions and the labelling yield.

4.2.4. Dual beam irradiation

Most of the cyclotrons listed in Table 4.1 have the capability of simultaneous dual beam irradiation. For a facility needing to produce large

TABLE 4.2. THICK TARGET YIELDS:
¹⁸O(p,n)¹⁸F REACTION

Energy (MeV)	¹⁸ F yield	
	mCi/ μ A at saturation	GBq/ μ A at saturation
20→2.5	395	14.6
18→2.5	373	13.8
15→2.5	327	12.1
11→2.5	230	8.5
8→2.5	132	4.9

quantities of FDG for distribution to multiple PET centres, dual beam irradiation provides an option to meet the demand. The [^{18}F]fluoride activity produced in this mode may be delivered to two FDG synthesis units or pooled for delivery to one synthesizer.

4.2.5. Targets

The [^{18}F]fluoride target body may be constructed from silver, titanium, niobium or tantalum. Construction of targets is slightly different for different manufacturers. Historically used silver targets are being replaced by niobium and tantalum targets, as the silver ones require more maintenance. The fluoride produced by tantalum and niobium targets is more reactive, resulting in slightly higher FDG yields. The best choice is a robust target that does not require a lot of maintenance even if the yield is slightly lower, since the production of [^{18}F]fluoride is generally not limited at most small FDG facilities. Lower target maintenance also results in reduced radiation exposure to personnel maintaining the targets.

4.2.6. Yields

The total amount of [^{18}F]fluoride that can be produced is dependent on energy, beam current and irradiation time. Other factors influencing total yield will be the per cent enrichment of ^{18}O water, target body construction, and target design. As a simple example, one can expect approximately 111 GBq (3 Ci) of [^{18}F]fluoride in a single target during one hour of irradiation with a 10–13 MeV proton beam at a beam current of 50 μA , and approximately 16 GBq (4.5 Ci) for a higher energy machine (14–19 MeV). This yield can be doubled by running dual targets, and also by increasing the beam current and irradiating for a longer period. The saturation factor, however, limits the amount of ^{18}F that can be produced during long irradiations and the heat generated within a target also limits the beam current that may be put onto a target. Please refer to TRS 465 for a detailed discussion of these topics [4.3].

The ^{18}O enriched water used in the production of ^{18}F is usually 97–99% enriched in ^{18}O . If the enrichment is lower, more ^{13}N is produced from the $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ nuclear reaction, leading to potential radionuclidic contamination issues in the finished FDG. The enriched water may be collected after irradiation and purified for reuse. In this case, it is essential that the process of purification, usually re-distillation, is validated, ensuring [^{18}F]fluoride production of acceptable purity and the optimum labelling yield of FDG. Most facilities only use the water once and then discard it or send it back to be reprocessed by the manufacturer.

4.3. FDG PRODUCTION EQUIPMENT

FDG production equipment includes an automated FDG synthesis module and possibly a dispenser to fractionate the bulk radiopharmaceutical into unit doses. Associated hardware includes the lines to deliver fluoride from the target to the synthesis module and to deliver FDG bulk from the module to the dispenser. Also included are the hot cells in which the synthesis and dispensing modules would be placed.

4.3.1. FDG synthesis modules

For the obvious reason of radiation considerations arising from a very large quantity of radioactivity, practically all FDG manufacturing facilities use automated FDG synthesis modules to carry out the production of FDG. In all cases, modules must be placed within a shielded enclosure in order to reduce radiation exposure. A wide range of synthesis modules are available from various manufacturers. All FDG synthesis modules employ the nucleophilic displacement reaction for incorporation of ^{18}F fluoride into a suitable precursor for synthesis of labelled FDG (see Section 5 for details). Also, most FDG synthesizers produce FDG of similar yields in a comparable amount of time. Differences exist mainly in the way a synthesizer is set up, either using pre-packaged cassette inserts, or fixed tubing and vials with reagents prepared by an operator and loaded into a module. Another difference may be in the quantities of various reagents used in synthesis. In all cases, assembly of components and loading of reagents must be performed aseptically in order to avoid microbiological contamination and to comply with GMP requirements. A ready to load type cassette with the reagents already measured and components assembled may provide an advantage in terms of better control of aseptic handling, but may also result in additional operational costs in comparison with the 'manual' method which costs less, but requires careful (aseptic) handling. Selection would, therefore, depend upon several factors, most notably the technical competency of the staff and the cost. There is one major difference in chemical synthesis among these modules, and that is the manner in which hydrolysis of the protective groups in the synthesis is performed (see Section 5 for details). There does not seem to be a preference for base or acid hydrolysis; therefore, selection of an FDG synthesis module may depend almost entirely upon other factors, notably initial investment and operating costs. (With some synthesis modules, the mode of hydrolysis is selectable.) In order to ensure reliability and improved operator radiation protection, the possibility of installing two FDG synthesis units should be considered.

4.3.2. Dispensing equipment

In a production facility serving multiple PET facilities, bulk FDG is dispensed into individual vials or syringes. The two primary requirements are: radiation protection of operators through adequate shielding and protection of the product by performing the operation in a controlled environment. Depending upon the number of doses to be dispensed or the frequency of dispensing during the day, a facility may invest in elaborate dispensing equipment placed within a hot cell fitted with HEPA filtered air. Alternatively, a facility performing a limited number of such operations in a day may opt for a simpler laminar flow cabinet or an isolator containing a suitable liquid transfer apparatus to maintain sterile working conditions behind appropriate shielding. In either case, dispensing of FDG must be carried out in a class A sterile environment.

4.3.3. Delivery lines

Typically, [^{18}F]fluoride from the target must be transferred to the synthesis unit, where the ^{18}F is extracted from the irradiated aqueous solution and the ^{18}O enriched water is recovered. The transfer lines should be constructed from a plastic material, preferably PEEK (poly ether ether ketone) or some other radiation resistant material, and adequate radiation shielding must be taken into consideration. The lines should be cleaned and dried periodically, preferably without using organic solvents. Several lines should be installed even though they will not be used immediately, since it is easier to string the lines at the beginning than it is to try to add more lines later. Validation studies should include assessment of microbiological burden. Transfer lines should be kept empty and dry when not in use to minimize the risk of microbial growth in the lines.

4.3.4. Hot cells

The hot cell is a shielded enclosure for handling highly radioactive materials and serves as an isolator, providing a clean environment for the preparation of radiopharmaceuticals. The number of hot cells and their size is determined by the production capacity of a facility and the particular synthesizer being used. The thickness of lead shielding is determined by the quantity of FDG being processed; 75 mm of lead or the equivalent is typical. For radiation safety reasons, the air pressure inside hot cells should be maintained well below the pressure of the room in which a hot cell is situated. Furthermore, each hot cell should be equipped with an appropriate air handling system (with a minimum of inlet and outlet air filters). Lead glass windows or TV monitors should be provided to allow operators to observe operations. While a production hot cell

will generally not need manipulators or tongs, manipulators or a robot arm may be needed for dispensing hot cells, depending upon the dispenser used.

It is common to have two separate hot cells: one for housing synthesis modules (two FDG synthesis modules are recommended for redundancy) and another for the dispenser. Hot cells for synthesis modules should provide a class C environment. If multi-dose dispensing is to be performed, the dispensing hot cell should provide a class A environment over the dispensing area, along with a class B background environment in the rest of the containment. As an alternative solution, a shielded isolator system assuring class A working conditions can be used. In this case, the surrounding area can be class C or D. Dispensing cells should have a class B airlock system for the entry of disposable materials.

4.4. QUALITY CONTROL EQUIPMENT

A QC laboratory has two primary functions: to test FDG radiopharmaceutical and to test and analyse raw materials and supplies used in the production of FDG. Each QC lab should be equipped with a range of analytical instrumentation, including generic as well as specific equipment, allowing for the performance of required tests (see Section 6 for details of tests to be performed). Some equipment may not necessarily be required, but its availability improves the work flow and quality aspects of a facility. The criteria for selection of some equipment and its use in qualifying raw materials and FDG batches are discussed in the following sections.

4.4.1. Radiation measurement equipment

FDG must be tested for radionuclidic purity, radionuclidic identity and total activity. These tests can be accomplished using different types of radiation measurement equipment. This equipment is briefly described here. Not all such equipment must necessarily be available in a laboratory.

4.4.1.1. *Multichannel analyser*

The presence of a 511 keV gamma peak and absence of other gamma peaks is one of the criteria for the identification and purity measurement of the ^{18}F radionuclide present in FDG. The gamma spectrum can be obtained with a gamma spectrometer consisting of a single channel or multi-channel analyser with sodium iodide or germanium (GeLi or HPGe) detector. This test may be performed in another laboratory if the gamma spectrum need not be recorded for every batch of FDG.

4.4.1.2. *Gamma counter*

Determination of the radionuclide half-life in the product can be performed using a gamma counter such as a sodium iodide well counter, wherein the radioactivity is measured over a definite time period in order to calculate half-life. Some gamma counters can be used as multichannel analysers to determine the presence of ^{18}F and radionuclide contamination, but not necessarily for their identification.

4.4.1.3. *Dose calibrator*

A dose calibrator is required for the measurement of total radioactivity (radioassay) in product vials or syringes to be dispatched to PET facilities. Moreover, it can be used to determine radionuclide half-life.

4.4.2. Gas chromatograph

Identification and quantification of residual solvents (acetonitrile, ethanol, and perhaps ether) in the final solution may be performed with a gas chromatograph (GC). A GC instrument should be equipped with a flame ionization detector (FID) and an appropriate column (packed column or capillary column) for analysis of the residual solvents mentioned above. An integrator with software to identify and quantify residual solvents is a useful feature and is generally supplied with the equipment.

4.4.3. TLC radioactivity scanner

Thin layer chromatography (TLC) is used to determine both the radiochemical identity and the radiochemical purity of a final FDG product. A radioactivity scanner is recommended for quantitative measurement of radioactivity distribution corresponding to individual spots on the TLC. Radioactivity scanners suitable for quantitative analysis can either be gas proportional counters or scintillation counters mounted such that the entire plate is scanned.

4.4.4. HPLC

High performance liquid chromatography (HPLC) equipment can be used both to test raw materials and also for the measurement of radiochemical purity. HPLC equipment may or may not be required depending upon testing needs. However, availability of this equipment can facilitate validation studies during

initial set up and at times when major changes occur at a facility that may affect product quality. A HPLC system can be purchased as separate components (including a pump, columns and detectors), or as a complete integrated unit. Both a mass detector (an amperometric or refractive index) and a radioactivity detector are required when working with FDG. Both TLC and HPLC are used in routine, daily QC procedures.

4.5. MICROBIOLOGICAL TESTING EQUIPMENT

Assurance of the microbiological purity of final FDG product is achieved using tests for bacterial endotoxin (BET) and sterility. Laboratory equipment is available to quickly assess the presence of endotoxin in FDG product. Sterility assessments, however, are not possible prior to the release of a product for patient use. An indirect measure of sterility is undertaken through the membrane filter integrity test (often performed as a bubble point test). The equipment needed for these tests is described below:

4.5.1. Endotoxin test

The bacterial endotoxin test is based on the formation of a LAL reagent gel clot in the presence of endotoxins. This test must be carried out in a thermally regulated and vibration free environment. The gel formation may be inspected manually or with a turbidimetric device. Alternatively, an endotoxin test can be performed using an endotoxin test reader, which is simpler and saves a great deal of time. The device is based upon turbidity or kinetic measurement. The test requires approximately 20 minutes and supplies an easily readable test result and quantitative assessment of endotoxin levels.

4.5.2. Filter integrity test

In most facilities, FDG is not sterilized with steam, but rather manufactured under aseptic or low bioburden conditions with the final product being filtered through a membrane filter. Since sterility test results are not immediately available, assessment of membrane filter, integrity may be employed as a product release criteria for the indirect measure of sterility. The test entails measuring air flow through a filter and specifying the point at which the filter allows air (or nitrogen gas) to pass through. There are automated as well as manual systems available for performing this test. It must be cautioned that the filter integrity test does not replace the required sterility test.

4.6. GENERAL LABORATORY EQUIPMENT

In addition to the equipment described already, other equipment is required to have a fully functioning manufacturing facility. Although not all the equipment that may be required is listed, the important pieces of equipment that should be available at a facility are described below. This equipment is similar to that used in any normal chemistry laboratory and requires the same care regarding selection and maintenance. It should be remembered that even small samples of finished product can be highly radioactive, thus careful handling is necessary.

4.6.1. Fume hoods

For environmental and personal protection from chemicals and volatile solvents, at least one fume hood should be available in a lab. Fume hoods should have no air recirculation and should be located to minimize cross-drafts and turbulence. A face velocity of 0.5–0.6 m/s (100–125 linear feet per minute) of air is typically required, and should be continuously monitored. Typical safety measures, including fire safety and prevention of small pieces being sucked up the exhaust, etc. should be specified during equipment selection. The development of new synthesis procedures can also be carried out in these hoods as long as the amount of radioactivity is kept low and there is not a serious hazard of airborne radioactivity. A fume hood equipped with a charcoal filter will facilitate containment of volatile radioactivity.

4.6.2. Laminar flow cabinets

Setting up an FDG synthesizer for a production run may require the measuring and assembling of reagents and components in an aseptic manner. These and other aseptic operations are typically performed in a laminar flow cabinet (LFC). An additional LFC may be required for aseptic sampling/testing of the finished product or QC samples. These cabinets provide clean air in the working area and a constant flow of air out of the work area to prevent room air from entering. The air flowing out from the cabinet also suspends and removes contaminants introduced into the work area by personnel. The most important part of a laminar flow cabinet is a high efficiency particle retentive filter. Room air is taken into the unit and passed through a pre-filter to remove gross contaminants (lint, dust etc). The air is then compressed and channelled up behind and through the HEPA filter so that the purified air flows out over the entire work surface in parallel lines at a uniform velocity. Special versions of LFCs, called type II safety benches, provide both product and personnel protection. Isolators are considered to achieve the same results.

4.6.3. Particle counter

The validation and monitoring of various areas with controlled air environments requires the measurement of particle count and particle size. This is accomplished through the use of a suitable particle counter. Furthermore, it is also necessary to assess viable particles in critical areas, such as cleanrooms and LFCs. Microbial contamination can be monitored using agar plates both as settling plates and contact plates. The reading and possible classification of such microbiological samples can be outsourced.

4.6.4. Refrigerators and freezers

Many of the reagents used in chemical synthesis are temperature sensitive and therefore must be stored at lower temperatures. Other supplies such as endotoxin test kits may be temperature sensitive. Refrigerators should be specified for the required temperature range, and also sufficiently large to accommodate supplies necessary for the required lead time for procurements. Some synthesis supplies (for example mannose triflate) may require storage at -20°C , necessitating the availability of a freezer. A 24 hour continuous recording of temperature (with an alarm) will ensure that any malfunction is detected quickly and does not detrimentally affect stored material.

4.6.5. Ovens/incubators/sterilizers

Ovens, incubators and sterilizers are required only if a facility plans to prepare sterile and pyrogen free components (vials, stoppers, glassware), and also plans to perform sterility testing. Some samples for sterility or bioburden testing are to be incubated under controlled temperature conditions before a final reading is made.

4.7. MISCELLANEOUS LABORATORY EQUIPMENT

As in any analytical laboratory, various other instruments are needed, including a pH meter, an osmometer, a melting point apparatus and balances. A small item equipment budget should be allocated during the planning stage to cover these costs.

4.7.1. Melting point apparatus

Assessment of melting point can be used as an identification test for some reagents used in FDG manufacturing. A melting point apparatus is not mandatory, but is useful for quality testing of raw materials. If used, it is necessary that the apparatus is calibrated with primary melting point standards that have known melting points.

4.7.2. Osmometer

An osmometer may be required for initial validation studies and for periodic rechecks, but normally the isotonicity of a finished product is not checked and compliance with a specified value is trusted to have a constant composition and volume.

4.7.3. Balance

Analytical weighing balances are required in a QC laboratory and may be required in a production area. A balance can also be used to determine volume in a multi-dose vial containing final FDG product. The balance with a printer allows for the recording of weights, which is a good option for compliance with GMP documentation.

4.7.4. pH meter

Measurement of pH is one of the requirements before release of the final product; this may be done using either a pH meter or with pH paper. The latter method is preferred because a smaller test sample is required. It is, however, necessary that pH paper be validated for its suitability with the aid of a calibrated pH meter.

4.8. EQUIPMENT VALIDATION

A prominent feature pertaining to equipment in a GMP compliant facility is the validation of equipment regarding design, installation, operation and performance qualifications [4.4]. It is essential that equipment be correctly selected for the intended purpose. For example, a facility planning to manufacture FDG for distribution to multiple PET centres may want to invest in a cyclotron of higher energy, and have several FDG synthesizers available, and a facility planning to perform sterility testing on-site should plan for the associated equipment necessary to perform such tests.

It is essential that the manufacturer develop a validation master plan, which when implemented correctly and according to the plan would provide an overall assurance of quality within a facility. Having selected and procured the required equipment, installation is usually performed by the supplier. The user should review the installation process and ensure that the equipment is installed correctly and that various components are integrated as per the design. Installation is followed by operation qualification (OQ), which is undertaken by the supplier to demonstrate that the equipment, having been correctly installed, operates according to specifications. This is followed by performance testing, with emphasis on the intended application. The user must collect sufficient data through repeated applications verifying performance.

All equipment that can have a bearing on product quality should be subjected to validation at the time of initial use, and subsequently at other times when the equipment undergoes major maintenance, repairs or has been out of use for an extended period of time.

4.9. SUMMARY

An FDG manufacturing facility requires equipment specific to production and quality testing of FDG, as well as the equipment found in a typical analytical and chemistry laboratory. It is essential that equipment be selected carefully during the planning stage, taking into consideration its intended use. Certain equipment requires attention to radiation protection and therefore should be specified accordingly. Some equipment, typically the FDG synthesizer, should be available in duplicate to ensure a reliable supply of FDG. Finally, it is essential that equipment be validated at the initial phase of facility installation and at periodic intervals to ensure reliable performance.

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5. FDG PRODUCTION

5.1. INTRODUCTION

The 2- ^{18}F fluoro-2-deoxy-D-glucose injection, an analogue of glucose (also referred to as FDG, ^{18}F FDG, fludeoxyglucose or fluorodeoxyglucose), is a positron emitting radiopharmaceutical containing no-carrier added radioactive ^{18}F , and is used in conjunction with Positron Emission Tomography for diagnostic medical imaging. It has a molecular formula of $\text{C}_6\text{H}_{11}^{18}\text{FO}_5$ with a molecular weight of 181.26 Da. The structure of FDG is shown in Fig. 5.1. It is the subject of monographs in several pharmacopoeias, including the Ph.Int., USP and Ph. Eur.

FDG production is a multi-step process that begins with a particle accelerator (typically a small or medium energy cyclotron) which produces the ^{18}F fluoride radionuclide through proton irradiation of oxygen-18 enriched water (target material) in a small enclosed volume (typically, 0.5–2.5 mL). After sufficient irradiation time (usually not more than three hours), the radioactive ^{18}F fluoride is transferred to a radiopharmaceutical production laboratory for further transformation into FDG suitable for injection.

