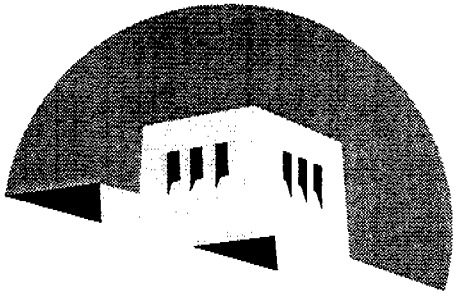

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Correspondence Continuing Education Courses for Nuclear Pharmacists and Nuclear Medicine Professionals

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Radiopharmaceuticals for Clinical PET: Formulation and Quality Control, Regulatory Issues and Professional Responsibilities

by:

Stephen M. Moerlein, Ph.D., B.C.N.P.
Michael J. Welch, Ph.D. and Barry A. Siegel, M.D.

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**RADIOPHARMACEUTICALS FOR CLINICAL PET:
FORMULATION AND QUALITY CONTROL,
REGULATORY ISSUES, AND PROFESSIONAL RESPONSIBILITIES**

STATEMENT OF OBJECTIVES

Upon successful completion of this course, the reader should be able to:

1. List the advantages of positron emission tomography (PET) as an imaging technique.
2. Define positron annihilation and coincidence detection.
3. Compare the different scintillation crystals used for PET.
4. Discuss PET scanner design and image reconstruction.
5. List three essential characteristics of clinical PET imaging procedures.
6. Explain how PET measurement of cardiovascular and metabolic parameters is related.
7. Describe two cardiovascular parameters that are measured by PET.
8. Discuss two aspects of metabolism that can be determined by PET.
9. Describe why PET blood volume tracers localize in blood.
10. Compare the radiopharmaceuticals for PET measurement of blood flow.
11. Explain why Fludeoxyglucose F 18 Injection, USP, is useful for measurement of tissue glucose utilization.
12. Understand how [^{15}O]oxygen and [^{11}C]acetate differ as tracers of oxidative metabolism.
13. Explain how myocardial infarction can be distinguished from myocardial ischemia using PET.
14. Describe the two methods for production of positron-emitting radionuclides.
15. List four cyclotron-produced nuclides employed for clinical PET.
16. Understand the basic principles of cyclotron operation.
17. List and explain two generator systems used for clinical PET.
18. Compare four compounding devices for formulation of PET radiopharmaceuticals.
19. Understand how oxygen-15 labeled tracers are made.
20. Compare two methods for formulating Ammonia N 13 Injection, USP.

21. Describe how [^{11}C]acetate is prepared.

22. Define resolubilization.

23. Explain how Fludeoxyglucose F 18 Injection, USP, is compounded.

24. List advantages of Fludeoxyglucose F 18 Injection, USP, as a PET radiopharmaceutical.

25. Describe how [^{68}Ga]gallium citrate is made.

26. Understand why in-process monitoring is important for drug quality.

27. Describe quality control (QC) testing for oxygen-15 labeled tracers.

28. Explain QC tests for Ammonia N 13 Injection, USP.

29. Discuss QC testing of [^{11}C]acetate.

30. Understand why thin-layer chromatography (TLC) is used for QC of Fludeoxyglucose F 18 Injection, USP.

31. Explain QC test requirements for [^{68}Ga]gallium citrate.

32. Discuss QC concerns for Rubidium Rb 82 Injection.

33. Understand USP sterility and apyrogenicity tests.

34. Discuss the advantages of bacterial endotoxin test (BET) for testing the apyrogenicity of PET tracers.

35. Differentiate between research PET and clinical PET.

36. Describe the regulation of tracers for research PET.

37. Explain two regulatory approaches to radiopharmaceutical formulation for clinical PET.

38. Define the terms RDRC, IND, NDA, and CGMP.

39. List and explain five professional roles for nuclear pharmacists involved with PET.

COURSE OUTLINE

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- C. Scanner Design

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IX. CONCLUSIONS

RADIOPHARMACEUTICALS FOR CLINICAL PET: FORMULATION AND QUALITY CONTROL, REGULATORY ISSUES, AND PROFESSIONAL RESPONSIBILITIES

by

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INTRODUCTION

Positron emission tomography (PET) is a specialization of nuclear medicine that has experienced recent growth because of its unique advantages over alternative diagnostic techniques (1). Unlike computerized axial tomography (CT) or magnetic resonance imaging (MRI), which visualize anatomical **structure**, PET permits noninvasive assessment of human physiology or organ **function**. This characteristic of PET is held in common with nuclear medicine in general, since data is derived from the tissue accumulation of tracer, and is thus intrinsically related to the biochemical and metabolic processes that affect the radiopharmaceutical *in vivo*.

Compared to conventional nuclear medicine imaging, PET has three major benefits, however. Numerous biochemicals and drug structures that cannot be labeled with ^{99m}Tc, ^{123}I or other γ-emitters can nevertheless be prepared as PET tracers because of the chemical nature of the positron-emitting nuclides used. Thus, many **new physiological processes** can be evaluated using PET. In addition, PET instrumentation has **superior image resolution** (2-3 mm limit) compared to planar imaging. Pathophysiology can therefore be more readily detected, perhaps at an earlier stage of disease development when medical intervention might be more effective. Finally, data acquisition by PET minimizes the problematic tissue attenuation, scatter and collimation effects that degrade conventional γ-scintigraphic images. Aside from better resolution, this conveys **greater sensitivity** to PET imaging procedures, and makes possible **tracer kinetic modeling** of physiological processes.

This continuing education lesson will explain the basic principles of positron emission tomography. The physiological rationale for the various clinical applications of PET will be reviewed. The medically-useful positron-emitting radionuclides will be described, together with their primary means of production in the

clinical setting. The incorporation of these radionuclides into clinically-useful PET tracers via automated or remotely-operated systems will be outlined, along with quality assurance concerns. The lesson will conclude with an examination of the current regulatory issues surrounding the preparation of these short-lived radioactive drugs, and will describe potential roles for nuclear pharmacists in this exciting new area of nuclear medicine imaging.

POSITRON EMISSION TOMOGRAPHY

Positron Decay

Proton-rich nuclei decay via either positron emission or electron capture (2). Whereas the latter process is important in conventional nuclear medicine because it results in the production of photons that are useful for conventional γ-scintigraphic imaging of nuclides like ^{123}I or ^{111}In, it is the emission of positrons that serves as the keystone for PET imaging. When the positron is emitted from the nucleus, it interacts with an orbital electron in its environment and undergoes **positron-electron annihilation** (Figure 1). The annihilation event creates **annihilation radiation**, which is the simultaneous production of two high-energy (511 keV) photons. Conservation of momentum laws demands that the two γ quanta are emitted at approximately 180° from each other; the near collinearity of these two photons makes possible the electronic collimation of PET.

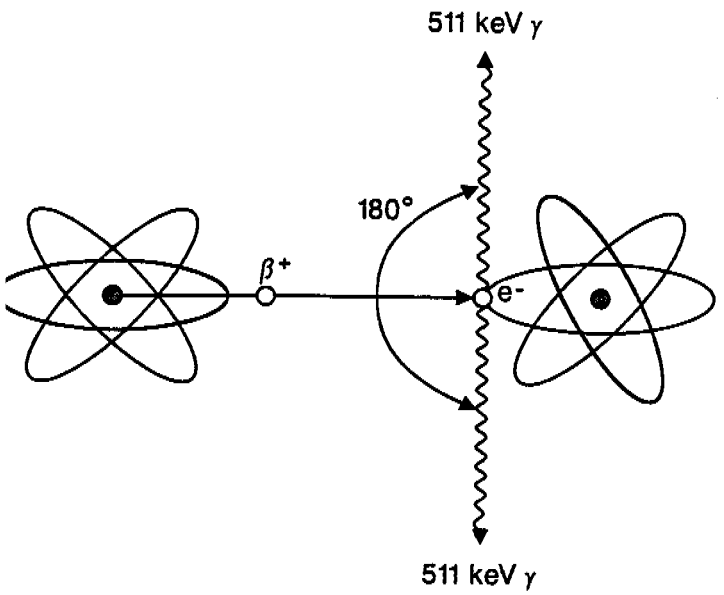


Figure 1. Positron decay with generation of annihilation radiation.

Coincidence Detection

The annihilation radiation that results from positron emission can be measured by two scintillation detectors connected to a **coincidence circuit** (Figure 2). This methodology is based on the fact that the annihilation photons always escape at a 180° angle from one another, and arrive at opposing detectors almost simultaneously. Such coincidence circuitry provid **"electronic collimation,"** since only annihilation events that occur within the straight line joining the two scintillators will be detected. Random counts that arrive at a single detector will be rejected. Thus, unlike conventional nuclear medicine scanners, heavy lead shielding with collimating septa are unnecessary for PET imaging.

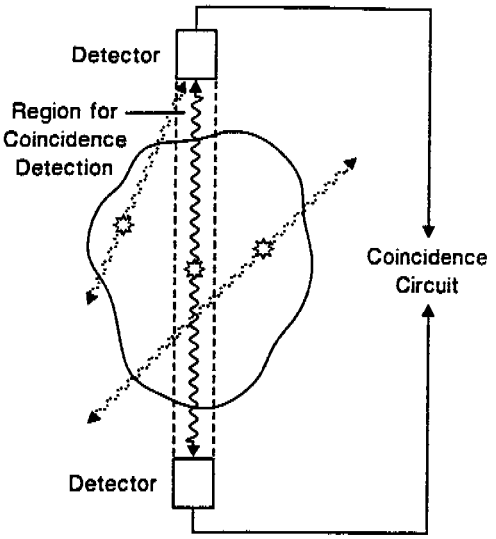


Figure 2. Coincidence circuit for detection of positron annihilation radiation. Note region for "electron collimation" between the two detector crystals.

Due to the relatively high energy of the 511-keV photons that are emitted, as well as the high count rates and high temporal rates that are involved, scintillation crystals for PET have special requirements (3). Although **sodium iodide** (NaI) can be used in PET scanners, this crystal is hygroscopic, has relatively poor stopping power, and has a relatively long dead time that limits temporal resolution. **Bismuth germanate** (BGO) crystals have greater stopping power, but like NaI also have the disadvantage of a long dead time. **Barium fluoride** (BaF_2) crystals can be used as scintillators for PET due to their fast temporal resolution. In comparing the crystals, the detection efficiency decreases in the rank order BGO > BaF_2 > NaI, whereas the resolving time decreases as BaF_2 > NaI > BGO (4). Most commercially-available PET scanners (3) utilize BGO crystals because their greater stopping power allows smaller scintillators to be used, thus giving increased overall spatial resolution to the PET system. Although less common, barium fluoride- and sodium iodide-based positron tomographs are also manufactured (3).

Scanner Design

The basic design of a PET scanner (5) consists of a

ring of scintillation detectors with associated electronics interfaced to a computer system (Figure 3). Annihilation events are detected by the circular array of coincidence circuits and are subsequently processed into images by e computer. PET images are derived from the coincidence lines for each circuit using **reconstruction algorithms**; the image of the count intensity is analogous to the intersection/overlap of the numerous coincidence lines. The count density in regions of interest can be used to acquire qualitative or quantitative information about the subject being scanned. **Qualitative imaging** simply assesses the relative count intensity within the field of view, whereas **quantitative imaging** requires tracer kinetic modeling of the PET data to yield absolute measurements. Examples of the latter are the determination of tissue perfusion in terms of mL of blood per 100 g of tissue per minute, or the measurement of tissue metabolism in units of mg of substrate per g of tissue per minute.

detectors) is proportional to tissue density (5). It is therefore necessary to correct for this effect by measuring the tissue attenuation of 511 keV photons within the field of view. This is accomplished by a **transmission scan**, in which an external positron-emitting source is employed to image the patient using CT-type data collection. Commercially-available PET machines typically utilize $^{68}Ge \rightarrow {}^{68}Ga$ for this purpose, either in the form of a ring source or as a rotating rod assembly.

IMAGING APPLICATIONS

There exists a myriad of radiopharmaceuticals that have been used with positron emission tomography on a research basis (6,7). For such tracers to find use as labeled drugs in the clinical setting, however, certain prerequisites must be met. These prerequisites supplement the radiation dosimetry and quality control

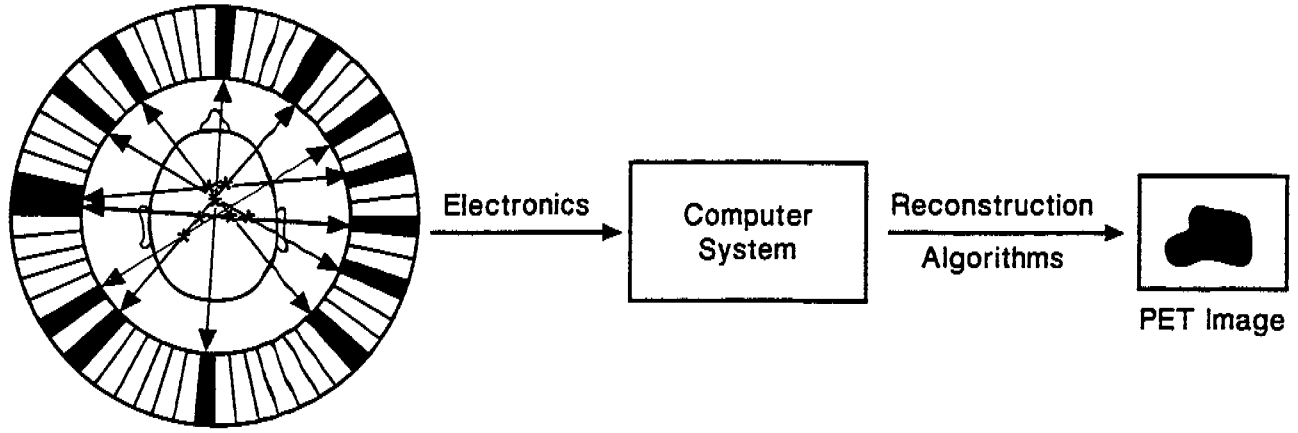


Figure 3. Basic PET scanner design, with circular array of coincidence circuits interfaced to a computer system.

Tomographic visualization of an organ requires numerous tomographic sections, and clinically-utilized PET scanners consist of several rings of detectors that are capable of collecting data from multiple tomographic image planes ("slices") of the patient simultaneously. Clinical PET scanners deliver 7-64 tomographic slices (3), which can be combined longitudinally to give **3-dimensional images** of the subject.

Aside from the above mode of image acquisition, in which the patient remains immobile within the aperture of the tomograph, the patient can also be moved longitudinally through the scanner in a stepwise manner. This permits the **whole-body biodistribution** of a tracer to be ascertained, which is useful for oncology studies nd for determination of human radiation dosimetry information.

In PET imaging, the probability for the annihilation photons to interact with tissue (rather than coincidence

(QC) requirements that apply to all PET tracers used in humans, and determine whether a tracer is appropriate for routine clinical application or for research purposes only.

The specific prerequisites for clinical PET tracers are diagnostic efficacy, imaging protocol simplicity, and radiopharmaceutical compounding efficiency. **Efficacy** of the PET study in disease diagnosis is, of course, central to its utility in answering clinical questions that impact optimum delivery of health care. **Simplicity** of the imaging protocol facilitates rapid diagnosis and a streamlined clinical operation; PET studies that require lengthy modeling of tracer kinetics are too cumbersome and time-consuming to be used on a routine basis. **Efficiency** in compounding the labeled drug is also necessary to assure timely delivery of radiopharmaceuticals in the quantities needed to meet scheduled patient loads in the PET clinic.

The PET tracers that satisfy these requirements for routine application in clinical PET are listed in Table 1. Both cyclotron- and generator-based agents are available. The imaging procedures and the physiological basis for using these positron-emitting drugs are discussed in this section; radionuclide production and compounding techniques will be presented later.

There are several physiological functions that can be assessed noninvasively with PET. These functions are broadly categorized as **cardiovascular parameters**, including blood volume and blood flow, or **metabolic processes**, such as glucose utilization or oxidative metabolism. Cardiovascular parameters impact **delivery** of nutrients to the tissues, whereas metabolic processes affect the **utilization** of nutrients. These aspects of physiology are interrelated, and their assessment by PET is often evaluated together. Blood volume is determined using [^{15}O]carbon monoxide or [^{68}Ga]gallium citrate, whereas blood flow is measured by [^{15}O]water, Ammonia N 13 Injection, USP, or Rubidium Rb 82 Injection. Glucose metabolism is ascertained using Fludeoxyglucose F 18 Injection, USP, and oxidative metabolism is measured using [^{15}O]oxygen or [^{11}C]acetate. Characteristics of these radiopharmaceuticals and their associated imaging procedures are given in Table 1.

Table 1

Clinical PET Imaging Procedures

Physiological Functions	Labeled Drug	Physical Half-Life	Scan Duration[a]	Clinical Applications
Blood volume	[^{15}O]Carbon monoxide	2 min	5 min[b]	Organ blood volume, left ventricular function
	[^{68}Ga]Gallium citrate	68 min	60 min	Pulmonary vascular permeability
Blood flow	[^{15}O]Water	2 min	2-3 min[b]	Cerebrovascular defects, organ perfusion, coronary artery disease, myocardial perfusion reserve
	Ammonia N 13 Injection, USP	10 min	8-12 min	Coronary artery disease, myocardial perfusion reserve
	Rubidium Rb 82 Injection	76 sec	2-8 min	Coronary artery disease, myocardial perfusion reserve
Glucose utilization	Fludeoxyglucose F 18 Injection, USP	110 min	15 min[c] 60 min[d]	Brain tumors, seizures, mental utilization depression, dementia, stroke, myocardial viability, thyroid carcinoma, liver tumors, neoplastic disease
Oxidative metabolism	[^{15}O]Oxygen	2 min	40 sec	Myocardial viability, cardiomyopathies
	[^{11}C]Acetate	20 min	20 min	Cerebral oxygen consumption

a) Imaging time only; overall procedure typically requires an additional 30 min for positioning of patient and transmission scanning. Unless otherwise noted, scan begins immediately after radiopharmaceutical injection.
b) Scan starts 2 min after inhalation/injection of labeled drug.
c) Scan begins 45 min after injection of tracer.
d) Whole body scan 30 min after injection of radiopharmaceutical.

Cardiovascular Parameters

Blood Volume

Imaging of the blood volume of an organ is often necessary to adequately delineate tissues from the blood compartment. This is especially relevant to heart imaging, where the fraction of blood within the field of view is high. Blood volume may be determined using [^{15}O]carbon monoxide gas or [^{68}Ga]gallium citrate solution.

[^{15}O]Carbon monoxide is useful for this purpose because it binds to hemoglobin *in vivo* and is thus confined to the red blood cells of the vascular compartment during the imaging session (8). The short half-life of this cyclotron-produced tracer make it a convenient adjunct to PET studies that use other tracers. The radioactive gas is inhaled by the subject over 1-2 minutes, and imaging of the blood pool occurs over an additional 2-3 minutes.

[^{68}Ga]Gallium citrate is a generator-produced radiotracer that is also used for PET measurement of the vascular space. Gallium-68 binds *in vivo* to the plasma protein transferrin, which remains within the blood compartment due to its large molecular weight. Since this radiopharmaceutical has a relatively long half-life of 68 minutes, it is not useful for adjunctive blood volume correction of PET images derived from other radiopharmaceuticals. It has instead found utility as a marker of pulmonary vascular permeability (9). The tracer allows assessment of the extent of plasma leakage into the pulmonary space; in the healthy state the ^{68}Ga activity is confined solely to the vascular bed. The half-life of gallium-68 is appropriate for this application because it permits accumulation of activity outside of the vascular space prior to PET imaging.

Blood Flow

The evaluation of blood flow is an important clinical use for PET. Blood flow is essential for adequate maintenance of tissue nutrition, and interrupted organ perfusion is a major cause of pathology. Moreover, assessment of tissue perfusion is also relevant to metabolic measurements made with PET, since it affects delivery of the radiotracer to the organ of interest. From the clinical perspective, indications for PET blood flow studies include evaluation of cerebrovascular defects, coronary artery disease, and organ perfusion in conjunction with metabolic studies.

Essential characteristics of a tracer of blood flow are that the radiopharmaceutical be deposited in tissues in direct proportion to blood flow, and that the deposited radioactivity be retained for the duration of the scan. Tissue accumulation can involve a variety of mechanisms, including passive diffusion or active uptake, and tissue retention may be due to binding to intracellular compounds or due to dilutional effects.

[^{15}O]Water is the most versatile radiopharmaceutical for measurement of tissue blood flow. It is a freely-diffusible agent whose tissue accumulation does not decrease at high blood flow rates. Because the

measurement of blood flow is rapid (2-3 minutes) and the tracer half-life is short, multiple PET studies can be repeated within the same subject during a single imaging session. This is a useful characteristic for evaluation of cerebral blood flow in different states of arousal, or of myocardial blood flow during stressed and resting conditions. [^{15}O]Water is predominantly used for blood flow measurement in the brain (10-12). The radiopharmaceutical can also be used to quantify myocardial blood flow (13), but it is not the tracer of choice for this clinical application. Clearance of the blood background activity is slow relative to the 2-minute physical half-life of the radiopharmaceutical, and images of the heart made with [^{15}O]water must thus be corrected for blood volume using [^{15}O]carbon monoxide.

Ammonia N 13 Injection, USP, is a flow tracer that is predominantly used for PET studies of myocardium (14-16), although brain studies have also been reported (17). The extraction of this radiopharmaceutical is flow-dependent (diffusion-limited), with tissue uptake decreasing as blood flow increases. [^{13}N]Ammonia is fixed wthin tissues due to its reaction with glutamine synthetase (Fig 4), yet the tissue retention of this tracer is independent of metabolic conditions in the heart. Because of the relatively long half-life of nitrogen-13 ($t_{1/2}$ = 10 min), very high myocardium-to-blood ratios are achieved, with excellent tissue resolution compared to images obtained with [^{15}O] water or Rubidium Rb 82 Injection. Despite this advantage, the relatively long half-life of nitrogen-13 precludes stress/rest perfusion studies in quick succession, such as those performed with [^{15}O]water or [^{82}Rb]rubidium chloride.