The ^{18}F fluoride is collected inside an FDG synthesizer in a hot cell. Several automated chemical manipulations are carried out within the synthesizer, leading to a product which is ultimately formulated into a physiological injection solution and subjected to either sterilizing filtration or steam sterilization. The final product, FDG, can then be collected directly into a sterile injection vial or further fractionated (dispensed) into several different vials or syringes. The synthesizer and the dispenser (if used) are placed inside lead shielded hot cells to provide protection to operators from the ionizing radiation emanating from the product. The hot cells are also designed to provide an environment of air

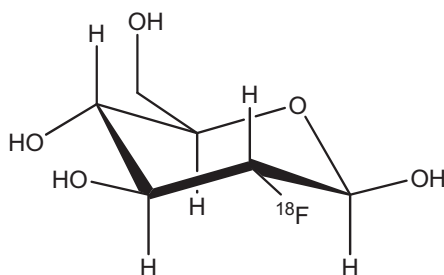


FIG. 5.1. Structural formula of 2- ^{18}F fluoro-2-deoxy-D-glucose.

classification compatible for pharmaceutical manufacturing. The entire FDG manufacturing process may be confined to the cleanroom environment or within controlled zones to help ensure the pharmaceutical quality of the finished product. A clean environment is particularly important for FDG manufacturing when the product is not subjected to terminal sterilization. Attention to aseptic manufacturing, therefore, is an essential component of FDG manufacturing.

The final step in the FDG manufacturing process is the assessment of quality and assurance of conformity to required quality specifications. Therefore, before a product is released for patient use, a series of quality control tests are to be performed on a representative test sample. The required quality parameters are assessed with validated test methods and equipment. Records are generated and the required documentation is evaluated for correctness prior to product release.

The frequency of FDG production depends entirely upon the scope of a producing facility and the number of PET centres being served by a facility. It may be synthesized only once or twice during a 24 hour period in a small production facility, followed by packaging and delivery to PET sites. On the other hand, production may be performed multiple times a day in a busy facility. FDG is provided to PET centres as a ready to use solution with all the necessary quality attributes of an injectable product. The solution may be packaged in single dose or multiple dose glass vials and generally does not contain any preservatives.

5.2. SYNTHESIS OF FDG

Synthesis of FDG begins with the production of [^{18}F]fluoride in a cyclotron, typically in a target chamber containing [^{18}O]H₂O, followed by a nucleophilic reaction with 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl- β -D-mannopyranose (mannose triflate), and subsequent de-blocking of the protecting groups (acetyl), resulting in FDG formation (Fig. 5.2). Synthesis is generally performed in an automated synthesis module placed in a hot cell with a controlled air environment. Several synthesis modules are commercially available, and all are practically based on the method reported by Hamacher et al. [5.1]. The production yield is reasonably good, typically >65% (corrected to EOB) within 25–45 minutes after collection of [^{18}F]fluoride.

The precursor molecule for the radiochemical synthesis of FDG is 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl- β -D-mannopyranose (see Fig. 5.2(1)), commonly called mannose triflate. This is a sugar molecule containing a suitable leaving group (trifluoromethanesulfonyl, also called triflate) for a facile nucleophilic reaction at carbon 2 in the molecule, while the other four potential reaction sites are blocked with protecting groups (tetra-acetyl).

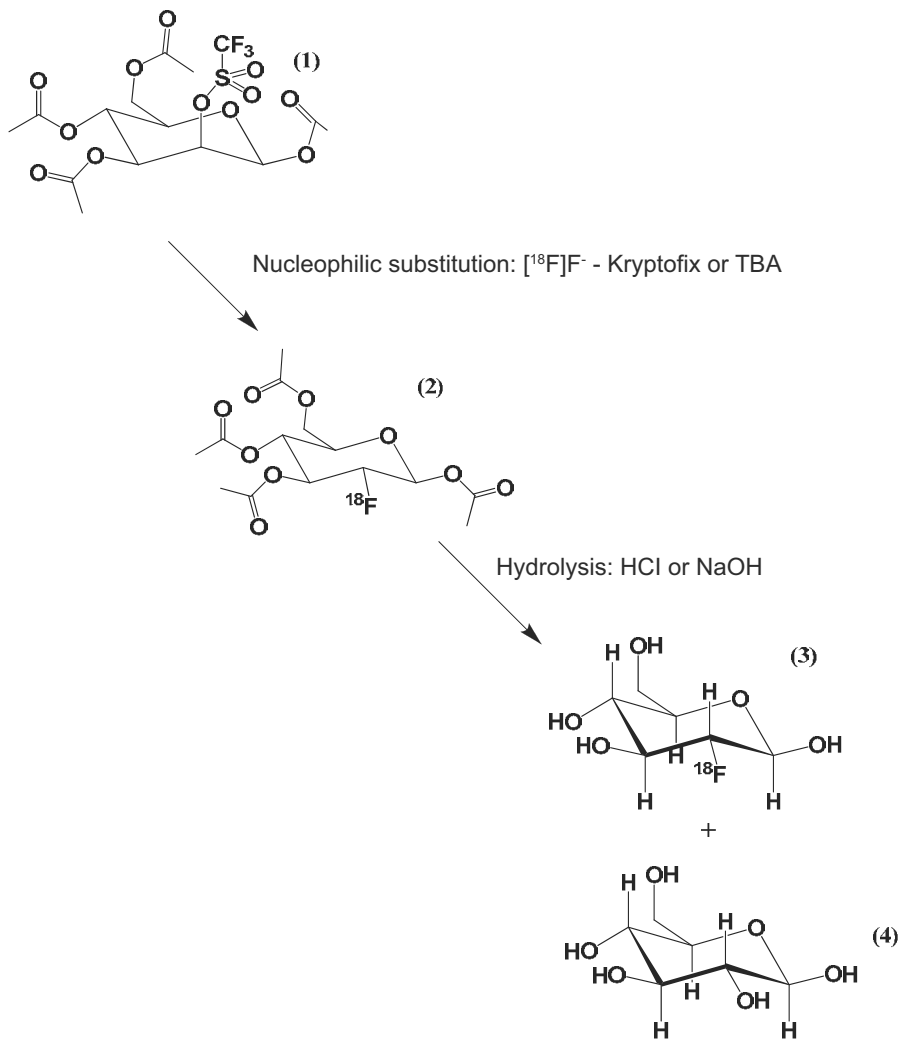


FIG. 5.2. Schematic of FDG synthesis.

In order to accomplish radiolabelling of glucose, the leaving group (triflate) is displaced by radioactive ^{18}F fluorine through nucleophilic substitution. The nucleophile (^{18}F fluoride) approaches the reaction centre from the opposite side of the leaving group and displaces the triflate. These types of reactions are referred to as $\text{S}_{\text{N}}2$ or bimolecular substitution reactions. These reactions lead to the formation of the intermediate tetra-acetylated fluorodeoxyglucose (see Fig. 5.2(2)). During this step, the conversion of the stereochemical centre of precursor

mannose into glucose takes place. The leaving group, triflate is converted to trifluorosulfonic acid ($\text{CF}_3\text{SO}_2\text{OH}$), which is removed at a later stage in the purification process.

In the subsequent step, the protective acetyl ester groups are removed by acid or base hydrolysis, leading to formation of the final product, FDG (see Fig. 5.2(3)). Non-radioactive D-glucose (DG) (see Fig. 5.2(4)) is a major by-product resulting from unreacted mannose triflate and will be present in all FDG preparations.

A brief explanation of the key features of this chemistry is provided below; a full explanation can be found in original literature [5.1]:

- *Why does the precursor molecule need acetyl protection?* It is necessary to make a substitution reaction possible at the desired location within the precursor molecule. The fluoride anion tends to form very strong hydrogen bonds with any type of polar groups such as hydroxyl groups present in sugars. This strong hydrogen bond formation prevents the fluoride from reacting in the desired nucleophilic substitution. Therefore, all hydroxyl groups of precursor are protected by acetyl ester moiety.
- *Why is Kryptofix 2.2.2 used?* Kryptofix 2.2.2 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8,8,8]hexacosane) is a phase transfer catalyst. On the one hand, it helps to solubilize the [^{18}F]fluoride anion in an anhydrous reaction solvent (acetonitrile). On the other hand, it helps to separate the strong ion pair formed between [^{18}F]fluoride and potassium by ‘caging’ the potassium cation. This helps to keep the fluoride free from interaction with potassium and make it available for a nucleophilic displacement reaction.
- *What is TBA?* TBA stands for tetrabutylammonium carbonate, which is an alternative phase transfer catalyst, and may be used instead of Kryptofix 2.2.2. Some synthesizers could use either TBA or Kryptofix. When TBA is used instead of Kryptofix 2.2.2 in a synthesis, a suitable quality control procedure for determination of TBA present in the FDG product is needed. A minor disadvantage of TBA use is that it needs to be converted from commercially available hydroxide into carbonate form. In this book we make the assumption that Kryptofix is used as the phase transfer catalyst.
- *Why is drying necessary?* The fluoride ion becomes more reactive under anhydrous conditions, creating a high and consistent yield of the fluorinated precursor of FDG. Drying is easily accomplished through azeotropic distillation of water with acetonitrile. Azeotropic distillation takes place at 55°C . After this, total drying is achieved by heating for a short while (3–5 min) at 85°C . Automated synthesis modules all use a combination of heating with vacuum and a trickle of inert gas (He or N_2) to remove the acetonitrile vapours and accelerate the drying process.

— *How is D-glucose (DG) (4) formed in the reaction?* D-glucose is always formed as a by-product of FDG synthesis from the unreacted precursor (see Fig. 5.2(1)) by hydrolysis of tetraacetylmannose triflate into D-glucose. Hence, D-glucose is mentioned in the Ph.Int. as a principal peak in the quality control test for chemical purity.

The typical steps taken during FDG synthesis are summarized in Table 5.1, along with process control parameters. Each step is explained further in the paragraphs to follow.

TABLE 5.1. STEPS IN THE SYNTHESIS AND PURIFICATION OF FDG

Step	Operation	In-process controls ^a
1	[¹⁸ F]fluoride production: ¹⁸ O(p,n) ¹⁸ F Irradiation of oxygen-18 enriched water in the water targets attached to the cyclotron by a beam of protons.	Target cooling; beam energy and current; beam efficiency; duration of irradiation
2	Trapping of [¹⁸ F]fluoride and recovery of oxygen-18 enriched water: Components: Anion exchange cartridge; K ₂ CO ₃ and Kryptofix 2.2.2. or tetrabutylammonium (TBA) carbonate.	Resin cartridge preparation; reagents qualification; radioactivity tracking
3	Drying of [¹⁸ F]fluoride: Azeotropic evaporation with acetonitrile at >85°C, ~10 min; Process may be repeated several times.	Temperature of reaction vessel; duration
4	Labelling of glucose with [¹⁸ F]fluoride: (nucleophilic substitution reaction) Component: tetraacetylmannose triflate; Solvent: anhydrous acetonitrile Temperature: 80–90°C; time: ~5 min.	Reagent qualification; temperature of reaction vessel; duration
5	Removal of protective groups (hydrolysis): Acidic or basic hydrolysis Reagents: HCl (1M); >100°C; time: ~8 min. <u>or</u> NaOH (1-2M); room temperature on resin cartridge or at ~50°C in solution; time: ~3 min.	Temperature of reaction vessel; duration

TABLE 5.1. STEPS IN THE SYNTHESIS AND PURIFICATION OF FDG (cont.)

Step	Operation	In-process controls ^a
6	Purification and formulation of the final FDG product: Solid phase extraction (SPE) cartridges (different combinations of alumina; ¹⁸ C; cation exchange and/or ion retardation depending on the synthesis module). Various formulations are used, depending upon the synthesizer type and model: Hypertonic NaCl (or bicarbonate); citrate; ascorbate; NaH ₂ PO ₄ buffer; sterile water for injection; saline.	Resin cartridges preparation; radioactivity tracking
7	Sterilizing filtration: 0.22 µm microorganism retaining filter.	Filter integrity
8	Sampling for QC; Quality assessment to ensure conformity with required quality specifications.	Representative sample; test protocols; quality test results
9	Dispensing into multiple vials or unit dose syringes for distribution.	Measurements; activity per vial or syringe
10	Packaging and shipping of FDG.	Package dose rate

^a ‘In-process controls’ are the key parameters for successful completion of production. Monitoring of these parameters also facilitates GMP compliance, since it is important that the manufacturing processes have built-in control methods and procedures in order to provide better reliability and to have an audit of the process. Examples of the parameters that can be controlled and recorded during FDG production are shown in this table for the purpose of eventual troubleshooting.

5.2.1. Step 1: Irradiation of ¹⁸O water with protons

The ¹⁸O(p,n)¹⁸F reaction with ¹⁸O enriched water produces ¹⁸F. Typical irradiation parameters include:

- ¹⁸O enrichment, typically >95%;
- Chemical purity of ¹⁸O enriched water, higher than 99.99%;
- Target volume, ranging from 0.5 to 2.5 mL;
- Proton beam of 8–19 MeV;
- Beam currents of 20–100 µA;
- Irradiation time from 30 min to 3 h.

A detailed discussion of cyclotron targetry and radionuclide production is beyond the scope of this book, but can be found in the literature, including Refs [5.2, 5.3]. The total amount of [¹⁸F]fluoride which can be produced is

dependent on energy, beam current and irradiation time. Other factors influencing total yield will be ^{18}O enrichment in water, chemical purity of enriched water, target material, target volume and target design. As discussed in Section 4, one can expect approximately 111 GBq (3 Ci) of [^{18}F]fluoride in a single target during one hour of irradiation with a 10–13 MeV proton beam at a beam current of 50 μA , and approximately 167 GBq (4.5 Ci) for a higher energy machine (14–19 MeV). The yield can be enhanced by increasing beam current and irradiation time as well as by using dual targets. The chemical purity of enriched water is critical for longer irradiations with high beam currents. The benefit of longer irradiation needs to be carefully optimized, as the yield reaches a saturation point with long irradiations. Also, heat generated within a target limits the beam current that may be put onto a target. Nevertheless, with a customary useful FDG yield of >65% (EOS yields corrected for decay), several curies of FDG can be produced in a single irradiation/production cycle for in-house use, as well as for distribution to other PET centres.

The oxygen-16 present in the target water leads to the production of ^{13}N through an (n, α) reaction, which is a radionuclidic impurity. Nitrogen-13 is a radionuclide decaying through positron emission with a half-life of 10 minutes and hence a major part of the ^{13}N will decay during the synthesis of FDG, leaving trace amounts. Nitrogen-13 can appear in several chemical forms including nitrate, nitrite, nitrogen and ammonia, depending on target conditions. Also, depending on the method of synthesis and purification of FDG, some amount of ^{13}N may be present in the final product, which will result in a shorter measured half-life.

5.2.2. Step 2: Extraction of [^{18}F]fluoride from the $\text{H}_2\text{}^{18}\text{O}$ target

After irradiation of enriched water, the mixture $^{18}\text{F}/[^{18}\text{O}]\text{H}_2\text{O}$ is transferred from the target onto a pre-conditioned anion exchange separation cartridge such as a QMA (quaternary ammonium anion exchange) SepPakTM column. The ^{18}F ions are retained on the cartridge, while unused [^{18}O] H_2O and cationic and other impurities are removed from the target and collected in a waste vial. Trapped ^{18}F is subsequently eluted from the cartridge with a solution containing K_2CO_3 and the phase transfer catalyst (Kryptofix 2.2.2) in acetonitrile and pharmaceutical grade water. The [^{18}F]KF/Kryptofix complex eluted is collected in the reaction vial. Quantities of K_2CO_3 and Kryptofix 2.2.2 vary depending upon the synthesis module. Typically, >95% of ^{18}F activity is retrieved. It is to be noted that chloro-deoxyglucose (CIDG), a potential chemical impurity in FDG, may form if an anion exchange resin is used in chloride form and is not conditioned properly. This potential impurity can be controlled in FDG by displacing chloride ions from the resin column with carbonate ions during conditioning.

The unused ^{18}O enriched water can be recovered from the waste vial for further use. However, it is important that impurities are removed through an efficient purification process prior to reuse for production of $[\text{}^{18}\text{F}]\text{fluoride}$. The recovered $[\text{}^{18}\text{O}]\text{H}_2\text{O}$ water from different batches can be pooled together and purified. However, the quality of the purified enriched water must be verified prior to its use for production of $[\text{}^{18}\text{F}]\text{fluoride}$. Purification (not to be misconstrued as enrichment) is required to remove the dissolved organics (acetonitrile, acetone and ethanol) arising from various sources, particularly with non-cartridge synthesis modules. The cost of the enriched water may be a determining factor in a decision to reuse it. GMP protocols in some Member States may not allow the reuse of ^{18}O enriched water.

5.2.3. Step 3: Drying of $[\text{}^{18}\text{F}]\text{fluoride}$

Effective drying of fluoride (virtual freedom from water) is a critical factor for a nucleophilic reaction to occur efficiently, leading to an eventually high yield of FDG. The required dryness is achieved through repeated azeotropic evaporation with anhydrous acetonitrile at $\sim 85^\circ\text{C}$ under inert gas and/or vacuum. It is essential that during each solvent removal step, the mixture be completely dry, and also that vessel temperature does not exceed 100°C in order to prevent the decomposition of Kryptofix 2.2.2.

Nucleophilic displacement reactions with fluoride are known to be quite difficult and unpredictable because of the fluoride ion being a weak nucleophile in an aqueous media, leading to very poor yields. In a polar aprotic media such as acetonitrile, fluoride undergoes nucleophilic reactions rather quickly. However, for fluoride to become an effective nucleophile, it must be available as reactive fluoride. The $^{18}\text{F}/\text{K}_2\text{CO}_3/\text{Kryptofix 2.2.2}$ complex is effectively an organic cation/inorganic anion salt soluble in acetonitrile, making the $[\text{}^{18}\text{F}]\text{fluoride}$ available in a highly reactive form.

5.2.4. Step 4: Labelling of the mannose triflate with the ^{18}F

In the synthesis of $[\text{}^{18}\text{F}]\text{FDG}$ based upon the method of Hamacher et al. [5.1], the 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl-beta-D-mannopyranose (mannose triflate) precursor reacts with $[\text{}^{18}\text{F}]\text{fluoride}$ through nucleophilic displacement. Although various precursor substrates have been described in literature, the use of triflate as the leaving group in the nucleophilic reaction with $[\text{}^{18}\text{F}]\text{fluoride}$ is found to be the most efficient, rapid and clean option. The reaction between the dry mixture of $^{18}\text{F}/\text{K}_2\text{CO}_3/\text{Kryptofix}$ prepared in the previous step and mannose triflate in anhydrous acetonitrile at $\sim 85^\circ\text{C}$ provides a high yield of intermediate labelled ^{18}F in less than 5 minutes. An added advantage

of using acetylated mannose triflate is that after the nucleophilic displacement of the triflate group by ^{18}F , the acetyl groups can easily be removed by hydrolysis (acid or base) to yield FDG.

5.2.5. Step 5: Removal of the protective acetyl groups by hydrolysis to form FDG

The final chemical step in FDG synthesis is removal of the four acetyl protecting groups, which is easily accomplished through hydrolysis with either a mild acid or a base. Both methods are equally effective.

Alkaline hydrolysis is the most commonly used method in commercial synthesis modules, since it requires less time and a lower temperature. In this case, the ^{18}F -labelled intermediate with intact acetyl groups is treated with a mild base (1–2 M NaOH) at room temperature to remove the acetyl groups. Alkaline hydrolysis may be performed directly on a C-18 cartridge at room temperature instead of adding base to the reaction vessel [5.4].

One possible drawback is that alkaline hydrolysis has the potential for epimerization of FDG to [^{18}F]Fluorodeoxymannose (FDM), which is a radiochemical impurity that should be controlled in the FDG manufacturing process. It has been shown, however, that the formation of FDM is a possibility only if hydrolysis is performed at a higher temperature [5.5]; epimerization at room temperature is negligible with an NaOH concentration of $\leq 2\text{M}$.

5.2.6. Step 6: Purification and formulation of the final FDG product

FDG is purified by passing through a series of columns (such as SepPakTM cartridges) for removal of impurities. These columns could include (not necessarily in this order):

- Cation exchange for removal of Kryptofix 2.2.2 or TBA;
- Alumina for removal of unreacted [^{18}F]fluoride;
- Ion retardation for neutralization and pH adjustment;
- C-18 or similar lipophilic column for removal of unhydrolysed and partially hydrolysed lipophilic intermediates.

In some synthesis modules, the unhydrolysed intermediates are trapped on a C-18 column and impurities are washed out prior to hydrolysis. The final step of formulation process includes adjustment of isotonicity, pH and volume. Some synthesis units utilize cation exchange and ion retardation resins to neutralize a solution, while others use buffers and the addition of a calculated quantity of

hypertonic NaCl or Na₂CO₃ or NaH₂PO₄ to achieve the pH and volume required for the final product.

For formulations consisting of high activity, the addition of a stabilizer may be considered. It would then be essential to determine the safe and effective use of a stabilizer, as well as supplying a quantitative assessment of stabilizer amount in the final preparation.

5.2.7. Step 7: Sterilizing filtration

Sterilizing filtration is performed by passing purified FDG solution through a 0.22 µm filter. Sterilization with steam (autoclave) may be applied in addition to sterilizing filtration, but is not seen as mandatory. The application of steam sterilization has the advantage of relatively reducing environmental control during synthesis and dispensing. In the case of sterilization filtration, it is essential that its effectiveness is accompanied by the assurance of a low bioburden upstream, production under aseptic conditions and the testing of filters used for integrity prior to parametric release of the final product.

5.2.8. Step 8: Sampling for quality control and quality assessment

To sample for quality control and quality assessment, a representative test sample is removed from a well-mixed bulk solution. Sampling must be done aseptically to ensure no contamination of the final product. The sample size is usually about 0.5 mL for QC, and about 1.0 mL is retained in case repeat tests are needed or there are product complaints. A retention sample may not be necessary; this is determined by the applicable national regulation. Tests for required quality attributes are performed using a test sample and the results are compiled prior to release of FDG radiopharmaceutical for patient use.

5.2.9. Step 9: Dispensing

The qualified FDG may be delivered to a PET centre as a multi-dose vial without further manipulation, or it may be dispensed into unit doses using either manual or automated systems. This process must be done in an aseptic manner and in a controlled environment, as required by the applicable GMP regulation. The product vial (or syringe) and outer lead shielding should be affixed with labels containing product information, including product name, total activity at reference time, expiration time and other pertinent information. Samples of such labels are found in Section A–8 of the Annex to this book.

5.2.10. Step 10: Packaging and shipping

Two primary concerns during packaging and shipping are: radiation protection of workers and the general public, and the maintenance of product integrity. Compliance with the applicable regulations and guidelines for radiation protection and transportation of dangerous goods must be observed during packaging and shipping (for example, International Air Transport Association (IATA) regulations). FDG is shipped either in a multi-dose vial or as unit doses in a vial or in syringes. A lead container — together with some absorbent material to take care of inadvertent spillage — is packed in a secondary container. Appropriate labels must be affixed on the vials/syringes, the lead containers and on the final packages before shipping.

Section 7 provides details about FDG transport regulations. The dose rate at the surface and at one meter from the surface of final packages should be measured and should not exceed the transportation regulatory limits for the type of packaging utilized. Personnel involved in transport should be appropriately trained.

5.3. PRODUCTION CONTROLS

FDG must conform to required quality specifications before it can be released for patient use. The required quality attributes of FDG are discussed in full detail in Section 6. It is essential that several key parameters be controlled during manufacturing in order to maintain consistent and reliable production which results in a product conforming to required quality characteristics. In Table 5.2, the essential product quality parameters to be achieved in the manufacture of FDG, and how these may be realized through manufacturing controls, are listed.

5.4. GOOD MANUFACTURING PRACTICE

FDG is an injectable radiopharmaceutical, and hence must be manufactured in a manner compatible with the GMP regulations applicable for each production facility. The subject of GMP is not discussed here in detail, since the information is readily available in various GMP guidelines on radiopharmaceuticals manufacturing [5.6–5.8] and in Ref. [5.9].

Regulations regarding the manufacture of PET radiopharmaceuticals are evolving and hence there is no harmonized manner in which FDG must be produced. Clearly then, not all GMP guidelines for FDG manufacturing are the same. On the one hand, the need for compliance is not much different from the

TABLE 5.2. FDG PRODUCTION CONTROLS IN RELATION TO QUALITY ATTRIBUTES

Quality attribute	How to achieve during synthesis
Appearance	Carefully prepare purification cartridges for efficient purification of the product. Carefully assemble the reagents and 'kit' on the synthesis module during pre-synthesis set-up by practising aseptic handling of materials to render the solution free of particulate matter and microorganisms.
Radionuclidic purity	[¹⁸ O]water of >95% enrichment is recommended. If using recycled water, it must be purified, tested and validated prior to use in the production of a patient dose.
Radiochemical purity	Quality of raw materials and supplies must be verified and controlled. Care must be taken to ensure efficient purification at the end of synthesis through proper preparation and conditioning of purification cartridges. Process parameters such as time, temperature and pressure should also be under tight control and monitored.
Kryptofix	Use only the amount of Kryptofix 2.2.2 that has been validated during set-up. Efficient purification at the end of synthesis through proper conditioning of the purification cartridges.
Residual solvents	Controlled during synthesis. Efficient evaporation is the key parameter, which is equipment related and not necessarily controllable by the operator; however, the process of validation should ensure that this step is well in control. Second, some solvents may arise from cartridges during the process of conditioning. An operator must ensure the complete removal of solvents used for conditioning the cartridges.
Impurities	[¹⁸ F]FDM can be controlled by optimizing the hydrolysis temperature, time and concentration of sodium hydroxide. CIDG is likely to result from the presence of chloride ion in a reaction mixture arising from improperly treated anion exchange resin used for the collection of [¹⁸ F]fluoride. Proper rinsing of the cartridge will remove the unwanted chloride ions. Absence of these potential impurities should be verified through initial validation studies.
Endotoxin (pyrogen) and sterility	Microbial product contamination should be controlled through use of low bioburden raw materials and supplies used in synthesis, as well as by ensuring aseptic handling of materials and components during set-up. Sanitizing the synthesis module and delivery lines using validated procedures is an important pre-requisite in this regard.

GMP guidelines for manufacturing conventional pharmaceuticals (EU and WHO). On the other hand, there are GMP guidelines that are specifically tailored for manufacturing PET radiopharmaceuticals (US FDA). Regardless of the regulation in force, it must be understood by all concerned parties that the ultimate aim of an FDG manufacturing facility is to integrate applicable processes such that each product batch meets quality requirements.

It must be emphasized that due to the relatively large quantity of radioactivity being handled and the short half-life of ^{18}F , several restrictions are imposed that must be overcome during manufacturing. Furthermore, as the product is generally not subjected to steam sterilization and is approved for use through parametric release, it is essential that appropriate controls are applied during manufacturing.

Finally, proper planning and management in relation to the most critical components of GMP listed below should lead to a product that consistently and reliably conforms to the required quality attributes:

- The facility design should incorporate product protection considerations, including a controlled environment;
- Staff should have appropriate qualifications, experience, job specific training and a good ‘quality culture’;
- A quality assurance programme with appropriate authorizations should be in place;
- Materials management (procurement, quality verification, storage and use) should be considered;
- Documentation and records (standard operating procedures, batch records) must be properly maintained;
- Aseptic processing and monitoring are necessary;
- Appropriate equipment (production and quality control) must be used;
- Risk assessment and validation of processes should be undertaken.

5.5. SUMMARY

Nucleophilic substitution reaction is the only method used in the production of FDG. Furthermore, the production of FDG has been considerably simplified by the use of automated synthesis modules that are designed for operation under a controlled environment facilitating GMP compliance. A number of factors can potentially affect product yield, but generally it is not an issue, as most commercial synthesis modules are capable of producing large quantities of FDG very reliably. Due to the short half-life of ^{18}F , all the mandatory quality control tests needed for releasing an injectable product cannot be finished prior to the

release of FDG (parametric release). Therefore, control of materials and supplies and careful handling, in particular handling of synthesizer assemblies in an aseptic manner, should result in a product conforming to all the required attributes of quality and safety.

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6. QUALITY CONTROL AND QUALITY ASSURANCE OF FDG

6.1. INTRODUCTION

FDG must conform to various quality attributes of purity, efficacy and safety prior to being considered suitable for patient use. Customarily, monographs contained within the National Pharmacopoeia have been the official reference source of quality specifications for a pharmaceutical product. PET radiopharmaceuticals, including FDG, being emerging products, may not yet be incorporated into many National Pharmacopoeias. In such a situation, FDG quality specifications detailed in the International Pharmacopoeia, the European Pharmacopoeia or the United States Pharmacopoeia [6.1–6.3] may serve as valuable reference sources for establishing FDG quality specifications.

The 110 minute half-life of ^{18}F necessitates the application of QC test procedures that can be completed in a relatively short time period. Consequently, not all tests can be completed prior to release of a product for patient use (such as sterility), which necessitates parametric product release. In spite of this restriction, all tests except the sterility and the 60 minute endotoxin test can be performed within 30 minutes post-production. Moreover, ensuring a safe and high quality product requires application of GMP, strong quality management and validation of the entire system.

As has been mentioned earlier in this book, there are some minor differences in FDG quality specifications among the three major pharmacopoeias (Ph.Int., Ph. Eur. and USP). These are compared in the Annex to this publication. This section discusses quality parameters associated with FDG as represented in the International Pharmacopoeia. The FDG producer should verify the applicable regulation and develop quality parameters and protocols in adherence to that.

6.2. QUALITY MANAGEMENT

Testing a product for quality is only one aspect of overall quality management (QM); QM comprises not only quality assessment through testing, but also overall quality assurance and GMP practised at a producing facility. Achieving the necessary quality specifications in FDG radiopharmaceuticals, therefore, relies heavily upon careful planning and execution of GMP and quality management procedures that have been appropriately designed and subsequently validated for their suitability. A brief discussion on GMP and quality

management is provided in this section; more detailed information is available in Ref. [6.4] and is also readily available in the literature.

6.2.1. Good manufacturing practices

Radiopharmaceutical production is a controlled process guided by radiopharmaceutical specific GMP guidelines [6.5–6.7]. In essence, GMP encompasses the elements having a bearing on pharmaceutical product quality, including personnel, premises, equipment, starting materials, processes, quality control, documentation, packaging and shipping. It is essential that SOPs are developed and processes are validated, implemented and monitored.

Since PET radiopharmaceuticals are emerging products, protocols for the production of radiopharmaceuticals have evolved over the last decade. Presently, not all Member States have developed national GMP guidelines. On the other hand, leading organizations such as WHO, PIC/S (Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme), the FDA (USA) and the EC (European Commission) have established guidelines for manufacturing radiopharmaceuticals which could be adopted by Member States.

6.2.2. Quality control

Quality control is the day-to-day testing of products and raw materials. The purpose of quality control is to measure, analyse and evaluate all materials (whether a raw material used in a manufacturing process or a finished product) and ensure that their quality is judged to be satisfactory. A product can only be released for patient use when conformity to these specifications is demonstrated through testing. With implementation of a robust quality assurance programme, testing of a product for conformation to required quality specifications becomes a confirming exercise.

6.2.3. Quality assurance

Quality assurance is a measure of the overall performance of a manufacturing facility. It has implications affecting how processes and procedures are conducted within a facility. In this context, QA is a sum total of all activities that individually or collectively influence the quality of a product. It is to be noted that the GMP system is an integral component of QA. Unlike conventional pharmaceutical products, radiopharmaceuticals necessitate special handling during their manufacturing, owing mainly to the short half-lives of incorporated radionuclides, aseptic processing, parametric release of a product batch, and radiation protection requirements. Therefore, attention to detail and

adherence to GMP and quality management protocols is highly important in assuring product quality and validation for the parametric release of a product batch for patient use.

6.2.4. Validation and monitoring

Key features of a quality assurance programme include tests that are performed within well-established protocols (SOPs), and results that are presented with maximum confidence. All procedures for quality assessment should thus be developed, verified, and fine-tuned (validated) prior to their being put into practice for the testing of FDG batches. Monitoring of test results ensures the continued suitability of validation processes.

6.2.5. Documentation

Documentation is an integral component of GMP and the quality management system. All processes must be documented in the form of SOPs, and staff must adhere to these ‘official’ procedures during the manufacturing and testing of FDG. Associated records must be collected and properly filed. Several documents are provided in the annex to this publication and may be used as guidelines in the preparation of similar documents at a FDG production facility. These include a list of typical GMP documents, FDG batch record, Quality Control Certificate, vial and shield labels and the FDG package insert.

6.3. FDG QUALITY SPECIFICATIONS

The Ph.Int. has included FDG specifications in the latest edition [6.1]. As per the Ph.Int., the definition of FDG is as follows:

“Fludeoxyglucose (¹⁸F) injection is a sterile solution of fluorine-18 in the form of 2-[¹⁸F]fluoro-2-deoxy-D-glucopyranose (2-[¹⁸F]fluoro-2-deoxy-D-glucose), suitable for intravenous administration and that contains sufficient sodium chloride to make the solution isotonic with blood. It contains not less than 90% and not more than 110% of the content of fluorine-18 stated on the label at the reference date and time stated on the label. Not less than 99% of the total radioactivity is due to fluorine-18. Not less than 95% of the total fluorine-18 radioactivity is present as 2-[¹⁸F]fluoro-2-deoxy-D-glucose and 2-[¹⁸F]fluoro-2-deoxy-D-mannose, with the latter not exceeding 10% of the total. The content of 2-fluoro-2-deoxy-D-glucose is not more than 10 mg per V. (V=maximum recommended dose).” [6.1]

The Ph. Eur. and USP are generally in agreement with the above description of FDG in the Ph.Int., as well as in most aspects of FDG quality specifications, but with some noticeable differences. Furthermore, FDG quality specification criteria for product release and the tests that must be performed prior to approval of a product for human use are not globally harmonized at this time. Consequently, FDG quality specifications do indeed vary slightly across the globe. This important subject of FDG quality specifications and the differences between the Ph. Eur. and USP are discussed in some detail by Yu [6.8] as well as by Hung [6.9]. For useful discussion on quality control and quality assurance, reference is made to a section in a recently published book [6.10]. Table 6.1 lists the acceptance criteria for FDG quality parameters that appear in the Ph.Int.

In spite of the differences between pharmacopoeias, it should be clear that FDG to be administered into humans must conform to the quality attributes of purity, efficacy and safety, and that the product must possess the correct identity and strength. From the regulatory perspective, nationally applicable pharmacopoeia specifications for FDG should be followed.

6.4. QUALITY CONTROL OF FDG: DISCUSSION

FDG product must comply with all requirements stated in the monograph (Table 6.1). However, this does not imply that performance of all tests in the FDG monograph is necessarily a prerequisite for a producer in assessing compliance with the pharmacopoeia before release of a product. For some tests, a producer may obtain assurance that FDG is of pharmacopoeia quality from data derived, for example, from validation studies of manufacturing processes and from in-process controls. Therefore, development and implementation of GMP protocols and quality management become paramount in assurance of the quality. Globally, there seems to be variation in regard to the tests that are performed prior to the release of a product for patient use. An FDG producer must establish release criteria based upon risk factor analysis and within applicable regulations.

Test methods for FDG analysis are described in the pharmacopoeia. However, these methods should be modified to fit individual working environments and validated for their applicability. Furthermore, validated methods should be transformed into workable SOPs for routine applications. A producer may prefer to use alternative methods, and such variations should be acceptable if these are validated for their applicability and demonstrated to be equivalent to pharmacopoeia methods.

For test results to be valid, it is critical that a test sample be representative of the bulk solution. Therefore, sampling should be done carefully, ensuring that the bulk solution is thoroughly mixed, and the sample is of sufficient volume to

TABLE 6.1. QUALITY SPECIFICATIONS OF FDG ACCORDING TO THE Ph.Int.

Quality parameter	Specification	Test method
Appearance	Colourless or slightly yellow solution.	Visual inspection
Identity (radiochemical and radionuclidic)	The radionuclidic and radiochemical identity are combined in the following fashion: Either tests A and C, or B and C may be applied. A. Gamma ray spectrum exhibits a major peak of 511 keV; B. The half-life is between 105–115 minutes; C. Distribution of radioactivity on a TLC strip corresponds to FDG	A. Gamma spectrum, using a gamma spectrometer B. Dose calibrator or gamma counter C. TLC with radioactivity scanner
Radionuclidic purity	Not less than 99% of total radioactivity is due to ¹⁸ F.	Gamma spectrometer
Radiochemical purity	Not less than 95% of total radioactivity in the test chromatogram corresponds to FDG.	TLC with radioactivity scanner
Assay of radioactivity	±10% of stated activity	Dose calibrator
pH	pH value, 4.5–8.5	pH paper (validated with pH meter)
Chemical purity: Kryptofix 2.2.2	Not more than 0.22 mg/mL*	TLC
Chemical purity: tetraalkylammonium ions	Not more than 0.275 mg/mL* Only to be measured if employed in synthesis.	HPLC
Chemical purity: 2-Chloro-2-deoxy-D-glucose	Not more than 0.05 mg/mL*	HPLC
Chemical purity: 2-Fluoro-2-deoxy-D-Glucose	Not more than 1 mg/mL*	HPLC
Residual solvents: acetonitrile and ethanol	No more than 0.04% acetonitrile and 0.5% ethanol (Based upon USP and Ph. Eur. specifications); this quality parameter is not mentioned in Ph.Int.	GC with FID detector

TABLE 6.1. QUALITY SPECIFICATIONS OF FDG ACCORDING TO THE Ph.Int. (cont.)

Quality parameter	Specification	Test method
Bacterial endotoxins	Not more than 17.5/mL*	LAL (Limulus amoebocyte lysate)
Sterility	Must be sterile	Microbial growth in culture media

* **Note:** The Ph.Int., Ph. Eur. and USP define these limits in relation to the maximum injected volume V to a patient. For clarification in this table, values were calculated assuming a maximum volume (V) of 10 mL and specifications presented here as maximum concentration/mL.

perform all the required tests. Some tests are meant to be performed on undiluted samples, while others may require dilution, which must be done quantitatively to ensure accurate results. The proposed sampling station should be set up behind appropriate lead shielding to protect the operator from radiation.

It is to be noted that although a recommendation can be made regarding the value of conducting a particular test prior to releasing a product batch, the responsibility to ensure compliance with applicable regulations remains with the producer.

6.4.1. Visual inspection (appearance)

Acceptance criteria: A product should be clear, colourless and free from particulate matter. This test should be completed on every batch prior to product release.

Procedure: Hold the test sample in the path of a strong light beam and against a white and a black background to inspect colour and presence of particulate matter. To ensure radiation protection, the vial content should be viewed through a yellow lead glass. Non-tinted glass or indirect viewing using a mirror or video camera is preferred in order to eliminate the possibility of false observation of colour in the solution.

Discussion: A slight yellow colour in the preparation is acceptable according to Ph.Int. However, experience shows that FDG preparations are generally colourless. Therefore, a ‘slightly yellow’ coloured product should be treated with caution as this occurrence indicates the likely presence of impurities arising during manufacturing, most likely with a breach in the purification process. Use of non-tinted lead glass is recommended to eliminate false positive test results.

Visual inspection is indeed a measure of process performance and validation. Presence of particulate matter in a test sample indicates possible failure at various stages of FDG manufacturing, including failure of the sterilizing filtration, inadequate cleaning and control of glassware and components, inadequate environmental control during assembly of reagents in the pre-installation stage or perhaps operator error. Note: An extensive visual inspection may be performed on a reserve sample of a preparation several half-lives into post-production.