Rubidium Rb 82 Injection is a short-lived ($t_{1/2}$ = 76 sec) generator product used for PET perfusion studies of heart (16,18) and for evaluation of blood-brain barrier patency in oncology (19). The major advantage of this flow tracer is that PET studies can be performed without an in-house cyclotron. Like [^{15}O]water, the short half-life of ^{82}Rb permits rapid sequential imaging of patients during interventional studies. Disadvantages of this tracer are the relatively high energy of the positrons that are emitted, and clearance from the blood pool that is slow relative to the half-life of the nuclide.

Rubidium ion is an analog of potassium, and is preferentially taken up by myocardium via active transport. Because the intracellular potassium pool is large, the efflux of rubidium from myocardium is slow, and tissue retention of radioactivity is high. However, due to the short physical half-life of this radionuclide the imaging interval is limited, and the target-to-nontarget ratios are thus relatively poor. In addition, measurement of blood background activity for correction is difficult. Two methods have been employed to correct myocardial ^{82}Rb images for blood pool activity. The arterial concentration of tracer can be derived from an image taken at steady-state during **constant infusion**, with a subsequent image taken 90 seconds after the infusion is stopped that shows predominantly myocardial tissue (20). Alternatively, for PET devices with high temporal resolution and sensitivity, ^{82}Rb can be administered as an intravenous **bolus injection** (21). The earlier time frames in this case represent primarily the heart chamber blood

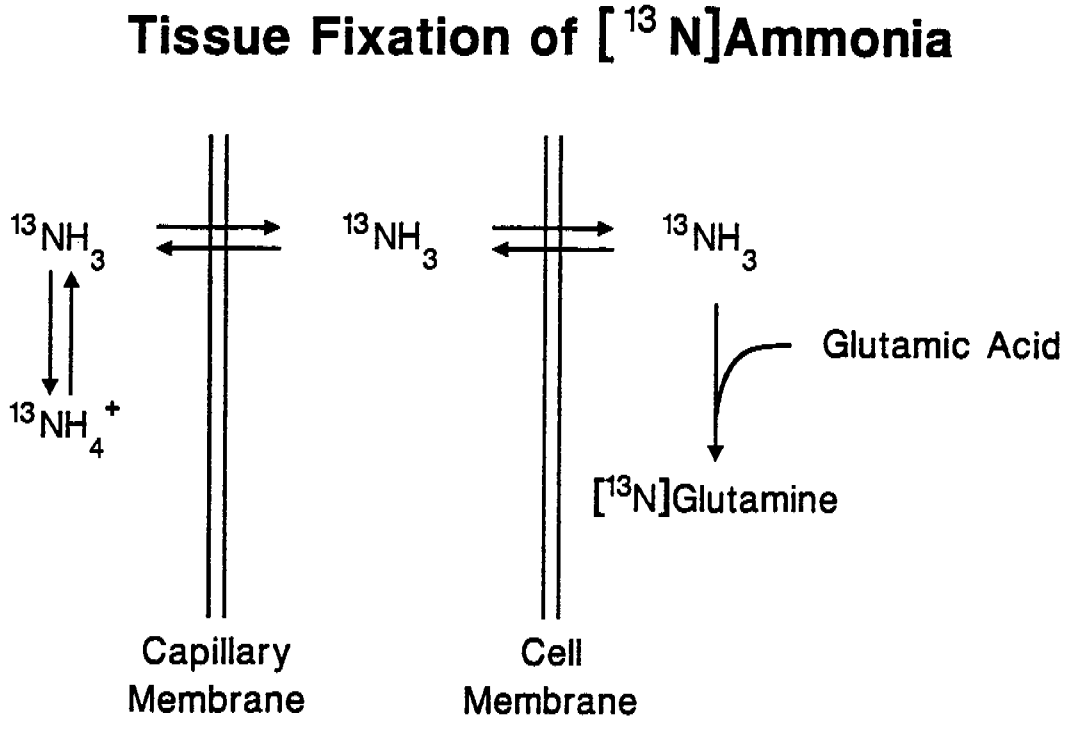


Figure 4. Tissue fixation of [^{13}N]ammonia via reaction with glutamine synthetase.

volume, and correction of later scans for blood background can be made.

Metabolic Processes

Glucose Utilization

Glucose is widely-used in tissues as an energy source, and assessment of glucose utilization *in vivo* is important for evaluating the vitality of organs and their candidacy for therapeutic intervention. **Fludeoxyglucose F 18 Injection, USP ([^{18}F]FDG)** has been used with PET for this purpose. This radiopharmaceutical is perhaps the most useful of all PET tracers due to its diverse applicability, ease of preparation, and convenient half-life. The numerous indications for clinical use of [^{18}F]FDG are listed in Table 1, and includes diagnostic imaging of the brain, heart, liver, and thyroid, as well as of neoplasms (22). As shown in Figure 5, this derivative of glucose participates in the initial steps of glucose metabolism (carrier-mediated transport and hexokinase-mediated phosphorylation), and therefore acts as a general tracer of aerobic or anaerobic flux. A beneficial characteristic of [^{18}F]FDG is that it is **metabolically "trapped"** *in vivo*; phosphorylated [^{18}F]FDG is not further metabolized via glycolytic or glycogen-synthetic pathways (Figure 5). Thus, tissues accumulate radioactivity in proportion to their glucose utilization rate without the complicating effects of time-dependent redistribution of labeled metabolites. In practice, PET images of [^{18}F]FDG are acquired 45-60 minutes after injection of the labeled drug.

Oxidative Metabolism

Besides glucose utilization, an important metabolic parameter that can be measured by PET is oxidative metabolism. The simplest radiopharmaceutical for this purpose is **[^{15}O]oxygen**, which is biochemical converted to [^{15}O]water in the final steps of all aerobic metabolic reactions. The predominant application of this tracer is for determination of the **regional cerebral metabolic rate for oxygen (rCMRO$_2$)** (23,24). Metabolic PET images are acquired by scanning the subject 40 seconds after inhaling the radioactive gas.

In the myocardium, uptake of [^{15}O]oxygen is slow and egress of metabolite [^{15}O]water is rapid, so an alternative tracer is required for measurement of oxidative metabolism in the heart. This tracer is **[^{11}C]acetate**, which enters the Krebs cycle in a substrate-independent manner and is converted to [^{11}C]carbon dioxide in direct proportion to the overall oxidative metabolic rate of the heart (Figure 6). The metabolism of [^{11}C]acetate is determined via PET measurement of the clearance of [^{11}C]carbon dioxide from myocardium over a 20-minute interval (25).

[^{11}C]acetate is employed clinically for evaluation of myocardial viability (Table 1). It is often used in concert with a flow tracer to distinguish **infarction** (dead myocardium) from **ischemia** (salvageable heart tissue). More sophisticated PET procedures involve the imaging of [^{11}C]acetate as well as a flow tracer and [^{18}F]FDG (26). In this combination of studies, ischemic tissue will have high uptake of [^{18}F]FDG but poor utilization of

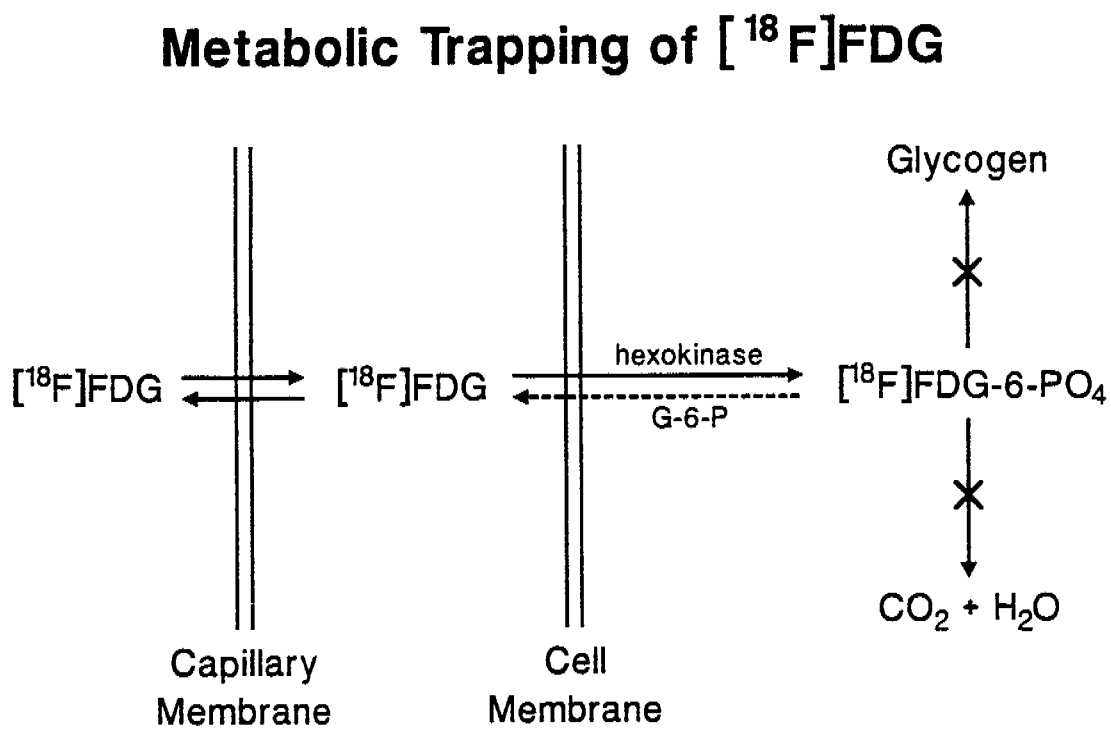


Figure 5. Metabolic trapping of [^{18}F]FDG by hexokinase-catalyzed phosphorylation.

[^{11}C]acetate, since there is a biochemical shift to anaerobic carbohydrate metabolism in ischemia. By contrast, infarcted myocardium (which is dead tissue) will utilize neither tracer. Soon after injection, [^{11}C]acetate can also be used to determine myocardial blood flow (27). When used in this manner as a **flow tracer**, clinical procedures are streamlined and radiation burden to the patient is minimized, since administration of an additional PET radiopharmaceutical for blood flow correction is not necessary.

Cyclotrons are machines that electromagnetically accelerate charged particles to very high velocities for irradiation of target materials. Specifically, the ions are propelled in a circular path by an alternating electric field in a constant magnetic field (Figure 7). The high-energy particles thus created are needed to surpass the threshold energies required by the nuclear reactions used for nuclide production (Table 2).

Cyclotrons are classified by the energy to which they are capable of accelerating particles, and differ in the

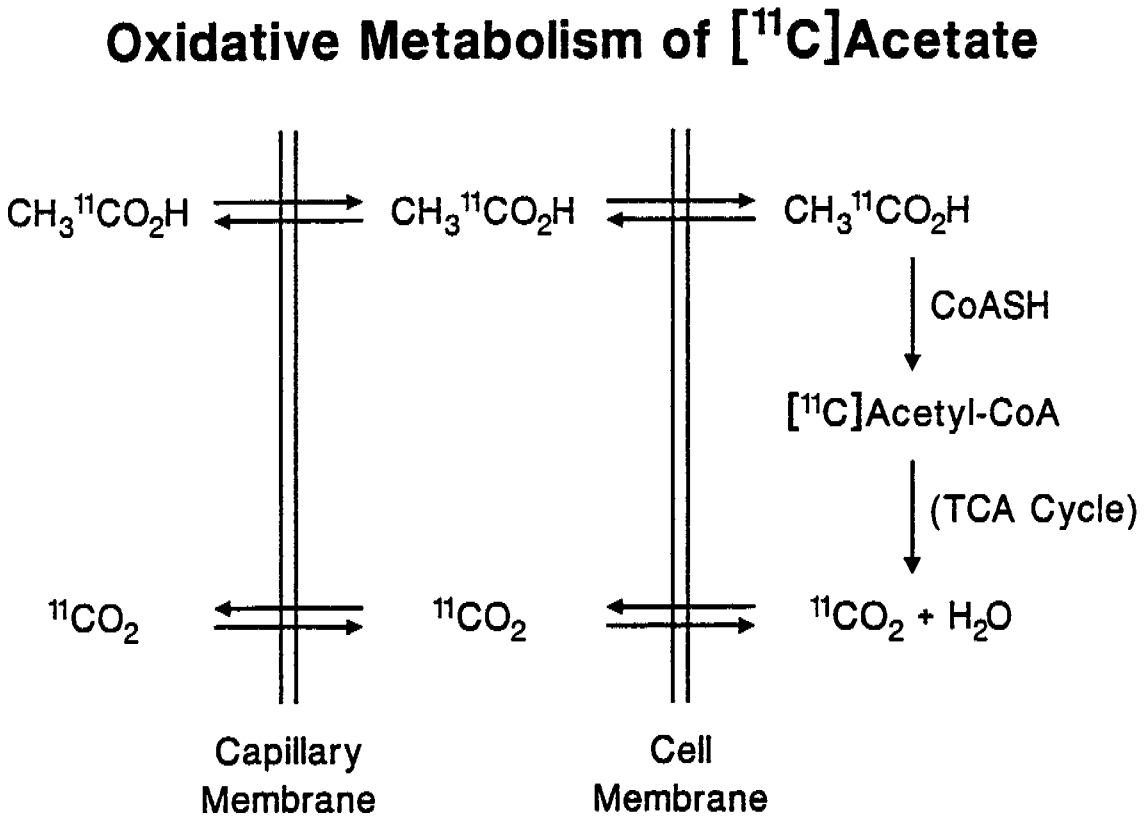


Figure 6. Substrate-independent oxidation of [^{11}C]acetate.

RADIONUCLIDE PRODUCTION

The initial step in compounding a PET radiopharmaceutical is the creation of the radionuclide. The radionuclides used for clinical PET are listed in Table 2, together with their half-lives, positron energies and principle means of production. Because PET tracers are relatively short-lived, nuclide preparation generally occurs within the confines of the PET facility using either medical cyclotrons or radionuclide generators. Of the nuclides shown, only fluorine-18 can be used in a practical manner for off-site production of PET tracers.

Cyclotron-Produced Radionuclides

Cyclotrons are used for the production of the majority of radionuclides used for positron tomography. types of particle beams that they generate (29). Accelerators for production of the nuclides in Table 2 are generally low-energy, high beam-current machines, and are either single-particle or multi-particle devices. Medical cyclotrons are designed to propel either positive ions or negative ions, although in the latter case the particles are converted to positively-charged species immediately prior to impinging upon the target. The predominant particles used for cyclotron production of positron-emitting nuclides are protons and deuterons (29).

The radionuclides shown in Table 2 are produced in batches of several hundreds of millicuries within cyclotron bombardment intervals of 10-120 minutes. Such high levels of radioactivity are necessitated by the relatively short half-lives of these nuclides, together with

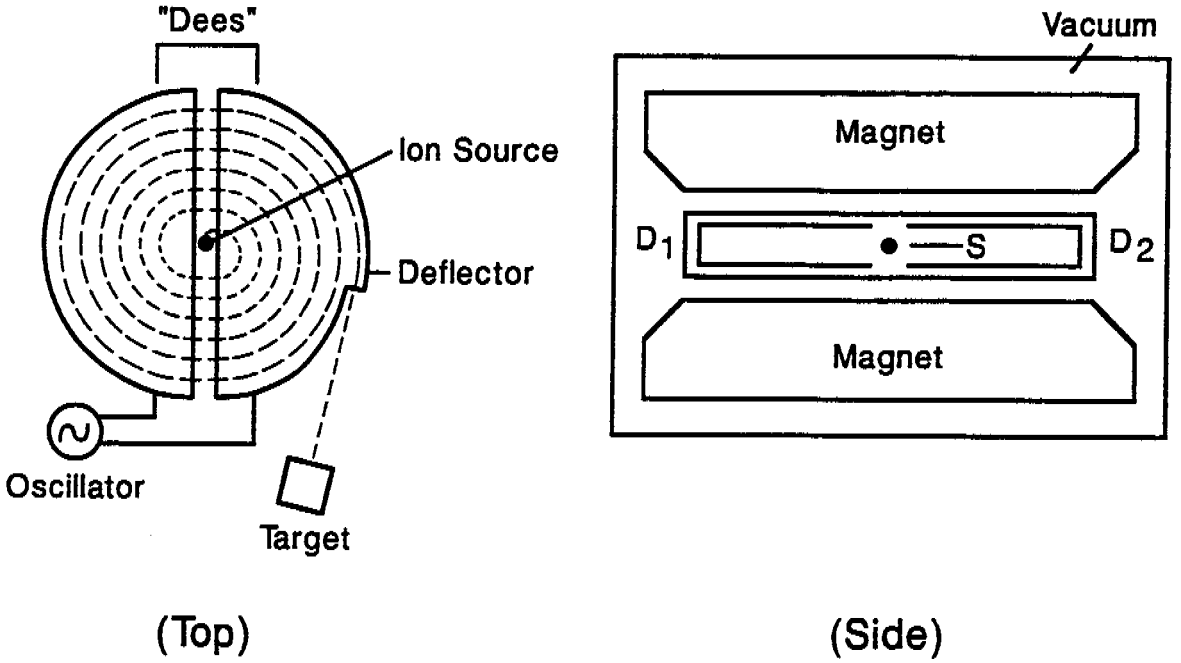


Figure 7. Cyclotron production of radioisotopes.

the time required for radiopharmaceutical compounding. Oxygen-15, nitrogen-15 and carbon-11 are produced by irradiation of gaseous target materials. The radionuclides thereby created are delivered as gases via metal tubing from the target area to radiosynthetic equipment which is used to incorporate them into drug structures. The preferred method for producing ***oxygen-15*** is via deuteron bombardment of naturally-abundant [^{14}N]nitrogen gas, although for single-particle cyclotrons the (p,n) reaction on relatively expensive [^{15}N]nitrogen gas can also be used. Similarly, the preferred reaction for production of ***nitrogen-13*** is the (p,α) reaction on naturally-abundant [^{16}O]oxygen gas; for lower-energy protons the (p,n) reaction on isotopically-enriched ^{13}C must be used. The universal means for producing ***carbon-11*** is via proton irradiation of [^{14}N]nitrogen gas.

Table 2

Radioisotopes for Clinical PET

Cyclotron-Produced:

Nuclide	Half-Life[a]	E_p(MeV)[a]	Nuclear Reactions[b]	
Oxygen-15	2 min	1.72	^{14}N(d,n)^{15}O	^{15}N(p,n)^{15}O[c]
Nitrogen-13	10 min	1.19	^{16}O(p,α)^{13}N	^{13}C(p,n)^{13}N[c]
Carbon-11	20 min	0.96	^{14}N(p,α)^{11}C	
Fluorine-18	110 min	0.64	^{18}O(p,n)^{18}F[d]	^{20}Ne(d,α)^{18}F[e]

Generator-Produced:

Nuclide	Half-Life[a]	E_β(MeV)[a]	Decay Sequence
Rubidium-82	76 sec	3.35	^{82}Sr → ^{82}Rb
Gallium-68	68 min	1.90	^{68}Ge → ^{68}Ga

a) Data from reference 28.
b) Data from reference 29.
c) Secondary reaction used with low-energy, single-particle cyclotrons.
d) Product is high specific-activity [^{18}F]fluoride ion.
e) Product is low specific-activity [^{18}F]fluorine gas.

Fluorine-18 differs from the above nuclides in that it can be produced in two ways. Low specific-activity [^{18}F]fluorine gas is produced via cyclotron bombardment of neon-20 gas containing a few percent fluorine. The more useful method for producing fluorine-18, however, is as high specific-activity [^{18}F]fluoride ion from irradiation of isotopically-enriched [^{18}O]water. [^{18}F]fluoride ion and [^{18}F]fluorine gas differ in the types of chemical reactions that can be employed in labeling procedures.

Generator-Produced Radionuclides

An alternative source of radionuclides for the preparation of PET radiopharmaceuticals is provided by generator systems (30). The two generator systems used in clinical PET are the ^{82}Sr→^{82}Rb generator and the ^{68}Ge→^{68}Ga generator (Table 2). Compared to cyclotrons, radionuclide generators are much **less expensive** in terms of capital investment, maintenance, and staffing requirements. The major disadvantage of the generator-produced radionuclides for PET is that they are **metallic species** that can be attached to substrates only via bulky bifunctional chelates. It is thus difficult to prepare generator-based radiolabeled biochemicals or drugs for PET, unlike the case for cyclotron-produced nuclides that are attached to substrates via covalent bonds.

A further disadvantage of the generator-produced radionuclides for PET is that the energies of the emitted positrons are relatively high. Whereas the maximum positron energy (E_β) of the cyclotron-produced nuclides shown in Table 2 ranges from 0.6 - 1.7 MeV, E_β for ^{82}Rb and ^{68}Ga is 3.3 MeV and 2.9 MeV, respectively

(28). The **higher positron energy** of the latter two nuclides leads to a greater radiation burden to the patient, as well as diminished spatial resolution in PET images.

germanium-68/gallium-68 generator is commercially-available as a system bearing up to 100 mCi of ^{68}Ge that delivers up to 85 mCi of gallium-68. The gallium-68 daughter is eluted from the generator using 1 N

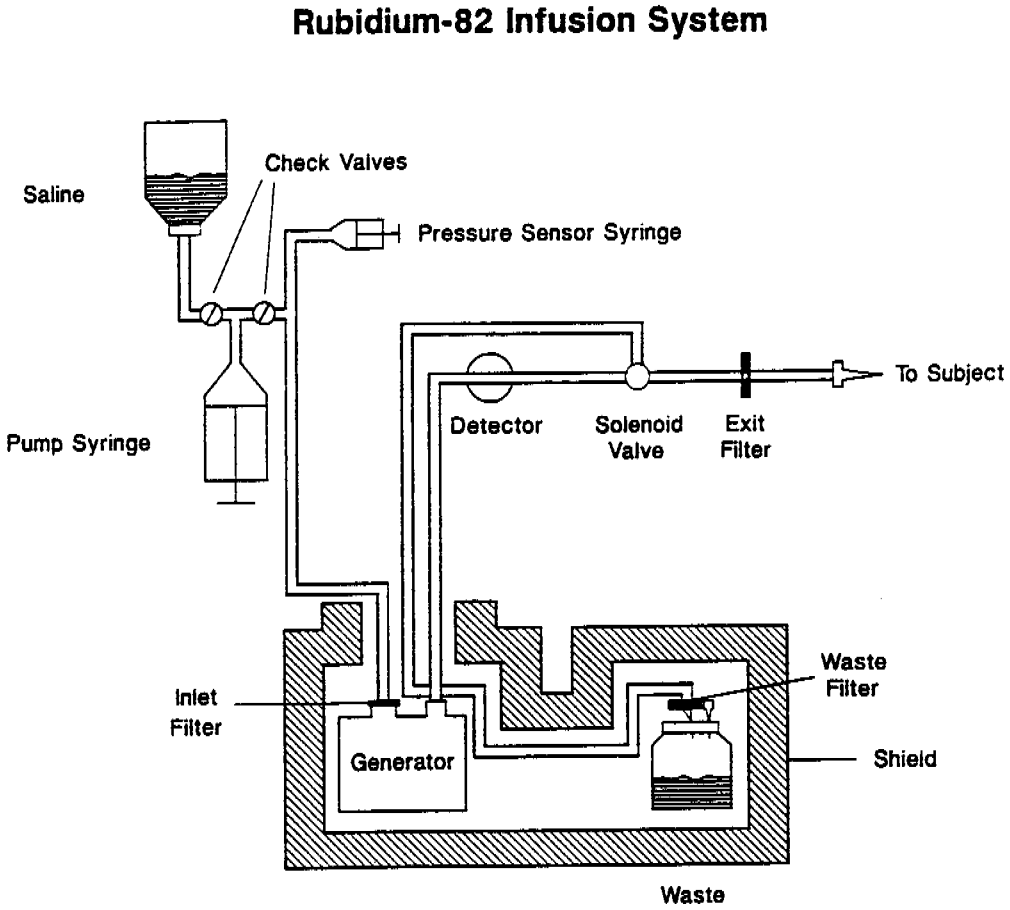


Figure 8. Rubidium-82 infusion system.