6.4.2. Radionuclidic identity and purity

Acceptance criteria: The measured physical half-life of a test sample should be 105 and 115 minutes. A test should be completed on every batch prior to product release.

The gamma spectrum of a test sample should show a major peak at 511 keV, and a sum peak at 1022 keV, depending on geometry and detector efficiency. No less than 99% of gamma emissions should correspond to ^{18}F . This test should be performed periodically.

Procedure: For a half-life measurement, place a small aliquot of the test sample in a dose calibrator or in a well counter. Record the initial radioactivity (A_0). Record the radioactivity again after at least 10 minutes (measured precisely) (A_{10}). Calculate the half-life from the two measured values as per the formula:

$$T_{1/2} = 0.693t/[2.03 \cdot [\text{Log } A_0 - \text{Log } A_{10}]]$$

where $T_{1/2}$ and t are in minutes.

Record the gamma spectrum (NaI or HPGe) of a test sample that has been diluted appropriately (and quantitatively) to provide the optimum number of counts.

Discussion: *Half-life.* Half life can be determined within acceptable limits using counting equipment, such as a dose calibrator or a well counter, by measuring radioactivity of the sample to be tested at two or more time points, then making the decay calculations. In practical consideration to the short half-life of ^{18}F and the need to release the product as soon as possible, a precisely measured count at two points within a 10 minute interval is sufficient to determine the physical half-life of ^{18}F . A 10 second counting duration is adequate. The measured half-life will be lower if ^{13}N impurity is present in FDG.

Gamma spectrum. The mere presence of a 511 keV or 1022 keV peak in the γ ray spectrum is not sufficient to determine radionuclidic identity. Impurities such as ^{13}N (arising from an ^{16}O impurity in the target) and/or other positron emitters will not be detected, as gamma peaks with an energy of 511 keV and a

1022 keV sum peak are a common feature of positron emitters. Therefore, a combination of gamma spectrum and the half-life measurements together provide the best assurance of the identity and purity of the radionuclide ^{18}F .

6.4.3. Radiochemical identity and purity

Acceptance criteria: *Radiochemical identity.* In a TLC chromatogram of FDG test sample, the retention factor (R_f) of the principal peak corresponds with that of the reference standard of non-radioactive FDG ($R_f \sim 0.4$). This test should be completed on every batch prior to product release.

Radiochemical purity. Not less than 95% of radioactivity in the test chromatogram is found at the spot that corresponds with the reference standard of FDG. The test should be completed prior to product release.

Procedure: Prepare a test sample having the number of counts suitable for the radioactivity detector. On a silica gel TLC plate (10 cm \times 2 cm), apply about 5 μL (or any suitable volume) of test sample side by side with a cold FDG standard sample. (After initial validation and periodic checking thereafter, it may not be necessary to apply cold FDG every time). Allow the spots to air dry (no heat should be applied for drying). Meanwhile add a sufficient amount of acetonitrile:water mixture (95:5 vol./vol.) mobile phase to the TLC chamber, allow a few minutes for the chamber to become saturated with the mobile phase. Insert the TLC plate in the chamber; the solvent level must be below the test spot. Allow the solvent front to migrate to the top of the TLC plate. Remove the TLC plate and mark the solvent front. Measure the radioactivity counts on the plate using a TLC radioactivity scanner (alternately, apply the cut and count method). Calculate the R_f and RC purity from the measured counts. The cold FDG can be visualized by spraying the developed TLC plate with 1% P-anisidine reagent [6.11].

Discussion: Radio-TLC provides an easy and reliable means to determine radiochemical identity and purity of FDG. Similar (within experimental limitations) R_f values of the principal spot in the test sample and the FDG reference standard confirm the radiochemical identity of FDG. An initial and periodic validation process should include TLC analysis of a test sample with an authentic reference sample of [^{19}F]FDG (cold FDG); R_f values should be identical within the statistical error of repeated measurements. In a validated system, concurrent spotting of cold FDG along with the [^{18}F]FDG test sample may not be necessary for every batch prior to release. It must be realized that the TLC does not separate [^{18}F]FDM from FDG and hence [^{18}F]FDM, if present, will not be detected.

Quantitation with a radioactivity scanner provides a radiochemical purity measurement. On the silica gel stationary phase using the mobile phase consisting of acetonitrile and water (95%:5%; vol./vol.), the three entities of

interest can be separated with good resolution (R_f values: fluoride, 0.00; FDG, ~ 0.4 ; and partially hydrolyzed tetraacetyl impurities, ~ 0.5 – 1.0). For consistent results and reduction of artefacts, the mobile phase should be freshly prepared and silica gel plates should be properly stored and handled. It is fairly normal to experience variations in R_f values of analytes on TLC plates from different manufacturers, even from different batches from the same manufacturer. Therefore, reproducibility and reliability should be verified with every new lot of silica gel plates.

Additionally, Radio-HPLC may be employed. The process must be validated so that all possible components, including fluoride, FDG, and partially hydrolysed and unhydrolysed impurities can be separated. Care must be exercised in interpretation of results, since the HPLC method using dilute NaOH as the mobile phase underestimates the partially hydrolysed or unhydrolysed components, as these are hydrolysed on the column. Although very useful in determining the [^{18}F]FDM and chemical impurities, the equipment is more complex to use and costlier to maintain. Also, a higher level of staff competency is required.

Assessment of [^{18}F]FDM in [^{18}F]FDG preparation may or may not be required depending upon the method of hydrolysis. In the case of base hydrolysis, FDM may be formed. This should be evaluated during the initial validation study and periodically as needed.

6.4.4. Radioassay

Acceptance criteria: A product label should contain information pertaining to the concentration and total radioactivity in a product vial (or the patient dose) at the specified reference time. A measurement should be completed on every batch prior to product release.

Procedure: Using properly calibrated measuring equipment (such as a dose calibrator), measure the radioactivity of a known volume of test sample (for example, an accurately measured aliquot of an FDG batch). Calculate the radioactive concentration and record it in MBq/mL or mCi/mL. Similarly, measure the total amount of radioactivity in the container and record it in MBq/mL or mCi/mL.

Discussion: Radioactivity is measured in a dose calibrator which is calibrated with an appropriate reference standard such as ^{137}Cs (662 keV). The product vial label should indicate total radioactivity as well as the concentration (MBq/mL or mCi/mL) of FDG at the time of reference.

6.4.5. pH

Acceptance criteria: pH should be within a range of 4.5–8.5, assessed using a suitable pH measurement system. Tests should be completed on every batch prior to product release.

Procedure: Place a drop of test sample on a pH strip. Allow sufficient time for the colour to develop. Record the results.

Discussion: With the allowed broad range of acceptable pH for FDG solution, the use of a pH meter is not mandatory, nor is it practical, since a pH meter requires a relatively large volume of sample. A narrow range pH strip should be used and validated with reference pH standards to ensure applicability and suitability.

6.4.6. Chemical purity

Chemical contaminants may arise from procedures employed in the synthesis of FDG. These include residual organic solvents (such as acetonitrile and ethanol), catalysts (including aminopolyether), reagents and by-products, such as cold FDG, FDM, glucose and CIDG, depending upon the method applied for the synthesis of FDG. It is necessary to know the potential impurities present in the final preparation, and corresponding methods should be employed for analysis and control of potentially toxic substances. The potential chemical impurities present in FDG preparation are discussed below.

6.4.6.1. *Kryptofix 2.2.2 (amino polyether)*

Acceptance criteria: Not more than 0.22 mg/mL. This test should be performed on every batch prior to product release.

Procedure: 5 μ L each (or any suitable volume) of test sample and the reference standard of Kryptofix 2.2.2 (0.22 mg/mL) are spotted side by side on a silica gel plate (for example, 10 cm \times 2 cm). The spots are air dried without the application of heat. The plate is then developed with the mobile phase composed of methanol:30% ammonia (9:1, vol./vol.). The developed plate, after drying, is exposed to iodine vapour in a closed container to visualize the spots. An alternative method of spot visualization may be applied. The size and intensity of a spot of test sample should not exceed that of the reference standard. An alternative spot method involves spotting a test sample on a TLC plate without developing as a chromatogram; the air dried spot is exposed to iodine vapour to facilitate spot visualization.

Discussion: Although Ph.Int. allows a greater upper limit (0.22 mg/mL; see Table 6.1) for Kryptofix 2.2.2 in the final FDG preparation, with most of the

synthesis modules this impurity is well below 0.05 mg/mL and therefore achievable. Test and standard samples should be applied as small spots in order to avoid spreading. FDG production process validation should include testing for the presence of Kryptofix 2.2.2. at initial set up and periodically thereafter to ensure a continuous acceptable level of this chemical impurity in the finished product.

6.4.6.2. Chloro-2-deoxy-D-glucose (CIDG)

Acceptance criteria: Not more than 0.05 mg/mL (see Table 6.1). This test should be performed at the time of initial validation and periodically thereafter.

Procedure: This test method requires the use of HPLC equipped with a strong basic anion exchange column. The mobile phase utilized 1M NaOH. The mass detector should be suitable for carbohydrate detection and may be placed in tandem with a radioactivity detector. This system is also able to detect FDG and FDM.

Discussion: 2-Chloro-2-deoxy-D-glucose is a potential contaminant in ¹⁸F-FDG product when an anion exchange resin in chloride form is used during synthesis, and possibly from acid hydrolysis. An initial validation study and periodic revalidation is recommended to ensure that FDG preparation complies with the required chemical purity. For most PET centres with limited staff and equipment resources, this test could be performed by an external lab on decayed samples.

6.4.6.3. Residual solvents

Acceptance criteria: Not more than 0.04% acetonitrile and 0.5% ethanol in the FDG. This test should be completed on every batch prior to product release.

Procedure: The presence of acetonitrile in FDG is readily assessed with a gas chromatograph (GC) equipped with a suitable column (for example, Porapak-QS) and flame ionization detector. The GC equipment is readied prior to receiving an undiluted test sample. Approximately 2–5 µL of test sample is injected into the GC column and an analysis report is generated. Prior to analyzing a test sample, verification of proper operation of a GC system should be ensured through analysis of the standards of known residual solvent concentration.

Discussion: Acetonitrile and ethanol are used during synthesis, for reagent preparations and for the conditioning of purification cartridges. Traces of these organic solvents may potentially contaminate FDG, and therefore should be controlled.

6.4.6.4. Bacterial endotoxin test (BET)

Acceptance criteria: Not more than 17.5 EU/mL (see Table 6.1). The test should be completed on every batch. A batch may be released prior to test completion.

Procedure: The widely used and accepted test for assessing the presence of bacterial endotoxin in a radiopharmaceutical preparation is the gel-clot technique using limulus amoebocyte lysate (LAL). The bacterial endotoxin test can also be performed with devices that utilize the turbidity and kinetic measurement of gel formation. It is essential that a test be validated for potential inhibition (and hence a false negative result) and positive controls.

Discussion: The gel-clot test typically entails an incubation period of 60 minutes, which is much too long to wait for a 110 min half-life ^{18}F isotope. Consequently, product may be released for patient use prior to completion of this 60 min. test. However, it is possible to perform an ‘in-process’ LAL test with an incubation period of only 20 minutes or less, and this should be performed. In addition to the gel-clot method, two other methods — the turbidimetric and the kinetic — are possible alternatives that can be considered. A full 60 minute test may be performed at a specified time post-release if required. It is recommended that the shorter version LAL test be validated for its suitability and applicability. Endotoxin test results should meet acceptance criteria before the product is administered to humans.

6.4.7. Sterility

Acceptance criteria: FDG must comply with requirements for parenteral preparations, and must pass a sterility test. The product is released for patient use prior to completion of this test.

Procedure: The test must be initiated within a reasonable period of time, allowing for radioactivity to decay. A sterility test entails incubation of a test sample with two different growth media (soybean casein digest medium and fluid thioglycolate).

Discussion: The test can be performed in house or outsourced, depending upon the availability of resources. It may be necessary that the test sample is first sufficiently enough decayed to be transported as a non-radioactive material. It must be ensured through validation studies that the sample is stored in a way which does not influence the test outcome. In situations when a preparation fails the test, it becomes necessary to investigate the entire production system and processes for possible breaches in the manufacturing processes employed. Non-compliance with aseptic processing and human behaviour should be examined for corrective and preventive actions, and to evaluate the need for staff retraining. As

described in the next section, a filter integrity test should be required prior to product release if the product is not steam sterilized.

6.4.8. Filter integrity test

Acceptance criteria: The membrane filter integrity test is not mentioned in Ph.Int. However, it is a requirement of GMP guidelines on aseptic processing with final sterilizing filtration. It is highly recommended that this test be performed prior to product release.

Procedure: Connect a 50–60 cc syringe to a three way valve, a pressure gauge (reading >4.14 bar (60 psi)), and the filter being tested. (If using a vented filter, block the vent hole with a drop of oil). At the end of the filter, attach an extension tube, the other end of which is dipped in a beaker filled with water. As pressure is applied by pushing the plunger, record the pressure reading when a continuous stream of bubbles is formed in the water. The nominal pressure reading for an intact filter is >3.1 bar (45 psi).

Discussion: Although this test is not required by IP, the fact that sterility test results are not immediately available and that a preparation must be sterile, an assessment of filter integrity using a bubble point or pressure retaining test represents an appropriate indicative measure of the microbiological integrity of the product and performance of the aseptic processing. Therefore, it is highly recommended that a filter integrity test be performed after dispensing and prior to release of an FDG product batch. It must be emphasized that a filter integrity test does not replace the required sterility test.

6.4.9. Osmolality

Acceptance criteria: The FDG preparation should be isotonic. This test does not need to be performed if a product is not registered as an isotonic solution.

Procedure: An osmometer is used for measuring the osmolality of FDG solution. The equipment is calibrated with a known standard prior to use. Alternately, the osmolality of a solution can be calculated.

Discussion: A test for isotonicity may not be required, since FDG preparation is usually in saline. Also, for a small volume of parenteral solutions, osmolality is not critical. However, the test should be considered as a component of quality assurance, particularly when the final product is not in a saline solution (e.g. buffers) or when isotonicity is adjusted with hypertonic NaCl solution. It must be pointed out that the presence of residual solvents or addition of ethanol as a stabilizer in the final formulation can influence results and even hamper osmolality measurements. This test is recommended at the time of initial validation.

6.4.10. Stabilizer

If a stabilizer is added, the acceptable limit should be stated and the FDG preparation should conform to this requirement. The test should be completed prior to product release.

Discussion: Stabilizer may be added in a highly radioactive solution to reduce deterioration of product quality due to radiolysis. Toxicity, and the physiological and pharmacological effects of the additive should be known, and acceptable limits should be set. Specific tests must be developed for analysis of a particular stabilizer.

6.5. SUMMARY

There is no global harmonization in relation to required quality attributes. The three major standards — Ph.Int., Ph. Eur. and USP — although in agreement regarding most FDG quality attributes, do have certain differences. (Discussion in this section is based upon FDG specifications according to Ph.Int.) Nevertheless, it is essential for a manufacturer to ensure that FDG is safe for patient use and possesses the appropriate quality attributes. Test methods described in Ph.Int. or validated equivalent methods may be applied, and should be formulated into SOPs through validation and qualifying studies. Facility management should ensure that laboratories are equipped with the suitable instruments and that staff is qualified and adequately trained to perform the assigned QC functions. Moreover, GMP and quality assurance protocols must be rigidly applied in order to obtain a high level of confidence in test results and assure compliance with regulations.

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7. BASICS OF THE SAFE TRANSPORT OF FDG

7.1. INTRODUCTION

The consignor of the PET source is responsible for ensuring safe transport of the source. Discussion in this section considers only the transport of individual packages within a city and not those transported in overpacks or freight containers. The discussion considers the major tasks of the consignor.

7.2. GENERAL PROCEDURES TO BE FOLLOWED FOR TRANSPORT OF FDG

7.2.1. Familiarization with the regulations

The IAEA regulations form the basis of many national and international regulations for the transport of radioactive material. Transport of radioactive material is governed by national regulations of each country. IAEA Member States adopt IAEA regulations within the framework of local laws and international conventions to which a nation is party. Responsibilities are assigned within national regulations to consignor, carrier and consignee.

7.2.2. Package selection

Generally PET sources are transported in small activities. Type A packaging would be suitable for PET sources. Type A packaging is simple in design. The activity of a radioactive material permitted in a Type A package is subject to limits.

7.2.3. Procurement of an appropriately designed package

The suppliers of radiopharmaceuticals should ideally design suitable packages which meet the design requirements for Type A packages; these are specified in the regulations. Before the first use of a package, it should be tested to confirm that it has been manufactured in complete conformance with design regulations. The effectiveness of shielding should be assessed.

7.2.4. Approval of packages

Competent authority approval is not required for a Type A package intended for the transport of radiopharmaceuticals.

7.2.5. Limits on package content

The maximum activity of a radiopharmaceutical permitted in a Type A package is A_2 (0.6 TBq for ^{18}F).

7.2.6. Limits on radiation levels

The radiation level at any point on the external surface of a package should normally not exceed 2 mSv/h. The transport index (TI) of a package should not exceed 10.0.

The TI is an indicator of the radiation level in the vicinity of a package. Here is the procedure for determining the TI of a package: Determine the maximum radiation level in units of microsieverts per hour ($\mu\text{Sv/h}$) at a distance of 1 m from the external surface of the package. Divide it by 10. The resulting number is the transport index of the package. The value obtained above should be rounded up to the first decimal place (for example, 1.13 becomes 1.2), with the exception that a value of 0.05 or less may be considered to be zero.

7.2.7. Limits on contamination levels

In handling PET sources, it is good practice to check and confirm that contamination is not transferred. It is advisable to check gloves or other items of clothing of personnel routinely handling packages. Under normal transport conditions, non-fixed contamination on the external surface of any package should not exceed the following limits:

- (1) 4 Bq/cm² for β and γ emitters and low toxicity α emitters;
- (2) 0.4 Bq/cm² for all other α emitters.

Low toxicity alpha emitters include natural uranium, depleted uranium, natural thorium, uranium-235 or uranium-238, thorium-232, thorium-228 and thorium-230 when contained in ores or physical and chemical concentrates, and alpha emitters with a half-life of less than 10 days. These limits are applicable when averaged over any surface area of 300 cm². These limits also apply to the external and internal surfaces of conveyances.

7.2.8. Categorization of packages

Packages should be assigned to either category I-WHITE, II-YELLOW or III-YELLOW. Table 7.1 provides the criteria for such categorization. This is a necessary prerequisite to labelling. Where the transport index of a package satisfies the conditions of one category but the surface radiation level satisfies the conditions of a different category, the package should be assigned to the higher category. Category III-YELLOW is higher than Category II-YELLOW which is higher than Category I-WHITE. The category of a package should be determined on the basis of measured radiation levels, considering the package in isolation.

7.2.9. Marking

The following markings should be durably and legibly inscribed on each package:

- (a) An identification of either the consignor or consignee, or both. This marking may consist of the name or address of either the consignor or consignee, or may be a number identifying a way-bill or transport document which contains this information.
- (b) The UN marking as specified in Table 7.2.
- (c) The UN numbers and proper shipping names of the materials. The UN numbers applicable to this module are provided in Table 7.3.
- (d) The gross mass of a package, if it exceeds 50 kg.
- (e) The inscription, 'TYPE A' along with the international vehicle registration code (VRI Code) of the country of design origin and either the name of the manufacturer or other packaging identification specified by the competent authority of the country of design origin.
- (f) The trefoil symbol shown in Fig. 7.1 should be stamped on the outside of the outermost receptacle of each package. This should be plainly marked by embossing, stamping or other means resistant to the effects of fire and water.