The ***rubidium-82* generator** has found the greatest application in clinical PET (31). The parent nuclide strontium-82 has a half-life of 25.6 days, and the effective lifetime of the generator is about one month. The strontium-82 activity is bound to a column of hydrous tin oxide; the 76-second half-lived rubidium-82 is eluted from the generator using 0.9% sodium chloride (NaCl) solution. The short half-life of the daughter radionuclide precludes compounding procedures with rubidium-82. Instead, the generator eluant is passed through a dosimeter and sterilizing filter and infused directly into the patient for PET blood flow measurements. This self-contained infusion system (Figure 8) has been approved as a medical device by the FDA, and is commercially-available as a 150 mCi ^{82}Sr generator that delivers 85-100 mCi of rubidium-82 (31).

The ***gallium-68* generator** is also used as a radionuclide source for clinical PET (Table 2). The parent nuclide for this system is germanium-68, which has a 288-day half-life. This gives a practical lifetime of approximately one year to the generator. The hydrochloric acid (32). The acidic generator eluate is unsuitable for direct administration to humans, but the 68-minute half-life of gallium-68 facilitates buffering of the solvent pH, conjugate labeling to various radiopharmaceutical substrates (see below), as well as sterile filtration prior to administration to nuclear medicine patients.

RADIOPHARMACEUTICAL COMPOUNDING

Compounding Devices

Table 3 lists the typical batch yields and usual patient dosages for the radiopharmaceuticals used in clinical PET. Because of the short half-lives of the positron-emitting radionuclides involved, the compounding of these PET tracers commences with very high levels of radioactivity. To avoid excessive absorbed radiation dose to compounding personnel, various devices have been developed that permit the preparation of PET radiopharmaceuticals without direct manipulation by human hands. These compounding devices are mounted

within shielded hot cells or the cyclotron vault, and can be categorized as on-line systems, remotely-operated systems, automated systems, or robotic systems.

Table 3

Radiopharmaceuticals for Clinical PET

Labeled Drug	Typical Batch Yield	Usual Patient Dosage
[^{15}O]Oxygen	200-300 mCi	30 mCi
[^{15}O]Carbon monoxide	150-200 mCi	60 mCi
[^{15}O]Water	50-125 mCi	30 mCi
Ammonia N 13 Injection, USP	30-40 mCi	15 mCi
[^{11}C]Acetate	150-300 mCi	30 mCi
Fludeoxyglucose F 18 Injection, USP	100-300 mCi	10 mCi
Rubidium Rb 82 Injection	85-100 mCi	50 mCi
[^{68}Ga]Gallium citrate	40-60 mCi	8 mCi

On-line systems are suited for compounding PET tracers that are either formed directly in the cyclotron target during irradiation, or are prepared from target products using single, rapid synthetic steps (33). These systems deliver the tracer immediately to the patient for administration, which is suboptimal from the perspective of pre-release QC testing (see below). On-line systems are used for radiopharmaceuticals labeled with oxygen-15, since the 2-minute half-life of this nuclide constrains product manipulation. For longer-lived nuclides, drug compounding via remotely-operated, automated robotic systems is preferred.

Remotely-operated systems require the continuous intervention of a human operator during the compounding procedure (34-36). This approach to compounding involves the remote operation of a shielded production system through valves that are controlled by externally-mounted switches. These systems are easily instituted for drug preparation, but are also susceptible to significant run-to-run variation in production variables.

Automated systems facilitate radiopharmaceutical production using a synthetic system in which valves are controlled by timing circuits (37-40). Once reagents are added and the system is started, the entire compounding procedure continues to the final radiopharmaceutical product. Human intervention at each step of drug compounding is thereby eliminated. Such "black box" systems offer the advantage of minimal run-to-run variability in production conditions, but are relatively inflexible because a given system is capable of preparing only a single PET tracer.

Robotic systems compound radiopharmaceuticals via the movement of reagents between workstations using

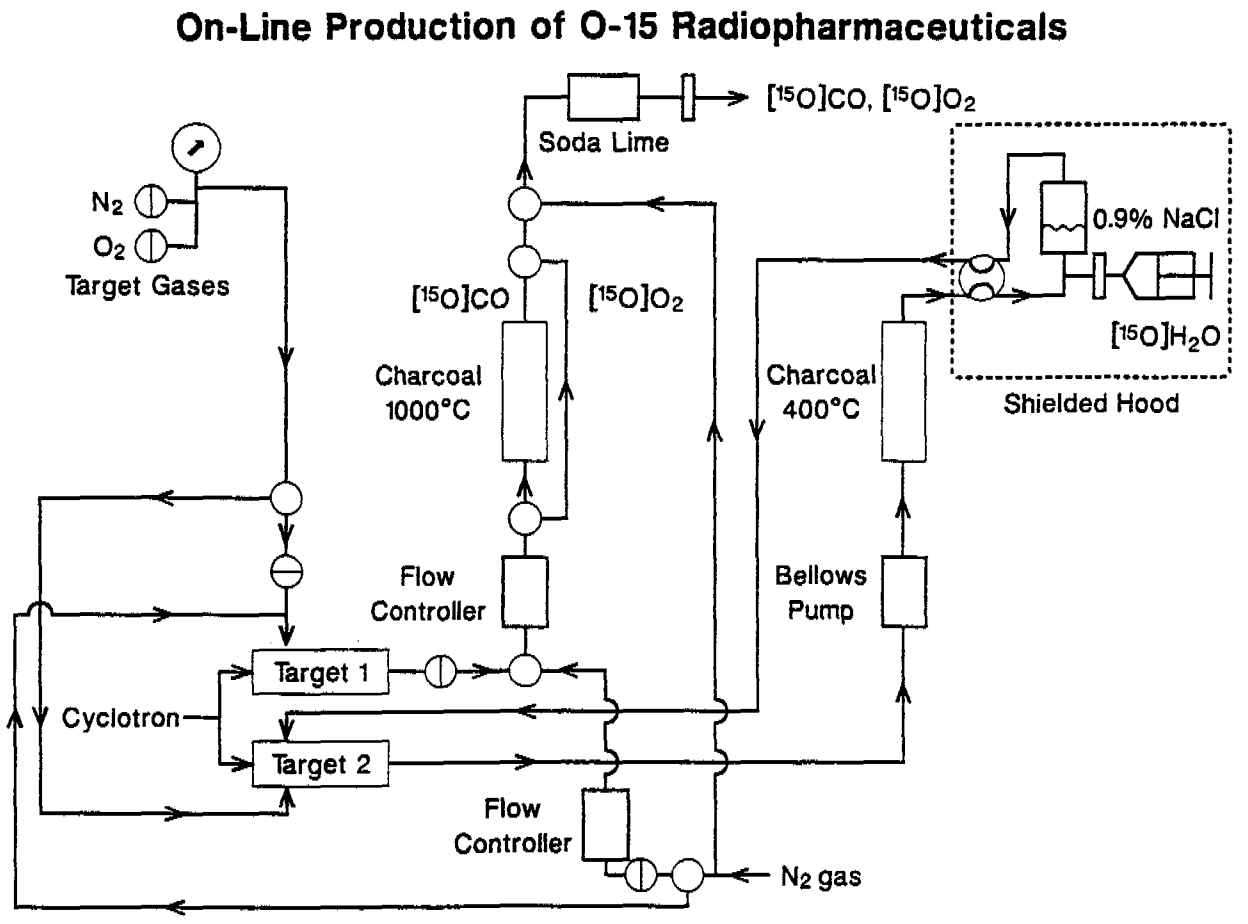


Figure 9. On-line production of oxygen-15 labeled radiopharmaceuticals.

robot arm that is controlled by a computer program (41-42). Like automated production systems, robotic compounding has minimal batch-to-batch variability in production conditions since human intervention is unnecessary. Because a robotic system can be used for compounding more than one PET tracer simply by changing the computer program, robotic devices offer the theoretical advantage of greater flexibility than automated systems for preparation of a single radiopharmaceutical.

The above drug compounding systems have been applied for the routine preparation of the PET tracers listed in Table 3. Before institution in the clinical setting, all compounding procedures must be validated, and continuously monitored thereafter to assure drug quality (see below).

Oxygen-15 Labeled Tracers

Oxygen-15 with its half-life of two minutes is the shortest-lived cyclotron-produced nuclide for clinical PET. The amount of synthetic manipulation of this nuclide in the compounding of PET radiopharmaceuticals is clearly limited by this fact, and ^{15}O-labeled tracers are rapidly prepared on-line using single reaction steps (33). The oxygen-15 labeled drugs used for clinical PET are [^{15}O]oxygen, [^{15}O]carbon monoxide and [^{15}O]water.

[^{15}O]Oxygen is a target product; the radioactive gas is formed *in situ* by irradiation of nitrogen gas containing a few percent oxygen (33). Following the irradiation interval (typically 5 minutes), further chemical processing of the target contents is unnecessary. The radioactive gas is simply transferred via tubing to a pressure-equalizing bag mounted within a radiation dosimeter, and ultimately inhaled by the subject for PET measurement of $CMRO_2$.

[^{15}O]Carbon monoxide is produced by passing target product [^{15}O]oxygen through a charcoal furnace heated to 1000°C (Figure 9) (33). The [^{15}O]oxygen gas is catalytically-converted to [^{15}O]CO, which is sent via metal tubing to the PET imaging facility using a bolus of high pressure nitrogen. The [^{15}O]carbon monoxide is collected in a sterile breathing bag mounted inside a wide-bore ionization chamber. When the radioactive gas has decayed to the appropriate level, the patient (already placed within the scanner) inhales the tracer through a filtered mouthpiece.