7.2.10. Labelling

The labelling of packages is an important method for communicating the presence of radioactive materials. The specific symbol chosen to identify cargo carrying radioactive material is the trefoil (Fig. 7.1).

Each package should bear labels conforming to one of the models shown in Fig. 7.2, Fig. 7.3 and Fig. 7.4. These labels should be affixed on two opposite sides of the outside of the package. The labels should not cover the markings

TABLE 7.1. CATEGORIES OF PACKAGES

Transport index	Maximum radiation level at any point on external surface	Category
0 ^a	Not more than 0.005 mSv/h	I- WHITE
More than 0 but not more than 1 ^a	More than 0.005 mSv/h but not more than 0.5 mSv/h	II-YELLOW
More than 1 but not more than 10	More than 0.5 mSv/h but not more than 2 mSv/h	III-YELLOW
More than 10	More than 2 mSv/h but not more than 10 mSv/h	III-YELLOW ^b

^a If the measured TI is not greater than 0.05, the value quoted may be zero.

^b Should also be transported under exclusive use.

TABLE 7.2. UNITED NATIONS MARKING FOR PACKAGES AND OVERPACKS

Item	UN marking
Package	United Nations number, preceded by the letters 'UN', and the proper shipping name.

TABLE 7.3. UN NUMBERS FOR RADIOACTIVE MATERIAL PACKAGES

Type of shipment	UN number	Proper shipping name
Type A	UN 2915	RADIOACTIVE MATERIAL, TYPE A PACKAGE, non-special form, non-fissile
Special arrangement	UN 2919	RADIOACTIVE MATERIAL, TRANSPORTED UNDER SPECIAL ARRANGEMENT

specified abvol./vol.ove. Any labels which do not relate to the contents should be removed or covered.

Each label should be completed with the following information:

- (a) *Contents*: The name of the radionuclide and the symbol (for example, ¹⁸F);
- (b) *Activity*: The maximum activity of the radioactive contents during transport expressed in units of becquerels (Bq) with the appropriate SI prefix symbol (for example, 0.004 TBq);

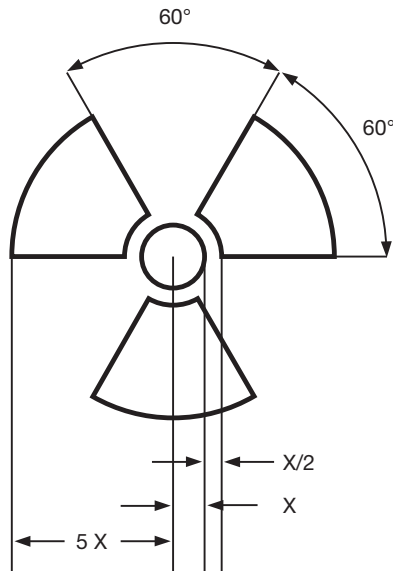


FIG. 7.1. Basic trefoil symbol with proportions based on a central circle of radius X . The minimum allowable size of X is 4 mm.

- (c) *Transport index*: No transport index entry is required for category I-WHITE.

7.2.11. Preparation of the package for transport

The consignor should measure radiation and contamination levels and confirm that levels are within the regulated limits. The consignor should include in transport documents the following information, as applicable, in this order:

- Name and address of the consignor;
- Name and address of the consignee.

7.2.12. Consignor's certification or declaration

The consignor should include a certification or declaration signed and dated by the consignor (Table 7.4) in the transport documents. Facsimile signatures are acceptable where applicable laws and regulations recognize the legal validity of facsimile signatures. If documentation is presented to a carrier by means of electronic data processing (EDP) or electronic data interchange (EDI)

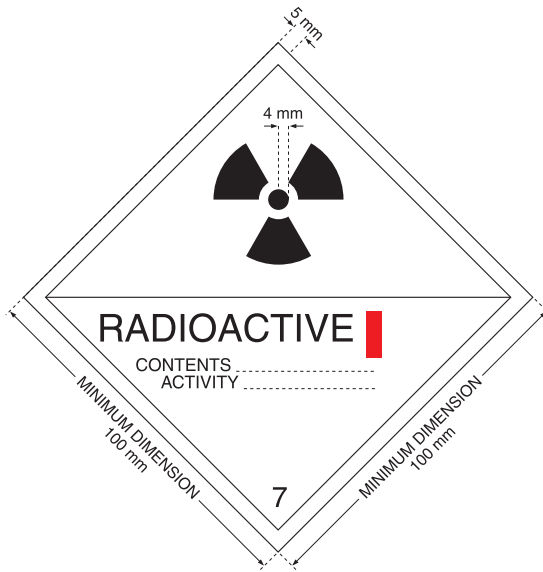


FIG. 7.2. Category I-WHITE label. The background colour of the label should be white, the colour of the trefoil and the printing should be black, and the category bar red.

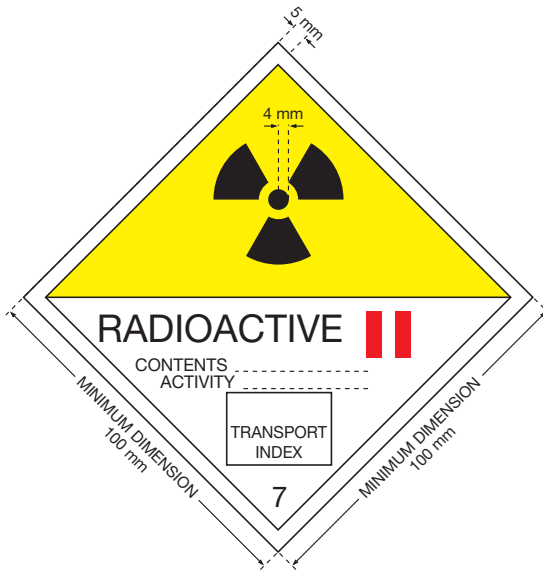


FIG. 7.3. Category II-YELLOW label. The background colour of the upper half of the label should be yellow and the lower half white; the colour of the trefoil and the printing should be black, and the category bars red.

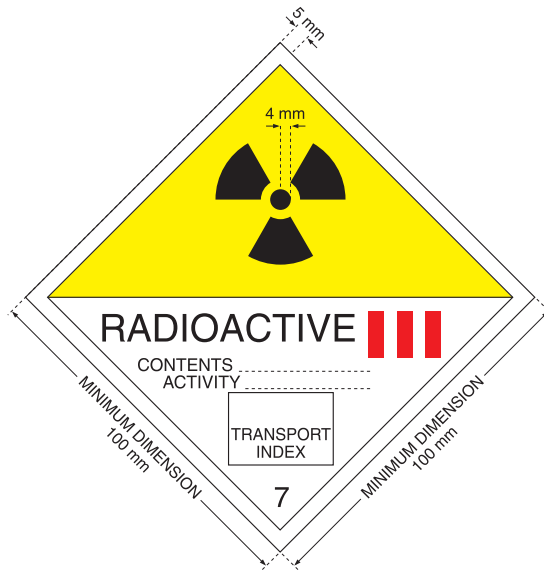


FIG. 7.4. Category III-YELLOW label. The background colour of the upper half of the label should be yellow and the lower half white; the colour of the trefoil and the printing should be black, and the category bars red.

transmission techniques, signature(s) may be replaced by name(s) (in capitals) of the person authorized to sign.

7.2.13. Information for carriers

The consignor should provide a statement in the transport documents regarding actions, if any, which are required to be taken by the carrier. The statement should be in the languages deemed necessary by the carrier or the authorities concerned, and should include emergency arrangements appropriate to the consignment.

7.2.14. Segregation during transport and storage

The consignor should inform the carrier about the need for segregation of packages containing radioactive material during transport and storage in transit from workers, members of the public, undeveloped photographic films and other dangerous goods. The segregation distance should be determined by a dose limit criterion of: (i) 5 mSv per year for workers in regularly occupied working areas and (ii) 1 mSv per year for members of the public in areas where the public has regular access. The distance from undeveloped photographic film should be

TABLE 7.4. TRANSPORT DOCUMENTS

Description of the consignment	Particulars of the consignment
The United Nations number assigned to the material as specified in the regulations.	UN xxxx (e.g. 2915)
The proper shipping name, as specified in the regulations.	e.g. RADIOACTIVE MATERIAL, TYPE A PACKAGE, non-special form, non-fissile
The United Nations class number 10.	7
The name or symbol of the radionuclide.	e.g. ¹⁸ F
Description of the physical and chemical form of the material.	Other form radioactive material
	Physical form
	Chemical form
The maximum activity of the radioactive contents during transport.	GBq/ TBq
The category of the package.	I-WHITE/ II-YELLOW/ III-YELLOW
The transport index of the package.	
The identification mark for each competent authority approval certificate.	Shipment
	<i>I hereby declare that the contents of this consignment are fully and accurately described by the proper shipping name and are classified, packaged, marked and labelled/placarded, and are in all respects in proper condition for transport according to the applicable international and national governmental regulations.</i>
	<i>Name and signature of consignor:</i>
	<i>Date:</i>
Consignor's certification / declaration.	

calculated using a radiation exposure criterion for undeveloped photographic film due to the transport of radioactive material of 0.1 mSv per consignment of such film.

Category II-YELLOW or III-YELLOW packages should not be carried in compartments occupied by passengers, except those exclusively reserved for persons specially authorized to accompany such packages.

7.2.15. Stowage during transport and storage in transit

Movement during transport may shift the position of packages within the conveyance if they is not properly secured. Therefore, consignments should be securely stowed. The number of packages in a storage area or transported within a conveyance should be restricted so that the sum of the TI in a conveyance does not exceed 50.0.

Radiation levels under routine transport conditions should not exceed 2 mSv/h at any point on, and 0.1 mSv/h at 2 m from, the external surface of a conveyance.

7.2.16. Contamination of a conveyance

If a package is damaged or leaking, access to that package should be restricted until the levels of radioactivity present on the surface fall below the contamination limits listed in Section 7.2.7.

7.2.17. Establishment of a radiation protection programme

A radiation protection programme (RPP) should be established for the transport of radioactive material. The nature and extent of the measures to be employed in such a programme should be related to the magnitude and likelihood of radiation exposures.

For occupational exposures arising from transport activities:

- (a) Where it is assessed that the effective dose may exceed 1 mSv but not 6 mSv per year, workplace monitoring or individual monitoring should be conducted to assess dose.
- (b) When dose is in excess of 6 mSv per year, individual monitoring should be conducted.

7.2.18. Emergency provisions

In the event of accidents or incidents during the transport of radioactive material, it is important to rescue the injured and fight fire, if any. Because of the short half-life of FDG, preventing access to the affected area until radioactive activity falls below specified contamination levels would be effective.

7.2.19. Training of personnel

Workers directly engaged in any activity involving packages containing radioactive material should receive appropriate training concerning radiation. Persons engaged in the transport of radioactive materials should receive training in the applicable regulations commensurate with their responsibilities.

7.2.20. Non-compliance

In the event of non-compliance with any limit in the regulations applicable to radiation level or contamination:

- (a) The carrier should inform the consignor if the non-compliance is identified during transport.
- (b) The consignee should inform the consignor if the non-compliance is identified upon receiving the material.

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Annex

EXAMPLES OF DOCUMENTATION MAINTAINED FOR FDG MANUFACTURING

Written procedures and the collection of recorded data are integral and key components of GMP compliance in manufacturing radiopharmaceuticals. Therefore, all processes and procedures having a direct or indirect influence on product quality should be written as standard operating procedures (SOPs). Also, data collected in evidence of product realization and quality assurance of a product should be available as records. Ultimately, a system of documents (SOPs, records, and other) should have the primary objective of establishing, implementing, monitoring and recording performance in an attempt to maintain quality in all aspects of manufacturing and quality assurance. Documentation can be overwhelming in the beginning, but with experience, good record keeping can be achieved and refined as a facility develops. A variety of documents must be developed, some of which are listed in this Annex. Sections A-2 to A-9 are only a few examples of SOPs, production batch records (BRs) and other documentation pertaining specifically to FDG¹. It must be emphasized that there is no unique way of writing documents. Examples provided in these annexes are only representative samples of BRs and SOPs derived from those in use at radiopharmaceutical manufacturing facilities². The bibliography presented at the end of this section can be reviewed to find more detailed information pertaining to documents preparation. While reviewing these examples, it is recommended that attention be focused on the style and flow of instructions rather than on technical details. Every production facility should develop its own specific protocols and procedures to ensure their applicability and suitability for the purpose intended.

In general, BRs and SOPs should be written as a set of simple step by step instructions that can be easily followed by an operator in daily work to complete various tasks with consistency and reliability. Some other features of these documents include objectives, applicability, responsibility, accountability, issuance dates, revision numbers, document numbers, production batch identification numbers, raw material numbers, etc. Such detail is essential for control of documents to ensure that only approved and the most current

¹ The examples of documents are unedited.

² King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, and Brookhaven National Laboratory, New York, USA.

procedures are being practiced. Furthermore, with accurate record keeping, it is relatively simple to trace all raw materials and components that were incorporated into a product, which in turn will facilitate troubleshooting and investigations in case of a product failure. It should be understood that SOPs and pertinent documentation support, but do not guarantee, good performance or results. It is essential to develop a well designed quality management system, work culture and ethics to achieve desired performance. Furthermore, SOPs can be used as training documents. The Annex is divided into the following sections:

- A-1: List of representative GMP documents;
- A-2: Example of a site master file content (based upon PIC/S guidelines);
- A-3: Validation master plan (VMP);
- A-4: SOP for document preparation;
- A-5: Example of a QC record;
- A-6: Example of a product release certificate;
- A-7: Example of a production batch record;
- A-8: Product labels;
- A-9: Typical example of an FDG package insert;
- A-10: Example of FDG quality control methodology;
- A-11: Raw materials purchase;
- A-12: Raw material qualification;
- A-13: Raw materials disposition;
- A-14: Raw materials record;
- A-15: Equipment related (calibration and validation);
- A-16: Equipment related (laminar flow cabinet);
- A-17: Document change control;
- A-18: Training log.

A-1. LIST OF REPRESENTATIVE GMP DOCUMENTS

Documentation is the key to operating a manufacturing facility in compliance with GMP requirements. Assurance that a product not only conforms to required specifications, but also that it has been manufactured by the same procedures under the same conditions every time is achieved through the application of validated procedures in the form of written instructions. Various documents (including standard operating procedures and records) are required to establish and achieve definitive modes of operation, monitoring of processes, and recording of production and quality assessment activities. These include at least the following:

- Manufacturing processes as instructions;
- Validation of critical steps prior to implementation;
- Facility: premises, equipment, storage, packaging and transport;
- Personnel qualifications and training;
- Records indicative of performance.

Below is an indicative list of SOPs derived from WHO guidelines (A WHO Guideline to GMP requirements: Part 1: SOP and Master Formulae) that manufacturers should develop and implement. Not all of the listed subjects have to be written as SOPs. Manufacturers should prepare SOPs as deemed necessary in order to achieve the desired quality results.

- (1) *Facility*
 - Site of the master file;
 - Validation of the master plan;
 - Controlled entries in the cleanroom;
 - Cleaning of the facility (the cleanroom in particular);
 - Environmental monitoring (viable and non-viable particle counts);
 - Glassware cleaning and sterilization.
- (2) *Equipment (production and QC)*
 - General procedures for validation (installation, operation, performance);
 - Operation instructions;
 - Calibration;
 - Performance monitoring;
 - maintenance and repairs;
 - Record of usage, repairs and revalidations.
- (3) *Raw materials*
 - Specifications;
 - Raw materials control number;
 - Supplier qualification;
 - Procurement: ordering, receipt, sampling, inspection, testing, and disposition;
 - Certificate of analysis (C.O.A.);
 - Quarantine, release and approval;
 - Storage;
 - Inventory control.
- (4) *Manufacturing*
 - FDG product specifications;
 - Master formula (production batch record);
 - Production procedures;
 - In-process controls;

- Gowning;
 - Raw materials traceability;
 - Product quarantine, storage and release criteria;
 - Distribution records;
 - Deviation control and reporting;
 - Corrective action plans.
- (5) *Labelling and packaging*
- Product labels (inventory and usage control);
 - Reconciliation of labels;
 - Shipping.
- (6) *Quality control*
- Test procedures;
 - Sampling plan for testing;
 - Raw materials testing and disposition;
 - Finished product testing and disposition;
 - Summary protocol of QC results;
 - Product release certificate;
 - Reference standards;
 - Recertification/recalibration of QC equipment;
 - Preparation of reagents and materials for QC tests;
 - Validation study records;
 - Stability studies and shelf-life;
 - Documents inspection.
- (7) *Quality assurance*
- Document control, revision, and distribution;
 - SOP preparation, review and approvals;
 - Change control;
 - Production batch record review;
 - Product and raw materials release, rejection, disposition;
 - Customer complaints;
 - Product recall;
 - Product rejections and rework;
 - Inspection/internal audits;
 - Employee records;
 - Training (technical and GMP) records;
 - Adverse event reports;
 - Investigations.

A-2. EXAMPLE OF A SITE MASTER FILE CONTENT
(BASED UPON PIC/S GUIDELINES)

1. General information

- 1.1. *Brief information on the manufacturer XXX*
- 1.2. *Pharmaceutical manufacturing activities as licensed by the competent authorities*
- 1.3. *Any other manufacturing activities carried out on the site*
- 1.4. *Name and address of site*
 - 1.4.1. Address:
 - 1.4.2. Telephones:
 - 1.4.3. Fax:
 - 1.4.4. 24 hour contact telephone:
- 1.5. *Type of actual products manufactured on-site*
 - 1.5.1. Radiotracers for positron emission tomography
 - 1.5.2. The substances handled on the site are radioactive
 - 1.5.3. The tracers produced in the unit are aimed exclusively for use in humans
- 1.6. *Short description of the site*
 - 1.6.1 The location and immediate environment of the site
 - 1.6.2 Size of the site
 - 1.6.3 Other manufacturing activities
- 1.7. *Number of employees engaged in the process*
 - 1.7.1. Routine production and quality control
 - 1.7.2. Storage and distribution
 - 1.7.3. Technical and engineering support services
 - 1.7.4. Total of above
- 1.8. *Use of outside scientific, analytical or other technical assistance in relation to manufacturing and analysis*
 - 1.8.1. Name: Manufacturer XXX
 - 1.8.2. Tel: NNNNNNNN
 - 1.8.3. Fax: nnnnnnnnn
 - 1.8.4. Scope
- 1.9. *Short description of the quality management system*
 - 1.9.1. Quality policy
 - 1.9.2. Responsibility of the quality assurance function
 - 1.9.3. Quality assurance system
 - 1.9.4. Audit programmes, reviewing results
 - 1.9.5. Assessment of starting materials
 - 1.9.6. Final product release

2. Personnel

- 2.1. *Organization chart*
- 2.2. *Qualifications, experience and responsibilities*
 - 2.2.1. Qualifications and experiences of key personnel
 - 2.2.2. Main responsibilities in the quality assurance system
- 2.3. *Outline of arrangements for basic and in-service training*
- 2.4. *Health requirements for personnel engaged in production*
- 2.5. *Personnel hygiene requirements*

3. Premises and equipment

- 3.1. *Premises*
- 3.2. *Nature of construction and finishes*
- 3.3. *Brief description of ventilation systems*
 - 3.3.1. Depression cascade
 - 3.3.2. Ventilation of the cyclotron vault
 - 3.3.3. Ventilation of the radiochemical laboratory
- 3.4. *Special area for handling highly radioactive materials*
- 3.5. *Brief description of water systems*
- 3.6. *Maintenance*
- 3.7. *Brief description of major equipment for the production and quality control laboratory*
 - 3.7.1. Isotope production
 - 3.7.2. Radio-tracer production (labelling)
 - 3.7.3. Final formulation, dose dispensing and sterile filtration
 - 3.7.4. Quality control equipment
- 3.8. *Maintenance*
- 3.9. *Qualification, validation and calibration*
- 3.10. *Sanitation*

4. Documentation

- 4.1. *Arrangements for the preparation, revision and distribution of necessary documentation for manufacturing*
- 4.2. *Other documentation related to product quality*
 - 4.2.1. Equipment specifications
 - 4.2.2. Specifications for disposables
 - 4.2.3. Standard operating procedures
 - 4.2.4. Quality control procedures
 - 4.2.5. Training procedures
 - 4.2.6. Computer programme specifications
 - 4.2.7. Documentation control of process deviations

4.2.8. Calibration and test documents

4.2.9. Validation reports

5. Production

5.1. *Brief description of production process for FDG*

5.1.1. The flow chart and critical process parameters

5.2. *Arrangements for handling of starting materials, finished products and sample storage*

5.3. *Arrangements for the handling of rejected materials and products*

5.4. *General policy for the process validation*

6. Quality control

6.1. *Brief description of the quality control system*

6.1.1. Analytical and biological testing

6.1.2. Batch documentation and release of final document

6.1.3. Final release of a production batch

7. Contract manufacture and analysis

8. Distribution, complaints and product recall

9. Self-inspection

10. Other

10.1. *Abbreviations*

10.2. *Laboratory layout with the flow of materials engaged in FDG production processes and zone classification*

10.3. *Sterility and bacterial endotoxins validation report*

10.4. *Quality assurance system, list of standard operating procedures involved in FDG production*

10.5. *Validation master plan*

10.6. *Table of contents*

10.7. *Follow-up of changes to SMF*

A-3. VALIDATION MASTER PLAN (VMP)

In general, any aspect of radiopharmaceutical production operation, including new facilities, new processes, new equipment, and significant changes to premises, facilities, equipment or processes which may affect product quality directly or indirectly, should be qualified and validated. This aspect of GMP is

achieved through development and implementation of a validation master plan (VMP). Validation may be defined as the documented action of proving that any procedure, process, equipment, material, activity or system actually leads to the expected result. Therefore, validation applies to all new processes prior to approval for routine application, as well as to existing processes which are to be periodically revalidated for continued suitability and applicability. In relation to GMP, validation includes:

- Manufacturing and testing processes and procedures;
- Product specifications and acceptance criteria;
- Equipment;
- Premises;
- Controlled environment;
- Personnel;
- Documentation and reports;
- Computer control systems.

VMP is a summary document and should therefore be brief, concise and clear, but should contain sufficient information for the document to be functional. It should not repeat information documented elsewhere, but refer to existing documents. Furthermore, the VMP document should consist of the elements important to producing radiopharmaceuticals including:

- What will be validated?
- Who will be responsible for the validation tasks?
- How will the processes and procedures be validated?
- How will the equipment be qualified and validated?
- How will the validation be documented?
- What are the criteria by which a successful validation will be judged?

This section only summarizes the essential elements of validation. In-depth discussion on the subject is readily available in the published literature, some of which are cited at end of this section. A producer should determine the level of validation process through risk management analysis and develop a VMP comprised of at least the following components:

- Reinforcing a commitment to GMP through formal policy statements describing the overall philosophy regarding validation;
- Stating key elements of a validation programme, the organizational structure of validation, schedules and responsibility;

- Defining qualifications and validation work required to ensure that critical aspects of their particular operation are controlled (this requires three stages: process design, process qualification and revalidation);
- Targeting of all personnel involved in validation;
- Clearly defining the responsibilities of those performing validation;
- Providing for flexibility and direction to deal with changes;
- Complementing the manufacturer's site master file;
- Maintaining continued validation status. Ensuring an ongoing revalidation programme following the initial implementation through formal periodic review (possibly annually);
- Qualifying and controlling automated and computerized processes.

It is essential that the validation process become an ongoing project and that results are well documented.

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A-4. SOP FOR DOCUMENT PREPARATION

SOP No. 01-01-001 Procedure for documentation (Preparation, review, approval, distribution and control)		Page 1 of 1
	Revision No.	Effective Date
	Prepared by:	Date:
	Reviewed by:	Date:
	Approved by:	Date:

Purpose:

To establish a procedure for documentation preparation and control, including drafting, reviewing, approval, distribution and documentation change policy.
(This is an SOP for writing an SOP).

Responsibility:

Quality assurance staff or assigned staff

Note:

- This procedure describes the method for document preparation and handling, including: drafting, review, approvals, disposition and change control;
- All documents shall be authorized by the appointed person(s); unauthorized documents shall not be used;
- All documents have a unique and controlled identification number;
- Copying and distribution of documents shall be controlled;
- Only current documents shall be in use;
- SOPs shall be reviewed at regular intervals.

Procedure:

1. New standard operating procedures or revisions of existing SOPs shall be initiated and prepared by staff members familiar with the process.
(A process being written into a SOP should be tried, tested, verified and ultimately validated for applicability and durability).
2. A draft SOP must be reviewed by another person (or persons) familiar with the process.
3. The drafting procedure and validation data are reviewed by QA staff or an appointed person with authority and responsibility.
4. A new SOP is subsequently approved for use in routine practice if its performance is found to be satisfactory.
5. A unique ID number is assigned to new SOPs. A revised SOP, on the other hand, should continue to have the previously assigned SOP number, but with a new revision number.
6. For a revised SOP, the older version is marked as 'expired' or 'replaced' or another distinct notation meaning 'not in use anymore'. Copies of all previous SOP versions should be removed from their point of use and from wherever they are stored.
7. The original document must be securely filed and safe-guarded from inadvertent or deliberate modification.
8. Copies of the approved SOPs should be issued and controlled by the QA group or an assigned authorized person. Copies should be numbered and their distribution controlled and recorded.

A-5. EXAMPLE OF A QC RECORD

Quality Control Section: Finished Product QC Record Form No.: QC-XX-YY			
Product: [¹⁸ F]Fluorodeoxyglucose (FDG) injection	Rev. No. _____	Effective Date: _____	Page 1 of 3
Item Code: _____	Prepared by: _____		Date: _____
Lot No.: _____	Reviewed by: _____		Date: _____
Except for a sterility test, each lot must meet all specifications prior to release.			
Manufacturing Date: _____			
Calibration Date/Time: _____			
Expiration Date/Time _____			
Test	Specification	Result: Pass/Fail	Analyst
1. Sterility	Must be sterile.	_____	
2. Pyrogenicity	Must be apyrogenic.	To be recorded later	
	20 minutes test	_____	
	1 hour test	_____	
3. pH	4.5–7.5	_____	
4. Radionuclide identification	A. The gamma ray spectrum must reveal the presence of photo peak energy of 511 KeV, possibly up to 1022 keV.	_____	
	B. Half-life must be between 105 and 115 minutes.	_____	
5. Radionuclidic purity	No gamma emission other than at 511 and 1022 keV.	_____	

Quality Control Section: Finished Product QC Record			
Form No.: QC-XX-YY			
Product: [¹⁸ F]Fluorodeoxyglucose (FDG) injection	Rev. No. _____	Effective Date: _____	Page 2 of 3
Item Code: _____	Prepared by: _____		Date: _____
Lot No.: _____	Reviewed by: _____		Date: _____
	Approved by: _____		Date: _____
Except for sterility test, each lot must meet all specifications prior to release.			
Manufacturing Date: _____			
Calibration Date/Time: _____			
Expiration Date/Time _____			
Test	Specification	Result: Pass/Fail	Analyst
6. Specific concentration at calibration time/date	Report reading	_____ mCi/mL	
Total activity	Report reading	_____ mCi	
Volume	Report reading	_____ mL	
7. Radiochemical purity	Not less than 90%	_____ % _____	
8. Kryptofix	Not more than 50 µg/mL	_____ µg/mL	
9. Osmolality	250–350 mOsm/kg	_____ mOsm/kg	
10. Acetonitrile	Not more than 0.04% v/v	_____ % _____	
11. Ethanol	Not more than 0.50% v/v	_____ % _____	
12. Visual inspection	Must be clear, colourless and free from visible particles.	_____ _____	

Quality Control Section: Finished Product QC Record Form No.: QC-XX-YY			
Product: [¹⁸ F]Fluorodeoxyglucose (FDG) injection	Rev. No. _____	Effective Date:	Page 3 of 3
Item Code: _____	Prepared by: _____		Date: _____
Lot No.: _____	Reviewed by: _____		Date: _____
	Approved by: _____		Date: _____
Except for sterility test, each lot must meet all specifications prior to release.			
Manufacturing Date: _____			
Calibration Date/Time: _____			
Expiration Date/Time _____			
Test	Specification	Result: Pass/Fail	Analyst
13. Final package inspection	Conforms to packaging prescribed	_____	
14. Reserve sample	Received, logged and stored	_____	
<p>Q.C. Status: Pass _____ Fail _____</p> <p>By: _____ Date: _____</p> <p><u>For Q.A. use only:</u></p> <p>Production record review: _____ Reviewed by: _____</p> <p>Quality control record review: _____ Reviewed by: _____</p> <p>Product Disposition: Released _____ Rejected _____</p> <p>By: _____ Date: _____</p>			

A-6. EXAMPLE OF A PRODUCT RELEASE CERTIFICATE

Product Release Certificate

Manufacturer:

Product name: [¹⁸F]Fluorodeoxyglucose (FDG) injection

BATCH NUMBER: Date of production:

Pressure differential in class D cleanroom (production laboratory, >15 kPa)	Pass _____ or Fail _____
Current operator aseptic training	Yes _____ or No _____
Product specifications meet the requirements	Pass _____ or Fail _____
Deviations from product process/QC/specification	Yes _____ or No _____ If yes, action taken:
Product released for human use	Yes _____ or No _____
Maximum injection volume	(10 mL by default)
Product calibration time (Date and time zone)
Product expiry time (Date and time zone)
Production chemist	Sign and date:
QC chemist	Sign and date:
Post-release review by head of QC or QA	Sign and date:
Qualified person authorization for release	Sign and date:

A-7. EXAMPLE OF A PRODUCTION BATCH RECORD

PRODUCT: [¹⁸ F]Fluorodeoxyglucose (FDG) injection Item Code: _____ Lot No. : _____	Rev. No. _____	Effective Date:	Page 1 of 5
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:
Batch record approved for use: _____ <div style="display: flex; justify-content: space-around;"> Q.A. Signature Date </div>			
Date of Manufacture: _____ Calibration. Time/Date: _____ Expiration Date/Time: _____ (8 hours post calibration) Operator: _____ Checker: _____			

PRODUCT: [¹⁸F]Fluorodeoxyglucose (FDG) injection Item Code: _____ Lot No. : _____	Rev. No. _____	Effective Date:	Page 2 of 5
	Approved by:		Date:

A: Materials:

Operator	No.	Description	Qty.	Item Code	Lot No.
	1	Enriched (¹⁸ O) water for irradiation	2 mL		
	2	Kit mounted on the module Expiration date: _____	One set		
	3	Eluent mixture (Kryptofix 222/K ₂ CO ₃ in 1:1 water/acetonitrile) 600 µL in 1.2 mL vial Expiration date: _____	1 vial		
	4	Citrate/HCl buffer, 6 mL in 10 mL vial Expiration date: _____	1 vial		
	5	Acetonitrile HPLC grade, 7 mL in 10 mL vial Expiration date: _____	1 vial		
	6	Mannose triflate, 25 mg in 5 mL vial Expiration date: _____	1 vial		
	7	Ethanol, 5 mL in 10 mL vial Expiration date: _____	1 vial		
	8	Sep-Pak light Accell plus QMA cartridge Expiration date _____	1 Piece		
	9	Sterile water for Inj. in bag (250 mL) Expiration date: _____	1 Bag		
	10	30 cc syringes Expiration date: _____	2		
	11	Filter Millex-GS, 0.22 µm Expiration date: _____	1		
	12	Filter Millex-GS, 0.22 µm (vented) Expiration date: _____	1		
	13	FDG collection vial (30 cc) Expiration date: _____	1		
	14	Inlet reservoir, 10 mL	1		
	15	Depyrogenated serum vials, 5 mL Expiration date: _____			
	16	Sterile toppers, 20 mm, Expiration date: _____			
	17	Aluminum seals, 20mm			

Note: Operator to check mark or initial in column 1

PRODUCT: [¹⁸ F]Fluorodeoxyglucose (FDG) injection Item Code: _____ Lot No. : _____	Rev. No. _____	Effective Date:	Page 3 of 5
	Approved by:		Date:

Procedure:

Note: Operator is required to check mark each step upon execution.

1. Execute appropriate file to load the fluorine target with ¹⁸O water.
Request cyclotron beam current: _____ μA
BOT on @ _____; EOB@ _____
2. Open the nitrogen gas tank valve and turn on the power to synthesizer.
3. Double click the FDG icon on the desk top screen.
4. FDG synthesizer programme will open up in standby mode.
5. Click on the box 'Start the Procedure for FDG Synthesis'. If it is the second run of the day, click on the 'Start New Synthesis' box.
6. Remove the old kit from the synthesizer and empty the waste bottle.
7. Click 'Start Tests' on the FDG programme screen.

An automated system test without the kit begins. If all conditions are fulfilled, the window closes automatically after 15 seconds. If a non-critical condition failed, the user is requested to acknowledge the error before continuing normal operation. If a critical condition fails, it must be resolved before proceeding further.

8. A dialogue box appears requiring operator name, kit reference and batch identification. Fill the information in the box.
9. Install a new kit, and ensure that the enriched water recovery vial is attached (Kit is prepared in Class A LFH as per SOP XXX).
10. Clamp the kit. Click 'Begin Test' with this new kit in the dialogue box.
11. This test is a leakage test based upon the vacuum upholding in the kit tubing, with various valves open and closed. If a leak is detected, a message asks the operator to correct the problem. The test can be restarted. If it says kit test passed click 'Next'.
12. When all reagents are in place click 'Start Synthesis' (this takes a few minutes). The preliminary steps of synthesis such as reagent transfers, syringe hookups, etc. will commence. The module is now ready to receive the fluoride activity.

DO NOT CLICK SYNTHESIS UNTIL FLUORIDE IS COLLECTED.

PRODUCT: [¹⁸ F]Fluorodeoxyglucose (FDG) injection	Rev. No.	Effective Date:	Page 4 of 5
	_____	_____	
Item Code: _____	Approved by:		Date:
Lot No. : _____			

Procedure (Cont.):

Note: Operator is required to check mark each step upon execution.

13. Record E.O.B. time: _____ Total integrator current: _____ μA. Hrs
14. Collect fluoride-18 activity from the irradiated target onto the ion exchange column in the synthesis unit. Wait for a constant reading on the radiation detector for fluoride.
15. When the fluoride activity is considered to be fully recovered, click on the small FDG synthesis window on the screen to continue the hot synthesis process and write the measured F¹⁸ in the logbook.
16. At end of synthesis, collect the FDG.
17. Wash the target and fluoride line and make sure no wash is left in the line. Dry the line with clean air or nitrogen gas for at least 20 minutes, after closing the programme.
18. Return the unit to standby mode after closing the programme. Turn off the computer.
19. Close the gas cylinder valves.

C. Calculations:

1. EOB time: _____ EOS time or FDG measuring time: _____
2. At the end of synthesis, measure FDG in a dose calibrator.
 Measured FDG _____ mCi at _____,
 Elapsed time since EOB _____ mins.
 D.F.: _____, FDG corrected to EOB: _____ mCi.

 FDG EOB. Yield = _____ mCi / _____ μAh.
 = _____ mCi / μAh.
3. Weight of the empty collection vial: = _____ g.
 Weight of the collection vial with FDG: = _____ g.
4. Aseptically remove 1.5 mL in a syringe. Dispense 0.5 mL each into two pyrogen burned vials, one for sterility testing and the other for a reserve sample; send the remaining FDG in the syringe for QC analysis.
5. Total volume of FDG = _____ mL (Before sampling);
 Measured activity: _____ mCi/mL Decay time until noon: _____ min.
 Decay factor for noon calibration : _____
 Activity at noon = Activity at time measured _____ x D.F. _____
 = _____ mCi.
 Concentration at noon = Activity at noon _____ / Total volume _____
 = _____ mCi/mL

PRODUCT: [¹⁸F]Fluorodeoxyglucose (FDG) injection Item Code: _____ Lot No. : _____	Rev. No. _____	Effective Date: _____	Page 4 of 5
	Approved by: _____		Date: _____

Procedure (Cont.):

Note: Operator is required to check mark each step upon execution.

6. Using concentrations from #5 above, complete the following table.

Vial No.	Reading (mCi)	Activity at Calibration Time (mCi)	Approximate Volume and Distribution
1			0.5 mL QC
2			0.5 mL reserve
3			_____ mL PET center
4			0.5 mL for sterility test

7. Filter integrity test (SOP-XXX); Result: _____

8. Submit required samples for QC tests and reserve.

9. Labels control:

	U S E D						
	Issued	Reject	Record	Batch	Customer	Returned	Total
Vials							
Shields							

Note: If a corrective action is required, refer to SOP-XXX and fill out the form.

Operator: _____ Date: _____ Initial: _____

Checker: _____ Date: _____ Initial: _____

Supervisor: _____ Date: _____ Initial: _____

QA: _____ Date: _____ Initial: _____

Batch record complete and accurate. Returned labels disposed. QA: _____

A-8. PRODUCT LABELS


[¹⁸F]Fluorodeoxyglucose (FDG) injection is supplied in a vial, together with a radiation shield surrounding the vial. Both require identifying labels with clear information to prevent errors and mix-ups during storage, transportation, handling and use. An SOP must be written for label control, including blanks storage, issuance and reconciliation.

Due to radioactive considerations, empty vials are generally pre-labelled, sometimes only with partial information, which should include at least the product name, lot number and manufacturing date. Upon completion of QC tests and product release, the outer shield must be labelled, with fully completed required information. Sample labels are affixed on production batch records.


The examples of vial and shield labels shown below contain important information, such as:

- Manufacturer name and address;
- Product name;
- Product lot number;
- Production and expiration date and time;
- Amount of activity: Total and as concentration;
- Additional information as deemed necessary;
- ‘Caution: radioactive material’ with radioactive sign.

Secondary container (lead shield) label

Manufacturer name and address:	
<p>[¹⁸F]Fluorodeoxyglucose (FDG) injection Sterile and apyrogenic solution of 2-[¹⁸F]-fluoro-2-deoxy-D-glucose</p> <p>Expiration 8 hours post calibration <i>Caution: Do not use if cloudy or contains particulate matter</i></p>	<p>LOT# _____ _____ MBq/Vial _____ mCi/Vial concentration: _____ MBq/mL _____ mCi/mL at _____ Hrs on _____ _____ mL/Vial</p>
<p>Caution: radioactive material </p>	

Primary container (vial) label

Manufacturer name and address:	
[¹⁸F]Fluorodeoxyglucose (FDG) injection	
LOT# _____	mL/Vial
_____ MBq/Vial (_____	mCi/Vial)
At _____ Hrs on _____	
Expiration 8 hours post calibration	
Caution: radioactive material	

A-9. TYPICAL EXAMPLE OF AN FDG PACKAGE INSERT

[¹⁸F]Fluorodeoxyglucose (FDG) injection (Diagnostic: For intravenous administration)

Activity:	As per label on vial and shield
Calibration:	As per label on vial and shield
Expiration:	8 h post-calibration
Half-life:	109.7 minutes
Radiochemical purity:	Not less than 90% at expiration
Radionuclidic purity	Not less than 99.5%
pH:	4.5–7.5
Kryptofix content:	Not more than 50 µg/ml
Acetonitrile content:	Not more than 0.04% vol./vol.
Ethanol content:	Not more than 0.50% vol./vol.