[^{15}O]Water is produced by either the exchange of [^{15}O]carbon dioxide with water (33), or by catalytic reduction of [^{15}O]oxygen (43). For the exchange-labeling technique, $[^{15}O]O_2$ gas is first converted to [^{15}O]carbon dioxide by passage through a charcoal furnace heated to 400°C (33). The $[^{15}O]CO_2$ thereby produced is then used to exchange-label water (Scheme 1). This is accomplished by bubbling the [^{15}O]carbon dioxide gas through normal saline in a sterile bag held in

$$[^{15}O]O_2 \xrightarrow[400°C]{\text{Charcoal}} [^{15}O]CO_2 \xrightarrow{H_2O} [^{15}O]H_2O$$

an ionization chamber (Figure 9) (33). The readout from the ionization chamber is displayed at the cyclotron control desk. When sufficient $[^{15}O]H_2O$ has been exchange-labeled, the contents of the bubbling bag are withdrawn into a sterile syringe. The syringe is then capped with a rubber septum and automatically sent using a pneumatic transfer system to an ionization chamber located in the PET imaging facility. After the [^{15}O]water has decayed to the appropriate level, the radiopharmaceutical is administered to the patient via bolus injection.

An alternative means of producing this radiopharmaceutical is to reduce [^{15}O]oxygen gas from the target on-line using hydrogen gas and palladium catalyst (Scheme 2) (43). The resulting [^{15}O]water can be tubed to the PET imaging facility for administration to the subject as a constant infusion or bolus injection.

$$[^{15}O]O_2 \xrightarrow{H_2 / Pd} [^{15}O]H_2O$$

Although the batch yields for [^{15}O]water, [^{15}O]carbon monoxide. and [^{15}O]oxygen greatly exceed the typical adult patient dosages (see Table 3), the short half-life of oxygen-15 precludes compounding of these radiopharmaceuticals other than on a unit-dose basis. That is, $[^{15}O]H_2O$ and [^{15}O]CO are prepared individually for each PET perfusion and blood volume study, respectively. This unit-dose requirement holds for different patients, as well as for repeat studies on the same individual subject.

Ammonia N 13 Injection, USP

Because cyclotron irradiation of [^{16}O]water produces nitrogen-13 in a variety (NO_3^-, NO_2^-, NH_4^+) of chemical forms (44), the preparation of [^{13}N]ammonia from this target system requires a reduction step. This reduction is catalyzed by either titanium (III) chloride (37) or DeVarda's Alloy (44), which consists of copper, aluminum and zinc (Scheme 3). Following this reduction step, the [^{13}N]ammonia is distilled from the

$$[^{13}N]NO_3^- + [^{13}N]NO_2^- + [^{13}N]NH_4^+ \xrightarrow[\text{reduction}]{\text{catalytic}} [^{13}N]NH_4^+$$

solution vessel into 0.9% NaCl, which is then sterile-filtered. Remotely-operated (34) and automated (37)

systems for the preparation of multiple batches of this PET tracer have been developed.

An alternative preparation route is to generate the nitrogen-13 radioactivity already in the form of ammonium ion during cyclotron irradiation (45). In this way, the reduction/distillation steps of the above process can be avoided. This on-line means of production is possible using the $^{12}C(d,n)^{13}N$ and $^{13}C(p,n)^{13}N$ reactions. Disadvantages of this approach are that the carbon slurry target material has a limited lifetime, and that the proton-induced reaction requires expensive, isotopically-enriched carbon-13.

Table 3 shows that the batch yields for the preparation of Ammonia N 13 Injection, USP, are 2-3 times greater than the typical dosage of this tracer for PET study of myocardial perfusion. For PET facilities that have two or more tomographs, it is thus feasible to divide the radiopharmaceutical batch for simultaneous imaging of two different patients using two different scanners. In view of the 10-minute half-life of nitrogen-13 and the 30-minute PET imaging intervals typically utilized, sequential imaging of an individual in a resting/stress perfusion protocol with the same batch of drug is precluded, however. Compounding of Ammonia N 13 Injection, USP, must be done on a per-study, unit-dose basis.

[^{11}C]Acetate

The preparation of this PET radiopharmaceutical involves the carboxylation of methylmagnesium Grignard using [^{11}C]CO_2, followed by acid hydrolysis to yield [^{11}C]acetate (Scheme 4). Compounding systems differ in the techniques used to isolate [^{11}C]acetate from chemical and radiochemical byproducts. A remotely-operated system (35) has been developed whereby the [^{11}C]acetic acid is extracted into an ether layer while the acidic aqueous hydrolysis layer is discarded. The [^{11}C]acetate is subsequently back-extracted into aqueous 0.9% $NaHCO_3$ solution and sterile-filtered for human administration.

$$^{11}CO_2 \xrightarrow{CH_3MgBr} CH_3{}^{11}CO_2MgBr \xrightarrow{HCl} CH_3{}^{11}CO_2H$$

Such phase-extraction techniques are cumbersome and require the final product to be in basic solution. Alternative remotely-controlled systems exist whereby phase-extraction purification is replaced with purification via resin columns that remove contaminants from the solution of [^{11}C]acetate (46,47). Such solid-phase extraction of impurities has also been adapted to robotic compounding systems (48).

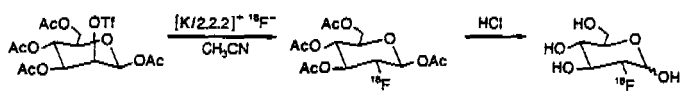
Table 3 indicates that the batch yield of [^{11}C]acetate is several times greater than the typical adult dosage of the labeled drug. Because [^{11}C]acetate is a **metabolic** tracer, repeat studies are not performed on the same subject, unlike the case for PET **perfusion** tracers. Nevertheless, the relatively large batch yield for this radiopharmaceutical means that when the drug compounded, the product can be dispensed to two separate patients for simultaneous imaging on two separate scanners. It is also conceivable that a single batch of the PET tracer could be used for sequential imaging of two different individuals using the same clinical PET scanner. Since each [^{11}C]acetate imaging study requires a total of 45 minutes, a minimum batch yield of 175 mCi of [^{11}C]acetate would be needed. This situation, however, is not likely to be commonly encountered in the clinical scenario.

Fludeoxyglucose F 18 Injection, USP

Although the monograph (49) for Fludeoxyglucose F 18 Injection, USP ([^{18}F]FDG) permits the compounding of this drug from low specific-activity [^{18}F]F_2, the method of choice for preparing this PET tracer uses [^{18}F]fluoride as a reagent. The reasons for this are that greater quantities of [^{18}F]fluoride can be produced for labeling, the labeling yields using [^{18}F]fluoride are higher than for [^{18}F]fluorine, and the final 2-[^{18}F]FDG product has superior specific activity and enantiomeric purity.

A complication of the use of [^{18}F]fluoride for compounding is that the ion must be completely anhydrous to be useful in nucleophilic labeling reactions. Considering that the target material is [^{18}O]water, removal of water from the [^{18}F]fluoride is a key step in the formulation of [^{18}F]FDG. This drying procedure is referred to as "resolubilization," since the goal is to remove the [^{18}F]fluoride from aqueous solution and redissolve it in an organic solvent that is suitable for radiofluorination reactions. **Resolubilization** is accomplished by first complexing the [^{18}F]fluoride to potassium [2.2.2]kryptofix or another strong base while still in aqueous solution, followed by addition of acetonitrile and azeotropic drying via heating. The dried [2.2.2]kryptofix-potassium [^{18}F]fluoride is redissolved in acetonitrile and then used for labeling reactions.

Fludeoxyglucose F 18 Injection, USP, is compounded via a two-step synthetic sequence using a protected sugar (1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranose) as the labeling substrate for resolubilized [^{18}F]fluoride (Scheme 5) (50). The



[^{18}F]FDG

[^{18}F]fluoride displaces the triflate group in the first step of the sequence, and the radiofluorinated intermediate is

then deprotected via acid hydrolysis to yield the [^{18}F]FDG product. Final radiopharmaceutical purification is achieved using solid-phase (C_{18} Sep Pak) extraction techniques.

This radiosynthetic procedure is relatively straightforward, which facilitates compounding in the clinical PET environment. The routine preparation of [^{18}F]FDG is possible using remotely-controlled (36), automated (38-40) or robotic (51,52) systems. The choice of which system to institute is based upon the relative advantages and disadvantages of each class of compounding device, as discussed above. These devices are capable of preparing [^{18}F]FDG in batches of several hundreds of millicuries, which is many fold larger than the typical adult human dosage of 10 mCi (see Table 3).

Since Fludeoxyglucose F 18 Injection, USP, has a physical half-life of 110 min, this PET radiopharmaceutical is almost always compounded on a multidose basis. The drug is prepared once daily for dispensing to several individual patients that are scanned successively throughout the workday. The high batch yield of this drug and its relatively long half-life also make possible the dispensing of [^{18}F]FDG dosages from an off-site, centralized nuclear pharmacy where the drug is compounded for distribution. This logistical convenience, together with the numerous indications for [^{18}F]FDG imaging, (Table 3) makes this radiopharmaceutical a particularly attractive drug for application in clinical PET.

[^{68}Ga]Gallium Citrate

Unlike the above compounding procedures, this PET radiopharmaceutical is prepared from a generator eluate. Four steps (42) are involved in the preparation sequence: i) generator elution, ii) addition to citrate, iii) neutralization and volume adjustment, and iv) filtration. As described earlier, the germanium-68/gallium-68 generator is eluted to give ^{68}Ga in 1 N hydrochloric acid. The volume of generator eluate that is used in the compounding procedure will vary, depending on the age of the generator and the amount of final product that is needed. The appropriate volume of gallium-68 solution is added to citrate buffer; the citrate is necessary as a ligand to complex with ^{68}Ga and prevent precipitation. The acidic solvent is subsequently buffered by the addition of one equivalent of 1 N sodium hydroxide. The neutralized solution of [^{68}Ga]gallium citrate is then volume-adjusted and sterilized via filtration into the final drug container.

A robotic system has been designed (Figure 10) whereby the generator-based radiopharmaceutical is compounded within eight minutes with a decay-corrected yield of 80% (42). For a 100 mCi ^{68}Ge/^{68}Ga generator with 85% elution efficiency, this corresponds to a batch yield of approximately 60 mCi of [^{68}Ga]gallium citrate, which is several times the typical adult human dosage of 8 mCi (see Table 3). This robotic device has the advantages of flexible adjustment of the eluate volume, radiation safety for personnel, and in-process monitoring of compounding steps. The system can also be adapted to the preparation of future PET tracers that are labeled with gallium-68 for clinical use.

Rubidium Rb 82 Injection

Rubidium Rb 82 Injection is unique as a generator-produced PET tracer in that the radiopharmaceutical is not isolated prior to patient administration; rather the generator eluate is infused directly into the subject under study (Figure 8). This approach to drug administration is mandated by the short half-life of the nuclide ($t_{1/2}$ = 76 sec), and has similarities to radiopharmaceuticals labeled with the short-lived cyclotron-produced nuclide oxygen-15. Because isolation of the final drug product for QC testing does not take place, special monitoring of generator characteristics such as generator yield, eluate flow rate, and radionuclidic breakthrough is required. These are discussed in the following section.