DESCRIPTION

[¹⁸F]Fluorodeoxyglucose (FDG) is a positron emitting radiopharmaceutical containing no-carrier added radioactive 2-[¹⁸F]-fluoro-2-deoxy-D-glucose, which is used for diagnostic purposes in conjunction with positron emission tomography (PET). It is administered by intravenous injection.

FDG is provided as a ready to use, sterile, pyrogen-free, clear, colourless solution containing citrate buffer. The solution is packaged in a multiple dose glass vial and does not contain any preservative.

Physical characteristics

Fluorine-18 decays by positron (β^+) emission. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron. Principal emission data for ^{18}F is provided in Table A-1.

TABLE A-1. PRINCIPAL EMISSION DATA FOR FLUORINE-18

Radiation/Emission	% per disintegration	Mean energy
Positron (β^+)	96.73	249.8 keV
Gamma (\pm)*	193.46	511.0 keV

* Produced by positron annihilation.

External radiation

The specific gamma ray constant for ^{18}F is 6.0 R/h/mCi (0.3 Gy/hr/kB) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4.1 mm lead (Pb). A range of values for the relative attenuation of radiation emitted by ^{18}F resulting from the interposition of various thickness of lead is shown in Table A-2.

TABLE A-2. RADIATION ATTENUATION OF 511 keV PHOTONS BY LEAD SHIELDING

Shield thickness (mm)	Coefficient of attenuation
0	0.00
4.1	0.50
8.3	0.25
13.2	0.10
26.4	0.01
52.8	0.001

The fractions remaining at selected intervals before and after calibration for use in correcting for physical decay of this radionuclide are shown in Table A-3.

TABLE A-3. PHYSICAL DECAY CHART FOR FLUORINE-18

Hours	Factor	Hours	Factor	Hours	Factor
-4.0	4.56	0.5	0.83	5.0	0.15
-3.5	3.77	1.0	0.68	5.5	0.12
-3.0	3.12	1.5	0.57	6.0	0.10
-2.5	2.58	2.0	0.47	6.5	0.085
-2.0	2.13	2.5	0.39	7.0	0.070
-1.5	1.77	3.0	0.32	7.A5	0.058
-1.0	1.46	3.5	0.27	8.0**	0.048
-0.5	1.21	4.0	0.22		
0*	1.00	4.5	0.18		

* Calibration time.

** Expiration time.

PHARMACOLOGY

General

[¹⁸F]Fluorodeoxyglucose (FDG) is a radiolabelled analog of glucose that is rapidly distributed to all organs of the body after intravenous administration. Optimal PET imaging is generally achieved between 30 and 40 minutes after administration.

Distribution

The extent of FDG binding to plasma proteins is not known.

INDICATIONS AND USAGE

FDG is indicated in positron emission tomography (PET) imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.

FDG is indicated in PET imaging in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function.

FDG is indicated in PET imaging in patients for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

CONTRAINDICATIONS AND WARNINGS

None known.

PRECAUTIONS

General

The use of FDG in patients with diabetes or hyperglycemia has not been well studied. It is recommended that patients be normoglycemic while undergoing PET imaging after an injection of FDG.

FDG should be administered only by personnel who are qualified through specific training in the safe use and handling of radionuclides. Care should be taken to ensure minimum radiation exposure to the patient and all personnel involved in the procedure by using the minimum essential dose of radioactivity consistent with safety and the relative value of diagnostic information.

As with other injectable drug products, allergic reactions and anaphylaxis may occur; FDG emergency resuscitation equipment and personnel should be immediately available.

Information to patients

The following information may be provided to patients. In order to minimize the dose of absorbed radiation to the bladder, adequate hydration should be encouraged to permit frequent voiding during the first few hours after intravenous administration of FDG. This may be achieved by having patients drink at least 250 mL of water prior to drug administration. To help protect themselves and others in their environment, patients should take the following precautions for the 12 hours following an injection: whenever possible a toilet should be used and this should be flushed several times after each use; hands should be washed thoroughly after each voiding or fecal elimination. If blood, urine or feces soil clothing, the clothing should be washed separately.

Diabetic patients

Transport of FDG into cells may be affected by fasting or by blood glucose changes associated with diabetes mellitus. Diabetic patients may require stabilization of blood glucose levels one day before and on the day of FDG administration.

Carcinogenesis, mutagenesis, impairment or fertility

Studies with FDG have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Teratogenic effects: Pregnancy category C

Animal reproduction studies have not been conducted with FDG. It is not known whether FDG can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Therefore, FDG should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus.

Nursing mothers

The effects of FDG administration on human breast milk are unknown. Because many drugs are excreted in human milk, caution should be exercised when FDG is administered to a nursing woman.

Paediatric use

The safety and effectiveness of FDG in paediatric patients with epilepsy is established on the basis of studies in adult and paediatric patients. In paediatrics, the recommended dose is 2.6 mCi. The optimal dose adjustment on the basis of body size or weight has not been determined.

The safety and effectiveness of FDG injection for the evaluation of malignancy or for the identification of left ventricular myocardium with reversible loss of systolic function in paediatric patients below the age of 16 years has not been established.

ADVERSE REACTIONS

Adverse reactions have not been reported for FDG in any publicly available reference sources and adverse drug reaction reporting systems. However, patients should be appropriately monitored for adverse drug reactions.

OVERDOSE

The effects of FDG overdose have not been reported.

DOSAGE AND ADMINISTRATION

The recommended dose of FDG for an adult (70 kg) is 185–370 MBq (5–10 mCi), as an intravenous injection for studies of malignancy, cardiology, and epilepsy.

In general, FDG should be administered after patients have fasted for 4–6 hours. For cardiac use, FDG may be administered either to patients who have fasted or to patients who have received a glucose load.

The optimum rates of administration and upper safe dose for FDG have not been established. The time interval between doses of FDG should be long enough to allow substantial decay (physical and biological) of previous administrations.

The final dose for a patient should be calculated using proper decay factors and measured using a suitable radioactivity calibration system before administration.

Patient preparation

Blood glucose levels should be stabilized before FDG is administered. In non-diabetic patients this may be accomplished by fasting 4–6 hours before FDG injection. Diabetic patients may require the stabilization of blood glucose on the preceding day and on the day of FDG administration.

In the case of cardiac imaging, administration of FDG to fasting patients limits the accumulation of FDG to ischemic myocardium. This may make localization of the ischemic region difficult because the surrounding myocardium will not be well visualized. Conversely, administration of FDG to patients who have received a glucose load (for example, 50–75 g, 1–2 hours before administration of FDG) allows the surrounding, non-ischemic myocardium to be seen and facilitates localization of ischemic areas.

Imaging

Optimally, it is recommended that positron emission tomography (PET) imaging be initiated within 40 minutes of FDG administration. Static emission scans are acquired 30–100 minutes after the time of injection.

Drug handling

FDG, like other parenteral drug products, should be inspected visually for particulate matter and discoloration before administration, whenever the solution and container visibility permit. FDG preparations containing particulate matter or colour should not be administered. They should be disposed of in a safe manner, in compliance with applicable regulations.

Aseptic techniques and shielding should be employed in withdrawing doses for administration to patients.

The contents of each vial of FDG are sterile and apyrogenic. To maintain sterility, aseptic technique must be used during all operations involved in the manipulation and administration of FDG.

FDG, like other radioactive drugs, must be handled with care, and appropriate safety measures should be used to minimize radiation exposure to clinic personnel. Care should be taken to minimize exposure to patients consistent with proper patient management. FDG should be used by or under the control of physicians who are qualified through specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

Storage

FDG should be stored upright in a lead shielded container at controlled room temperature.

BIBLIOGRAPHY

THE INTERNET DRUG INDEX, Fludeoxyglucose F18 Injection,
<http://www.rxlist.com/fludeoxyglucose-drug.htm>

A-10. EXAMPLE OF QUALITY CONTROL METHODOLOGY OF FDG

PRODUCT: [¹⁸F]Fluorodeoxyglucose (FDG) injection Item Code: _____	Rev. No. _____	Effective Date:	Page 1 of 10
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

Specifications and Sampling Plan

Test	Specification	Sampling Plan
1. Sterility	Must be sterile.	Use the contents of QC sterility test vial.
2. Bacterial endotoxin	≤ 175/V EU per mL	0.2 mL
3. pH	4.5–7.5	0.05 mL
4. Radionuclide identification	A. The gamma ray spectrum must reveal the presence of photo peak energy of 511 and possibly 1020 keV.	0.002 mL
	B. Half-life must be between 105 and 115 minutes.	0.005 mL
5. Radionuclidic purity	No gamma peak other than at 511 and 1022 KeV.	Determine from Item #4.
6. Specific concentration at calibration time and date Total activity and volume	Record reading	Determine from Item #4.
7. Radiochemical purity	≥ 95%	0.02 L
8. Kryptofix	≤ 50 µg/mL	0.002 mL
9. Osmolality	250–350 mOsmol/kg	0.03 mL

PRODUCT: [¹⁸ F]Fluorodeoxyglucose (FDG) injection Item Code: _____	Rev. No. _____	Effective Date:	Page 2 of 10
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

Specifications and Sampling Plan

Test	Specification	Sampling Plan
10. Acetonitrile	≤ 0.04%	0.0004 ml
11. Ethanol	≤ 0.5%	Determine from Item #10.
12. Visual inspection	Must be clear, colourless and free from visible particles.	None
13. Final package inspection	Conforms to packaging prescribed.	All
14. Reserve sample	Received, logged, and stored.	One vial

PRODUCT: [¹⁸F]Fluorodeoxyglucose (FDG) injection Item Code: _____	Rev. No. _____	Effective Date:	Page 3 of 10
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

Test Methods

Test	Method
1. Sterility test	Sterility testing can be done in-house or it can be outsourced. <i>Note: Product is released before completion of the sterility test results.</i>
2. Apyrogenicity	<i>Note 1: Perform in duplicate.</i> <i>Note 2: Use the sample as is, without dilution.</i> <i>Note 3: Positive and negative controls for both the one hour standard bacterial endotoxins test and the in-process 20 minute test must be done once a week.</i> <u>20 minute test:</u> 1. Dispense 0.1 mL of the sample into each 0.1ml reconstituted LAL tube. (sample) 2. Dispense 0.1 mL of sterile water for injection into each 0.1 mL LAL tube (negative control). 3. Dispense 0.1 mL of 5.0 EU/mL CSE in sterile water (prepared monthly) into each 0.1 mL reconstituted LAL tube (positive control). 4. Mix each tube gently. 5. Incubate each tube undisturbed in a dry block incubator for 20 minutes at 37°C ±1°C. 6. At the end of the incubation period, record the positive, negative and sample results. 7. Report as 'pass' if the negative controls and samples do not gel and the positive controls form a firm gel. (caution: handle tubes gently in order not to 'break' the gel).

PRODUCT: [¹⁸F]Fluorodeoxyglucose (FDG) injection Item Code: _____	Rev. No. _____	Effective Date:	Page 4 of 10
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

Test Methods

Test	Method
3. pH	Determine the pH of the sample using pH paper with a pH range of 4–8.
4. Radionuclide identification, radionuclidic purity and specific concentration	<p><u>General</u></p> <ol style="list-style-type: none"> 1. A 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 (if performed) is dependent on this assay. Use capillary or calibrated pipettes. 3. Dead time loss must be less than 10%. Sample size or counting geometry can be adjusted to meet the dead time criteria. 4. Only use a calibrated multi-channel analyser with Ge(Li), NaI or any other detector, calibrated for both energy vs. channel number and energy vs. efficiency. 5. The analyst must be familiar with the equipment and its operation. <p><u>Procedure</u></p> <ol style="list-style-type: none"> 1. Take a point source card which is a pre-cut cardboard 2 × 2 inches in size. 2. Fill a 1 µL pipette with FDG sample. Carefully wipe off the excess sample on the outside wall of the pipette. 3. Place the filled pipette over the centre of the point source card and cover with a piece of transparent tape.

PRODUCT: [¹⁸F]Fluorodeoxyglucose (FDG) injection Item Code: _____	Rev. No. _____	Effective Date: _____	Page 5 of 10
	Prepared by: _____		Date: _____
	Reviewed by: _____		Date: _____
	Approved by: _____		Date: _____
Test Methods			
Test	Method		
Radionuclide identification, radionuclidic purity and specific concentration (continued)	<p>4. Place the line source in the appropriate counting geometry. There are two calibrated counting geometries in the system; 10 cm and 20 cm.</p> <p><u>Note:</u> The counting geometry or the sample size may be adjusted such that the dead time is less than 10%.</p> <p>5. Set the counting time (live time) depending on the activity of the sample, usually 300 seconds.</p> <p>6. Count, analyse and print out the spectrum.</p> <p><u>Radionuclide identification</u></p> <p>A. <u>Gamma ray spectrum identification:</u> Identify all the photopeaks; the gamma ray spectrum must contain only photopeaks identifiable with gamma ray transition energies found in the decay scheme of the ¹⁸F, such as 511 and 1022 keV. If there are peaks outside of the standard ¹⁸F spectrum, determine the source of contamination.</p> <p>B. <u>Half-life determination:</u> A short term decay measurement is sufficient to accomplish this measurement. Count at least 5 µL of the sample (with a sufficient number of counts) into a calibrated dose calibrator; recount the same sample after some time using the same counter/dose calibrator.</p>		

PRODUCT: [¹⁸F]Fluorodeoxyglucose (FDG) injection Item Code: _____	Rev. No. _____	Effective Date:	Page 6 of 10
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

Test Methods

Test	Method
Radionuclidic identification, radionuclidic purity and specific concentration (continued)	Calculate the half-life using this formula: $T_{1/2} = \frac{0.693 \times t}{\ln A_0 - \ln A_t}$ where: A ₀ = activity at time zero; A _t = activity at time t; and t = time from A ₀ to A _t The half-life must be between 105 and 115 minutes. <u>Radionuclidic purity</u> Radionuclidic purity refers to the proportion of radioactivity due to the ¹⁸ F in the total radioactivity measured. Radionuclidic impurities may arise from impurities in target materials. <u>Specific concentration</u> Measure the activity of a known volume of FDG in a dose calibrator calibrated for ¹⁸ F and calculate the activity per mL (specific concentration).
Volume	<u>Volume of FDG</u> Refer to production batch record and obtain the volume of the material.
Total activity	<u>Total activity of FDG</u> Determine total activity as follows: Total activity in mCi = volume in ml × specific concentration in mCi/mL.

PRODUCT: [¹⁸F]Fluorodeoxyglucose (FDG) injection Item Code: _____	Rev. No. _____	Effective Date: _____	Page 7 of 10
	Prepared by: _____		Date: _____
	Reviewed by: _____		Date: _____
	Approved by: _____		Date: _____
Test Methods			
Test	Method		
5. Radiochemical purity	<p><u>Thin layer chromatography</u></p> <p>A. Materials TLC-SG on plastic backing NaI(Tl)-detector coupled with MCA or radiochromatogram scanner chromatography jar micropipettes 0.5 µL</p> <p>B. Chromatography solvent 95:5 v/v acetonitrile:water Mix well.</p> <p>Sample application and migration:</p> <p>a) Apply a 0.5 µL spot of the sample at the origin and allow to dry. Mark the spot position at the bottom of the strip.</p> <p>b) Place the strip in the TLC container filled with the mobile phase, and allow to develop until the solvent front reaches about 1 cm from the top edge of the TLC strip.</p> <p>c) Remove the strip, mark the solvent front and dry the chromatogram using compressed air.</p> <p>d) Scan the strip on a suitable TLC scanner with a quantitative output of counts and the scan.</p> <p>C. Results:</p> <p>FDG peak: $R_f = \sim 0.4$</p> <p><u>Impurities:</u> Fluoride: $R_f = 0.00$ Tetra-acetyl FDG (TA-FDG): $R_f = 0.8-1.0$ Partially hydrolyzed TA-FDG: $R_f = 0.5-0.7$</p>		

PRODUCT: [¹⁸F]Fluorodeoxyglucose (FDG) injection Item Code: _____	Rev. No. _____	Effective Date:	Page 8 of 10
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

Test Methods

Test	Method
6. Kryptofix	1. Prepare a standard of 50 µg/mL solution of Kryptofix 2.2.2. in methanol. 2. Apply two spots of 2 µL in separate lanes of a TLC strip of silica gel, one for the standard sample and the other for the test sample and allow to dry. 3. Place the strip into the chromatographic chamber containing mobile phase (9:1 methanol:ammonia) and allow to develop for about 15 minutes. 4. Remove the strip, mark the solvent front and dry the chromatogram. 5. Expose the chromatogram in the iodine chamber and view after 30–45 seconds. The spot corresponding to Kryptofix 2.2.2 on the standard sample lane is visible with an approximate R _f value of 0.32. The observed spot of the same R _f value as that of Kryptofix on the test sample lane should not be more intense than the standard.
7. Osmolality	Determine in duplicate the osmolality using 15 µL of the sample. The test method used depends upon the equipment to be implemented.
8. Acetonitrile and ethanol	<u>Instrument:</u> Gas chromatograph with FID detector <u>Instrument parameters:</u> Column: Steel column packed with Porapak — QS, 6' × 1/8" (O.D.), 50–80 mesh Carrier gas: Helium at 520 kPa cylinder outlet pressure @ 30 cc/min. flow rate Detector gas: H ₂ at 280 kPa cylinder outlet pressure @ 30 cc/min. flow rate Air at 400 kPa cylinder outlet pressure @ 30 cc/min. flow rate Detector : flame ionization detector (FID) Detector temp.: 180 °C Injector temp.: 220 °C

PRODUCT: ^{18}FFluorodeoxyglucose (FDG) injection Item Code: _____	Rev. No. _____	Effective Date:	Page 9 of 10
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

Test Methods

Test	Method
8. Acetonitrile and ethanol (continued)	<p>Column conditions: Initial column temp: 100° C Initial column hold time: 0 min.</p> <p>Column temp. programme Programme 1 final column temp: 160 °C Programme 1 column rate in °C /min: 10°/min. Programme 1 final column hold time: 0 mins.</p> <p><u>Mix standard</u> — 0.01% acetonitrile and 0.1% ethanol Initially prepare 1% acetonitrile by diluting 1 mL of acetonitrile in 100 mL water. Also prepare 10% ethanol by diluting 1 ml in 10 mL water. Transfer 1 mL of each into a 100 mL volumetric flask. Dilute to volume with water. Store in a closed and crimped vial (expiry: 1 year from preparation date).</p> <p><u>Method:</u> GC Preparation: Configure the gas chromatograph according to the instrument parameters above. A. <u>Calibration set-up.</u> Note: Calibration set-up may be omitted once it is already part of the data processing file. Inject 1 µL of the standard prepared as above. When the run is finished, save the data and calibration curve. The system is now ready for the injection and calculation of samples. B. <u>Sample analysis</u> Inject 1 µL of the test sample. From the print-out, obtain the percentages of acetonitrile and ethanol. The approximate retention times are as follow: a. ethanol — 3.6 min., b. acetonitrile — 4.3 min.</p>

PRODUCT: ^{18}FFluorodeoxyglucose (FDG) injection Item Code: _____	Rev. No. _____	Effective Date:	Page 10 of 10
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:

Test Methods

Test	Method
9. Visual inspection	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. Inspect the colour of the solution; it must be clear and colourless. Reject the lot if the test vial does not pass the test.
10. Final package inspection	Carefully examine the labels for identity and conformity to the labelling specified in the batch production record. Check for correct lot#, calibration, expiration time/date, total activity and volume.
11. Reserve sample	Collect a representative sample of each lot as reserve. Log it in the reserve sample log book and store in an appropriate place. Samples must be retained for at least three months after the expiration date.