QUALITY CONTROL

Like other areas of pharmacy practice, a key role of the pharmacist is responsibility for the quality of the drugs that are dispensed. Quality control of PET radiopharmaceuticals is based upon the same strict criteria that apply to radiopharmaceuticals used in conventional nuclear medicine clinics. The major difference between the formulation of PET tracers and conventional radiopharmaceuticals is in the greater number of compounding steps required in the former case. Because of the more complicated procedures involved in the preparation of radiolabeled drugs for PET, QC involves both final product testing and continuous monitoring of formulation procedures.

Process Validation and In-Process Monitoring

As outlined above, the formulation of radiopharmaceuticals for clinical PET often requires multi-step procedures using remotely-operated or robotic systems. Due to their relative complexity, these processes must be fully validated prior to clinical drug preparation. Process validation requires careful evaluation of all aspects of drug quality, as well as reproducibility and reliability in the formulation and delivery of tracer. After a production process has been validated, in-process monitoring of validated compounding procedures is an important ongoing aspect of clinical drug preparation. In-process monitoring is a way of "building-in" quality, as it permits early identification of formulation defects before the quality of the final product is compromised. In addition,

continuous monitoring of drug compounding processes is especially pertinent to the production of PET radiopharmaceuticals, since the short half-lives of these drugs often preclude their pre-release testing.

Radiochemical and Chemical Purity

Oxygen-15 Radiopharmaceuticals. Radiotracers labeled with oxygen-15 are analyzed using gas chromatography (GC) (33). This analytical methodology

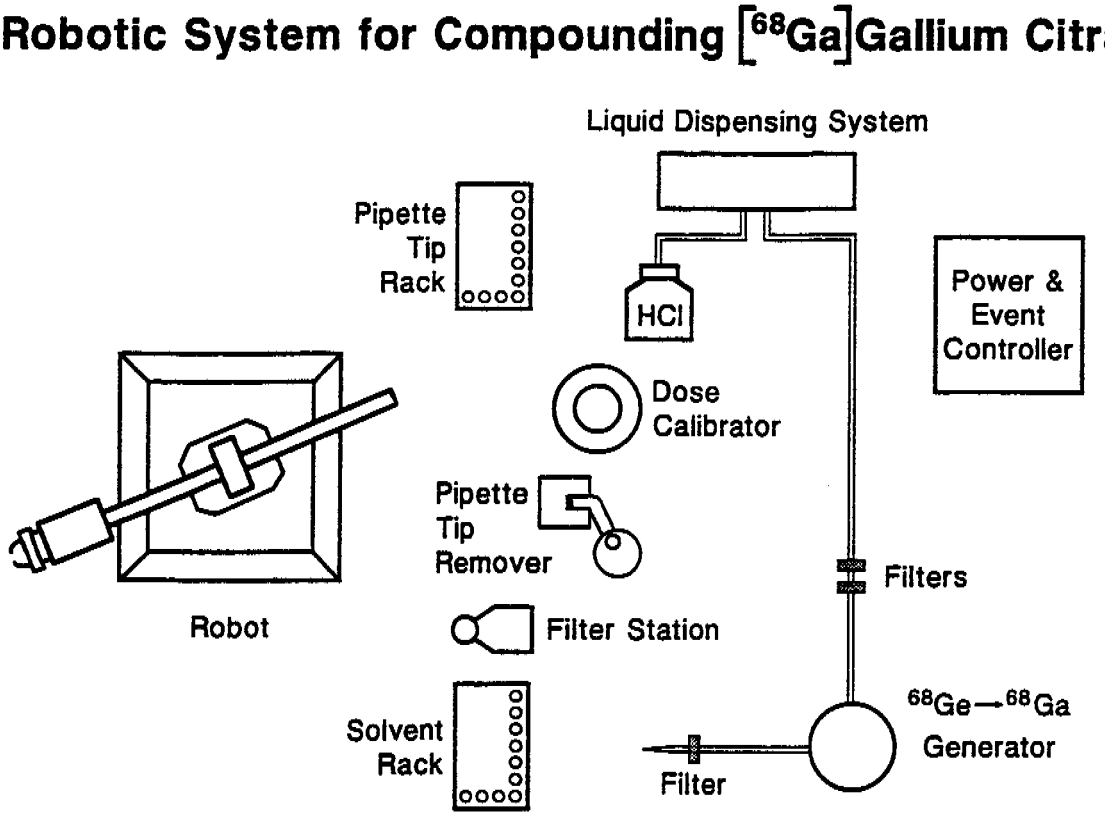


Figure 10. Schematic of a robotic system for compounding [^{68}Ga]gallium citrate injection.

End-Product Testing

Final product tests that are performed on PET radiotracers are similar to those performed on conventional radiopharmaceuticals, but are done on a more frequent basis, and utilize more sophisticated analytical instrumentation for determination of radiochemical and chemical purity. Drug quality of PET radiopharmaceuticals should meet standards set by existing USP drug monographs, and in all cases should be of high radiochemical and chemical purity, sterile, and apyrogenic. Radiochemical purity is an important characteristic to maximize in PET tracers, so that all derived imaging data pertains to the desired physiological process and patient radiation burden is minimized. Chemical purity is also an important component of quality control, since macroscopic contaminants may have pharmacologic or toxic effects. Sterility and apyrogenicity are essential characteristics of all labeled drugs dispensed for parenteral use.

is appropriate for use with the 2-minute half-lived oxygen-15, since retention times are generally short. Moreover, since this technique is based upon volatilization of the test sample before passage through a GC stationary phase, it is especially suited for quality control of [^{15}O]oxygen or [^{15}O]carbon monoxide. For these gaseous radiopharmaceuticals, a portion of the labeled drug is simply shunted into a GC injection loop, while the bulk of the radioactive gas is sent to the PET scanner for inhalation by the subject (Figure 11). Such an on-line QC system allows analysis of the same drug batch that is administered to the patient, and eliminates unnecessary personnel radiation dose.

Radiochemical purity is determined by detection of the various radioactive peaks in the GC eluate using a NaI(Tl) scintillation detector mounted at the exit tubin of the gas chromatograph. Impurities are identified on the basis of their retention time on the GC column. Typical impurities in oxygen-15 labeled PET tracers are

shown in Table 4 (33).

Table 4

Radiochemical Impurities in Oxygen-15 Labeled Gases

	% Impurity			
Radioactive Gas	[^{13}N]N_2	[^{15}O]O_2	[^{15}O]CO	[^{15}O]CO_2
[^{15}O]Oxygen	1-2	—	0-0.5	0-0.5
[^{15}O]Carbon monoxide	1-2	0-0.5	—	0-0.5
[^{15}O]Carbon dioxide	1-2	0-0.5	1-2	—

a) Data from reference 33.

Chemical purity of PET radiopharmaceuticals labeled with oxygen-15 is determined using a thermal conductivity detector (TCD) mounted after the NaI(Tl) detector at the exit tubing of the GC (33). As with the analysis of radiochemical purity, identification of chemical impurities is made on the basis of retention times on the GC column. With use of an appropriate standard curve, the areas of the peaks detected by the TCD give a direct measure of the mass of the impurities, and hence the pharmacologic dose administered to the subject. Perhaps the most important chemical contaminant to monitor in ^{15}O-labeled PET tracers is carbon monoxide, which binds irreversibly to hemoglobin *in vivo*.

USP (53). Although the purity of the drug can be determined using gas chromatography, it is more common to measure the radiochemical and chemical purity using high performance liquid chromatography (HPLC). As with GC, HPLC depends on the relative affinity of components for the stationary phase, and impurity identification is based on retention times. Anion-exchange columns are recommended as the stationary phase for [^{13}N]ammonia because they give a definitive retention time for the product. Detection of radioactive components is achieved using a NaI(Tl) crystal with associated electronics, and measurement of chemical constituents is accomplished using a refractive index (RI) detector.

The predominant radiochemical impurities in Ammonia N 13 Injection, USP, are radiolabeled nitrates that may have carried over during the reduction/distillation process. It is important to check product pH in this regard, because an excessively basic product suggests that there may have been codistillation of reductant solution into the product solution. The pH of Ammonia N 13 Injection, USP, is 4.5-8.5 (53).

Spot checks should be performed on this radiopharmaceutical to ascertain chemical purity (53). Assay for aluminum is needed if DeVarda's alloy was used in the production procedure, whereas assay for titanium is necessary if $TiCl_3$ was used as the reducing agent. For estimation of specific activity, a spot check

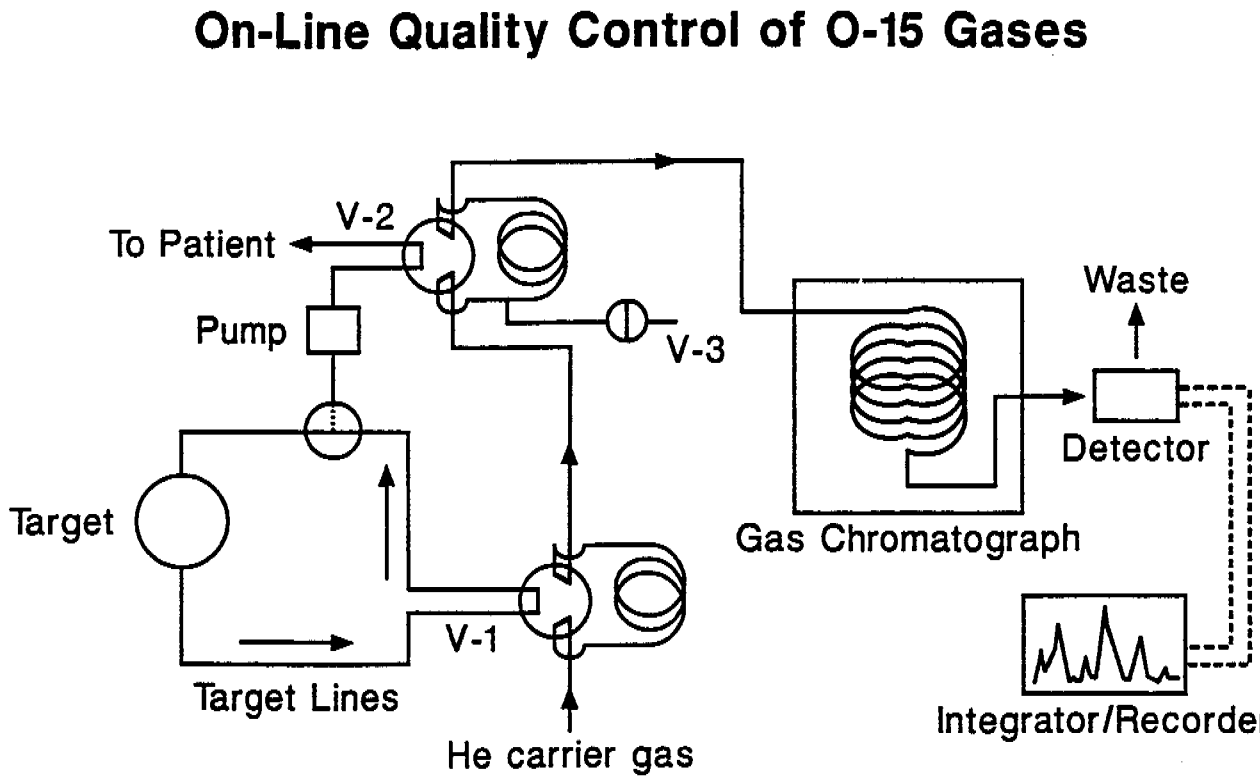


Figure 11. On-line quality control of gaseous oxygen-15 labeled radiopharmaceuticals.