A-11.RAW MATERIALS PURCHASE

<p>SOP No. XX-YY-ZZ</p> <p>Raw Materials Control: Purchase</p>		Page 1 of 2
	Revision No.	Effective Date
	Prepared by:	Date:
	Reviewed by:	Date:
	Approved by:	Date:
<p>Purpose: To establish a procedure for purchasing materials for manufacture and support activities of the organization.</p> <p>Responsible person: Appropriate section head</p> <p>Requirements:</p> <ol style="list-style-type: none"> 1. Each section must purchase materials needed for their section. 2. Inventory should be maintained for critical materials preferably every six months if stability of the materials allows it. 3. The section head must originate and endorse a purchasing request. 4. Materials used in manufacturing of product must preferably be purchased from approved vendor(s) for that material; a change of supplier or of a material itself requires qualification, validation and approval from QA prior to implementation. 5. Materials should be stored and used 'first in, first out'. 6. Where appropriate, all materials should have a certificate of analysis (COA) from the supplier. 		

SOP No. 05-02-001 Raw Materials Control: Purchase		Page 2 of 2
	Revision No.	Effective Date
	Prepared by:	Date:
	Reviewed by:	Date:
	Approved by:	Date:
<p>Procedure:</p> <ol style="list-style-type: none"> 1. Refer to the materials specifications data book for purchasing materials of correct specifications and from approved suppliers. 2. Initiate a purchase order (PO), including specific information about quantity, and if necessary, specific quality. Include information regarding required date, (for example, within 60 days) and shelf life. Follow-up the PO within an appropriate time frame, with the aim of ensuring an adequate supply of material on hand at all times, and allowing sufficient time for qualification and verification. 3. Verify the received supplies for conformity to quantity, quality and date requirements. 4. A non-conforming order remains an ‘open’ order; follow-up until the order is closed. 5. Maintain and update the supply orders/record receipts appropriately. 6. Determine if quality verification is required prior to use (checklist available with QC). 7. Transfer supplies to QC for verification of quality or store in a quarantine area. 8. Upon release from QC after verification, store supplies in a designated location and in a required environment (remember, first in, first out). 9. Update inventory. <p>Related SOP: SOP-XX-YY-ZZ — Raw Material Disposition</p>		

A-12. RAW MATERIAL QUALIFICATION

Quality Control Section: Raw Material Control			
Raw Material: Kryptofix 222 (4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8.] hexacosane) Item Code: XX-YYY	Revision No.	Effective Date:	Page 1 of 3
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:
Specifications and sampling plan			
Test	Specification	Sampling Plan	
1. Labelled	a. Kryptofix 222, Kryptaband 222, ACS or equivalent b. Formula weight (4,7,13,16,21,24- Hexaoxa-1,10-diazabicyclo[8.8.8.] hexacosane)= 376.5	All containers of a lot.	
2. Description	White powder or crystals.	One container of a lot.	
3. Identity			
a. TLC	R _f value of sample same as standard.	Use the same container from Item #2.	
b. Melting point	70–73°C	Use the same container from Item #2.	
4. Certificate of analysis	Present.		
Test Method			
Test	Method		
1. Labelled	Visually inspect each container's label for conformance to specifications.		
2. Description	Visually examine the contents of one container for conformance to specifications.		

Quality Control Section: Raw Material Control			
Raw Material: Kryptofix 222 (4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8] hexacosane) Item Code: XX-YYY	Revision No.	Effective Date:	Page 2 of 3
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:
Test	Method		
3. Identity	Visually inspect each container's label for conformance to specifications.		
a. TLC	1. Prepare a 50 µg/mL solution of the test sample in 0.5 mL of methanol. 2. Apply 2 µL spots in two separate lanes of a TLC strip (silica gel with aluminum backing), one for the standard and the other for the test sample. The spots should be applied 2 cm away from the bottom edge. Allow the spots to dry. 3. Place the strip into a chromatographic chamber containing approximately 10 mL of the mobile phase, and cover. 4. Remove the strip after 5–7 minutes, mark the solvent front and allow to dry. 5. Expose the plate in the iodine chamber and wait for a minute. Kryptofix is visible as a brown spot at an Rf value of 0.3–0.4 after development.		
b. Melting point	Determine the melting point of the sample using a calibrated melting point apparatus. Refer to Test and Assay, SOP # <u>XX-YY-ZZZ</u> .		
4. Certificate of analysis	A certificate of actual lot analysis should be requested from the supplier and attached to the test records.		

Quality Control Section: Raw Material Control			
Raw Material: Kryptofix 222 (4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8.] hexacosane) Item Code: XX-YYY Lot No. : _____	Revision No.	Effective Date:	Page 3 of 3
	Prepared by:		Date:
	Reviewed by:		Date:
	Approved by:		Date:
Manufacturer : _____ Mfr. Lot No: _____ Mfr. Expiration Date _____ Quantity Received : _____ Date Received _____			
TEST	SPECIFICATION	RESULT	BY
1. Labelled	a. Kryptofix 222, Kryptaband 222, or equivalent b. Formula weight (4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8.] hexacosane)= 376.5	_____	
2. Description	White powder or crystals.	_____	
3. Identity			
a. TLC	R _f value of sample same as standard.	_____	
b. Melting point	70–73°C	_____	
4. Certificate of analysis	Present.	_____	
Disposition : Released _____ Rejected _____ By : _____ Date : _____			

A-13. RAW MATERIALS DISPOSITION

<p>SOP No. XX-YY-ZZZ</p> <p>Raw Materials Control: Disposition</p>		Page 1 of 2
	Revision No.	Effective Date
	Prepared by:	Date:
	Reviewed by:	Date:
	Approved by:	Date:
<p>Purpose: To establish a procedure for receiving, quality verification, acceptance and storage of raw materials.</p> <p>Responsibility: Quality control staff</p> <p>Procedure:</p> <ol style="list-style-type: none"> 1. Materials requiring quality verification, whether purchased or prepared in-house are submitted to the raw materials laboratory in the presence of QC staff, who receive the material and make the appropriate entries in the (Raw Materials Receipt/Release Log). Materials not requiring acceptance testing are transferred immediately to appropriate locations. 2. QC staff perform an initial inspection of the external packages for obvious damage, and in-house materials for proper labelling. 3. QC staff perform acceptance testing according to prescribed procedures (Quality Control Test Manual). 4. Materials that conform to required specifications are assigned a control (Lot) number. 5. Relevant information and test data is recorded on the Raw Material Test Record specific to the material being tested; the Raw Material Log (FM-XX-YY-ZZZ) for the specific material is also updated. 		

SOP No. XX-YY-ZZZ Raw Materials Control: Disposition		Page 2 of 2
	Revision No.	Effective Date
	Prepared by:	Date:
	Reviewed by:	Date:
	Approved by:	Date:
<p>6. Completed forms and test records are transferred to Quality Assurance (QA) for approval.</p> <p>7. QA issues the required number of green ‘release’ labels containing information regarding material identification, item code, lot number and expiration date, if applicable.</p> <p>8. Quality Control (QC) staff affixes green labels on the released containers, and also mentions the number of containers released, and the date of release.</p> <p>9. Released material is handed over to the concerned section, and appropriate entries are made in the ‘Raw Materials Receipt / Release Log’.</p> <p>10. QC staff update their raw materials database with all relevant information regarding the materials received and released.</p> <p>11. The staff receiving the released material transfers it to the appropriate location and updates the inventory log.</p> <p>12. Materials not meeting quality control specifications are affixed with a red ‘reject’ label, and are stored in designated location until disposed of or returned to the supplier.</p> <p>Related SOP:</p> <p>SOP-XX-YY-ZZZ — Raw Material Purchase</p>		

A-14. RAW MATERIALS RECORD

Material Name	Qty. Recd.	Supplier	Supplier Lot No.	Date of Receipt	C.O.A. Pass/Fail	Test result (Pass/Fail)*	Expiration	Facility Lot No.**	Approved by

* Identity test, if applicable.

** Identification code designated by PET centre, specific to each shipment.

A-15. RELATED EQUIPMENT (CALIBRATION AND VALIDATION)

<p>SOP No. XX-YY-ZZZ</p> <p>Equipment Calibration and Validation</p>		Page 1 of 2
	Revision No.	Effective Date
	Prepared by:	Date:
	Reviewed by:	Date:
	Approved by:	Date:
<p>Purpose: To validate and maintain satisfactory performance of equipment used in production and in quality control, and provide verification to ensure high confidence in the outcome.</p> <p>Responsibility: Respective section staff</p> <p>Equipment and materials: Equipment being monitored Materials as required</p> <p>Schedule: At initial installation; As often as recommended by the equipment manufacturer; Possibly after major maintenance or whenever necessary.</p> <p>Procedure:</p> <ol style="list-style-type: none"> 1. Establish performance specifications and other requirements in relation to the intended use for the concerned equipment. 2. Apply the equipment specific procedures and collect experimental data for performance evaluation. 3. Analyse the data for assessment of performance; make necessary adjustments until satisfactory results are obtained. 4. As much as possible, reference standards against which equipment performance is being tested must be traceable to a primary standard of sufficient confidence (national or international standards, such as the Eu-152 source for the calibration of MCA). 		

SOP No. XX-YY-ZZZ Equipment Calibration and Validation		Page 2 of 2
	Revision No.	Effective Date
	Prepared by:	Date:
	Reviewed by:	Date:
	Approved by:	Date:

5. Perform calibration/validation as per manufacturer specified schedule and after a major maintenance or repair or whenever the outcome is suspected of being unreliable.
6. In the event of a minor repair that is judged to not adversely affect the finished product or outcome of a test, equipment is revalidated through verification only; equipment is subjected to use for the intended purpose and is demonstrated not to affect the outcome of the product or the test.
7. Record all validation data and measurements and adjustments, if any, in the respective equipment log.

Policy:
Equipment must be validated prior to use.

Acceptance criteria:
Equipment performance per specification and required output.

Reference:
Equipment manuals.

A-16. RELATED EQUIPMENT (LAMINAR FLOW CABINET)

<p>SOP No. XX-YY-ZZZ</p> <p>Laminar Flow Cabinet: Proper usage and care</p>		Page 1 of 2
	Revision No.	Effective Date
	Prepared by:	Date:
	Reviewed by:	Date:
	Approved by:	Date:
<p>Purpose:</p> <p>Proper usage and care of the biological LFC in the cleanroom.</p> <p>Responsibility:</p> <p>Production staff and QC staff</p> <p>Procedure:</p> <p>General Recommendations</p> <ol style="list-style-type: none"> 1. Practice good aseptic technique to maximize cleanliness and product safety. 2. Keep activity in the cleanroom to a minimum when cabinet is in use. 3. Keep all laboratory doors closed to prevent drafts that will disturb critical air flow characteristics. 4. Pre-plan cabinet usage, and place everything required for the complete procedure into the cabinet such that there is minimum movement through the air barrier (in or out) during the procedure. 5. Segregate clean and dirty materials while working in the LFC. 6. Do not place anything on the intake or exhaust grills. 7. Wear long sleeves and clean gloves when working in the cabinet. 8. Avoid particle shading materials and activities in the vicinity of the LFC (such as the opening of cardboard boxes). 9. Ensure the blower is turned on for the prescribed duration prior to commencing work in the LFC. 		

SOP No. XX-YY-ZZZ Laminar Flow Cabinet: Proper usage and care		Page 2 of 2
	Revision No.	Effective Date
	Prepared by:	Date:
	Reviewed by:	Date:
	Approved by:	Date:

Start-Up Procedure

1. Wash hands and lower arms with germicidal detergent; put on gowns and gloves prior to entering the cleanroom area.
 2. Turn on the lights and the blower (if not on already).
 3. Check the intake and exhaust grills to ensure that they are not blocked.
 4. Disinfect the entire work area inside the LFC; allow sufficient time for sanitization prior to commencing work.
 5. Wipe the external surfaces clean with disinfectant prior to placing the cabinet.
 6. Do not block the intake or exhaust grills.
- Place everything at least 4" (10.2 cm) inside the work area.
Segregate clean and contaminated items.

Cabinet Shutdown

1. Remove all items and equipment from the cabinet.
2. Clean up the spills (if any), and wipe all interior surfaces with a disinfectant.
3. Allow the cabinet to run for at least thirty minutes with no activity to allow time for all airborne contaminants to purge from the work area.

Preventive Maintenance

1. Observe the pressure differentials and other gauzes (record the critical parameter) and note variations triggering maintenance.
2. Check and replace the HEPA filters at regular intervals.

A-17.DOCUMENT CHANGE CONTROL

SOP No. XX-YY-ZZZ Document Change Control		Page 1 of 1
	Revision No.	Effective Date
	Prepared by:	Date:
	Reviewed by:	Date:
	Approved by:	Date:

Purpose: To assure systematic and controlled document change.

Responsibility: Document change originator section head

Scope:
 Controlled documents may be modified for any of the following reasons:

- Changes dictated by revision/amendments of GMP.
- Modifications in manufacturing processes and/or procedures.
- Modifications in test methods, specifications, raw materials and finished products.
- Changes arising out of the annual review (audit) of documents.
- Changes arising from corrective and preventive actions.
- Changes arising from continuous quality improvement.

Procedure:

1. Draft the modified document; provide a copy to the section head for initial approval and a copy along with validation data, if any, to the QA section for review (originator).
2. Upon agreement between all concerned parties, prepare the finished version of the modified document with all approvals.
3. Fill out the Document Change Form, indicate the modifications made and their justification (FM13-01-001).
4. Remove the superseded/obsolete document from the master folder and duly cancel it; attach the completed document change form to the cancelled document and store in the appropriate document change control (historical) folder (QAM).
5. Remove all copies of the cancelled document from points of use.
6. Update the master index.

Reference: QAM (Quality Assurance Manual)

A-18. TRAINING LOG

Training Matrix of Employee and Operations Note: Initials in the table denote individuals.		Number: NNN Revision: X Effective Date: DD-MM-YYYY Page: 1 of 4							
DOC Number	Title	AA	BB	CC	DD	EE	FF	GG	HH
QS001	Quality System	X	X	X	X	X	X	X	X
A002	Training and records: radiotracer chemistry laboratory operations	X	X	X	X	X	X	X	X
A001	Standard operating procedures writing	X	X	X	X	X	X	X	X
A003	Deviations							X	X
A007	QA unit tasks		X			X		X	X
Q023	Document control		X			X			
A006	Materials acceptance, release, and storage	X	X	X					
A008	Personnel tasks							X	X
A009	Response to non-conformance events, corrective action and preventive action		X			X		X	
A010	Logbook review		X			X		X	X
A011	Component inventory review		X			X			
A012	Change management		X			X		X	X
A013	Donning and doffing personal protective equipment	X	X	X	X	X	X	X	X
A014	Good documentation training	X	X	X	X	X	X	X	X
Q028	Pest control		X		X		X	X	X
Q029	Security access	X	X	X	X	X	X	X	X
Q037	Equipment validation		X		X	X		X	
Operation Maintenance Procedures									
Q026	Balance: operation, maintenance and cleaning	X	X	X					
Q020	Laminar flow hood: operation and maintenance	X	X	X					

Q036	Refrigerator operation and maintenance	X	X	X	X	X			
Q018	HPLC system: operation, maintenance and cleaning	X	X	X		X	X		
Q031	Particle counter operation and maintenance	X	X	X	X				
Q035	Bioscan pin diode operation, maintenance and setup	X	X	X	X	X	X		
Q015	Specific activity determination by semi-prep HPLC	X	X	X	X	X			
Q013	Capintec ionization chamber: calibration	X	X	X		X		X	
Q032	Wellcounter: operation and maintenance	X	X	X	X	X	X	X	
Q027	Temperature monitoring: refrigerator for test kit storage, red hood heating baths	X	X	X	X				
	<u>FDG Production</u>								
F020	FDG synthesis and product specifications	X	X	X					
Q021	Cleaning: laboratory, red hot cell and solvent hood	X	X	X					
Q007	Pyrogen testing	X	X	X	X				
Q022	Batch record: completion	X	X	X	X	X		X	X
Q024	Master batch record generation, revision and issuance		X			X			
Q005	Sterile MIV setup and labelling	X	X	X					
Q004	HPLC solvent: preparation	X	X	X					
Q010	SRI box: operation and maintenance	X	X	X	X	X	X		
A005	Pig: packaging, labelling and transport	X	X	X	X	X	X		
W001	HPLC waste disposal	X	X	X			X		
	<u>Pre-release Testing</u>								
Q014	pH determination	X	X	X		X			

Q002	TLC: AR 2000 TLC scanner: operating and maintenance and sample analysis	X	X	X		X		X	
Q006	Sterilization filter integrity test	X	X	X	X				
Q017	Visual inspection for clarity	X	X	X		X			
Q033	Product release				X	X		X	X
Q012	Half-life determination	X	X	X	X	X	X	X	
Q011	Residual solvents analysis by GC			X		X	X		
	<u>Post-Release Testing</u>								
Q019	Sterility testing	X	X	X					
	<u>Process Anomalies</u>								
CA001	HPLC and SRI box anomalies: corrective actions	X	X	X	X	X	X		
CA002	Sterile filter integrity test failure: corrective actions	X	X	X	X				
CA004	Pyrogen test failure: corrective actions	X	X	X	X				
CA005	Capintec anomalies: corrective action	X	X	X		X			
	<u>Facility Specific Training</u>								
	Laboratory standard	X	X	X	X	X	X	X	X
	Cryogen safety	X	X	X	X	X	X	X	X
	Hazardous waste generator training	X	X	X	X	X	X	X	X
	Benchtop/dispersibles training	X	X	X	X	X	X	X	X
	Radiological worker I	X	X	X	X	X	X	X	X
	Collaborative IRB training initiative (Group 1)	X	X	X	X	X	X	X	X
	Bloodborne pathogens awareness	X	X	X	X	X	X	X	X

	Compressed gas safety	x	x	x	x	x	x	x	x
	Facility specific training	x	x	x	x	x	x	x	x
	cGMP training	x	x	x	x	x	x	x	x
	Aseptic training	x	x	x					

ABBREVIATIONS

ALARA	As low as reasonably achievable
BET	Bacterial endotoxin test
BR	Batch record
cGMP	Current good manufacturing practice
CIDG	Chlorodeoxyglucose
COA	Certificate of analysis
CT	Computed tomography
DQ	Design qualification
EEC	European Economic Community
EOB	End of bombardment
FDG	2-[¹⁸ F]-fluoro-2-deoxy-D-glucose
FDM	Fluorodeoxymannose
FID	Flame ionization detector
GC	Gas chromatography
GMP	Good manufacturing practice
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography
HVAC	Heating ventilation and air conditioning
IQ	Installation qualification
LAL	Limulus amebocyte lysate
LFC	Laminar flow cabinet
MAL	Material transfer airlock
MRI	Magnetic resonance imaging
OQ	Operation qualification
PAL	Personnel airlock
PEEK	Polyetheretherketone
PET	Positron emission tomography
Ph. Eur.	European Pharmacopoeia
Ph.Int.	International Pharmacopoeia
PIC/S	Pharmaceutical Inspection Convention
PQ	Performance qualification
QA	Quality assurance
QC	Quality control
QP	Qualified person
RF	Radiofrequency system
RPO	Radiation protection officer
RPP	Radiation protection programme
SMF	Site master file

SOP	Standard operating procedure
TBA	Tetrabutyl ammonium (carbonate)
TI	Transport index
TLC	Thin layer chromatography
USP	United States Pharmacopeia
VMP	Validation master plan

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International Atomic Energy Agency

No. 22

Where to order IAEA publications

In the following countries IAEA publications may be purchased from the sources listed below, or from major local booksellers. Payment may be made in local currency or with UNESCO coupons.

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