Ammonia N 13 Injection, USP. Standards for this PET radiopharmaceutical have been established by the

using Nessler's reagent will detect carrier ammonia at the micromolar level.

[^{11}C]Acetate. Radiochemical and chemical purity of [^{11}C]acetate is also ascertained using HPLC (35). Gas chromatography analysis is inappropriate for QC of this radiopharmaceutical because thermal decomposition of the tracer occurs at the injection port. Thin-layer chromatography (TLC) is also not useful as an analytical technique because there is potential loss of volatile components like [^{11}C]carbon dioxide. HPLC is therefore used, since it involves direct injection of the radiopharmaceutical solution onto the chromatographic column without heating. Radiochemical purity is determined by on-line detection of radioactive peaks in the eluate from the HPLC column using a NaI(Tl) detector, and mass peaks can be measured using an RI detector. A reverse-phase HPLC column is recommended as the stationary phase for separation of [^{11}C]acetate from [^{11}C]carbon dioxide. The response of the RI detector following sample injection onto the HPLC can be compared with a standard curve for determination of the actual mass of any impurities present.

The major radiochemical impurity in [^{11}C]acetate is unreacted [^{11}C]carbon dioxide; potential chemical contaminants are carbon dioxide, magnesium or bromide. These contaminants can be measured via HPLC, although assay for magnesium or bromide requires ion exchange chromatography and is generally done in process validation tests rather than on a routine basis. Radiochemical purity and measurement of carbon dioxide content are achievable on a per-batch basis using reverse-phase HPLC. An additional aspect of chemical purity that is assessed on a per-batch basis is the final product pH, which should be in the range 4.5-8.5.

Fludeoxyglucose F18 Injection, USP. Standards for this labeled drug have been established by the USP (49). Testing of [^{18}F]fludeoxyglucose for radiochemical purity is achieved using TLC. Following development in a TLC chamber, the silica plates used as the stationary phase are analyzed with a TLC scanner, which integrates component radioactive peaks. Identification of impurities is made on the basis of R_f values. Although this analytical technique has lower resolution than GC or HPLC, it is preferred for routine clinical use due to its simplicity and low cost. Chemical impurities can also be measured in a qualitative manner using TLC with iodine chamber staining (52), although HPLC is more appropriate for initial process validation.

Potential radiochemical impurities in this radiopharmaceutical are unreacted [^{18}F]fluoride or the non-deprotected reaction intermediate tetraacetyl-[^{18}F]fluoromannopyranose (Scheme 4). A potentially-harmful chemical impurity in this radiopharmaceutical is the kryptofix 2.2.2 used to resolubilize [^{18}F]fluoride. The presence of this compound can be detected with TLC and iodine chamber visualization (52). It is also important to assay the final preparation for pH, since one of the formulation steps for this radiopharmaceutical involves treatment with hydrochloric acid. The pH of Fludeoxyglucose F 18 Injection, USP, is 4.5-8.5 .

[^{68}Ga]Gallium Citrate. Cyclotron-produced nuclid for PET rarely have radionuclidic contaminants due to the nuclide-specific nuclear reactions and the high-purity targets that are employed. Radionuclidic impurities in generator-based radiopharmaceuticals, however, are a more important aspect of quality control due to the ever-present potential for breakthrough. Radionuclidic purity in [^{68}Ga]gallium citrate is determined on a weekly basis by allowing the product to stand 24 hours or longer, and then measuring the positron emissions. Any gallium-68 activity remaining at this time will be due to decay of germanium-68 parent that has broken away from the resin and into the generator eluate. Acceptable levels are generally 10^{-2} μCi of ^{68}Ge per mCi of ^{68}Ga (32).

Radiochemical purity of [^{68}Ga]citrate is determined with a per-batch frequency using radio-TLC. As with [^{18}F]fludeoxyglucose, potential radiocontaminants are not volatile and can be easily resolved from the labeled drug using this relatively inexpensive analytical method. With this PET radiopharmaceutical, there are no macroscopic contaminants of special concern, although the pH must be checked to assure that it is within the range 5.5 - 8 (42).

Rubidium Rb 82 Injection. Standards for this radiopharmaceutical have been proposed by the US (54). The quality control testing for this PET perfusio tracer center on the fact that it is administered from a generator-based infusion system. Thus, QC testing of the properties of the generator eluate are required, along with an evaluation of the infusate delivery rate. The infusion system is operated in one of two modes, **bolus** infusion or **continuous** infusion, depending upon the tracer kinetic model that is to be applied to the perfusion imaging data (20,21). The strontium-82 / rubidium-82 infusion system must be initially calibrated, and periodically tested thereafter for its functioning in either of these modes of operation (55).

Radionuclidic purity must be evaluated for this generator-produced radiopharmaceutical. This is determined by measuring a sample of the generator eluate at least 1 hour after elution. At this time all of the rubidium-82 activity has decayed, and any residual radioactivity is due to parent radiostrontium nuclides. Radioactivity due to strontium-82 ($t_{1/2}$ =25 days) is measured on the basis of its 777 keV photopeak, whereas direct assay of any strontium-85 ($t_{1/2}$ = 64.5 days) contaminant requires a curve-stripping program with a γ-spectrometer for resolution of its 514 keV photopeak from the 511 keV gamma-line of ^{82}Rb (56) For each generator the ratio of ^{82}Sr to ^{85}Sr is known, so for routine assay a factor can be multiplied times the measured strontium-82 activity to give the amount of

strontium-85 contaminant in the sample. Typical breakthrough values are less than 10^{-5} μCi ^{82}Sr/mL/mCi ^{82}Rb (31), with ^{85}Sr/^{82}Sr impurity ratios of < 5.0 (57).

Because the positron-emitter is infused directly into the subject during imaging studies, the functioning of the device as a drug delivery system is an important component of routine quality control. The generator yield is measured by collecting 50 mL of eluate, measurement in a dose calibrator, and correcting activity to end of elution (31). The yield of ^{82}Rb is greater with higher infusion rates; for a typical flow rate of 50 mL/min, the yields of ^{82}Rb are usually 60-70% of theoretical (55). The elution profile for the system can be determined for different infusion rates (20-80 mL/min) by measurement of the eluate activity at 1-second intervals using the system's on-line detector. This information is used to assay the amount of activity infused into the subject, as well as the associated radiation burden (55).

There are no special precautions concerning the radiochemical or chemical quality of this labeled drug. Radiochemical purity testing of Rubidium Rb 82 Injection, USP, is not required on a frequent basis because the tracer is used directly as the monovalent anion and not chemically altered prior to infusion. Validation tests of the generator have shown high chemical purity; less than 0.1 μg of tin per mL of eluate is present (31). Because this level is nontoxic and labeling reactions are not used, routine testing of the chemical purity of this radiopharmaceutical is not necessary.

Sterility

Like other parenteral drugs, positron-emitting pharmaceuticals must be sterile to be suitable for use in humans. A sterile product is one that is free of living organisms, whether pathogenic or nonpathogenic. Official tests for drug sterility require that samples be incubated in **fluid thioglycollate medium** to check for the presence of facultative anaerobic and anaerobic bacteria, and in **soybean casein digest medium** for determination of fungi, molds, and aerobic and facultative anaerobic bacteria (58). These tests require 3-14 days for completion, so clearly cannot be performed with PET radiopharmaceuticals on a pre-release basis. This dilemma is shared with conventional radiopharmaceuticals that have relatively short half-lives. Positron-emitting radiopharmaceuticals should be tested for sterility on a daily or batch basis. Although the results of these tests are available after the patient has been administered the labeled drug, such quality control testing is important for in-process monitoring of compounding procedures, and for early correction of potential problems in product formulation.

Apyrogenicity

Pyrogens are substances that cause a pyretic response upon injection. This response is characterized by the onset of chills and fever 45-90 minutes after parenteral injection, accompanied by general malaise and headache that can last 3-4 days. The substances inducing this response are generally endotoxins of gram-negative bacteria or dead bacteria, but can also be from a wide variety of chemical classes. Because pyrogens are often smaller than 0.2 μm, terminal filtration can often render radiopharmaceuticals sterile, but not apyrogenic. For this reason, pyrogen testing of PET tracers should be performed on a pre-release basis whenever possible. For very short-lived radiotracers ($t_{1/2} < 10$ minutes), pyrogen testing should be done on at least a daily basis.

Traditionally, the presence of pyrogens in parenteral drugs is tested according to the USP by measuring the temperature rise in rabbits injected with the test sample (58). Initial tests involve hourly temperature readings over three hours. This technique is thus too slow for routine application with PET radiopharmaceuticals. An alternative *in vitro* test is also sanctioned by the USP, the **bacterial endotoxin test (BET)** (58). This technique involves mixing a sample of the test substance with **limulus amebocyte lysate (LAL)**, which clots in the presence of bacterial endotoxin. The mixture is incubated for 60 minutes; clotting indicates the presence of endotoxin. The test sample is compared to control solutions of known endotoxin concentration. The simplicity, sensitivity and reproducibilty of the BET promote its routine application for pyrogen testing of radiopharmaceuticals in the clinical setting. Although not yet official, a 20-minute BET technique has been proposed especially for use with short-lived PET tracers (59). This faster version of the official BET, once validated and officially adopted, makes practical the pre-release pyrogen testing of all positron-emitting drugs with half-lives $\geq$ 20 minutes.

REGULATORY ISSUES

Most positron-emitting radiopharmaceuticals are accelerator-produced and therefore lie outside the jurisdiction of the **Nuclear Regulatory Commission (NRC)**, which is responsible for by-product materials produced at nuclear reactors. The regulation of PET tracers thus differs significantly from conventional radiopharmaceuticals, which are predominantly by-product materials. The major regulatory body responsible for PET radiopharmaceuticals is the **Food and Drug Administration (FDA)**, which shares regulatory responsibility with state agencies for radiation safety issues.

There is an important distinction between PET used for research purposes and PET applied for the routine

clinical delivery of health care. This classification of activities has ramifications for the regulation of the positron-emitting tracers used in human subjects, as well as for the role that nuclear pharmacists play as members of the PET team.

Research PET

Research PET encompasses a wide breadth of activities, spanning the gamut of evaluative experiments that precede routine clinical use. These imaging studies range from PET scanning of animals to determine the localization of new tracers, to the imaging of human subjects to ascertain the kinetics of established radiopharmaceuticals in untested diseases. Like other areas of scientific investigation, research PET studies have a high probability of yielding only negative results. Despite the time-consuming nature of research PET, the experimental results derived from these investigations are invaluable to clinical PET. The novel tracers and imaging techniques that are developed through this process find eventual application in the clinical arena, and assure that PET retains its advantage as a medically-unique diagnostic tool.

The radiotracers used for research PET studies in humans are regulated through the **Radioactive Drug Research Committee (RDRC)**, which acts as an arm of the FDA at medical centers where such investigations take place. The goals of studies approved by the RDRC are to obtain basic pharmacokinetic information and biodistribution data for new drugs. The RDRC is comprised of several experts, including physicians, pharmacists, chemists and physicists, that review the proposed application of radioactive substances in humans. The preparation, quality control, radiation dosimetry, toxicology, and anticipated research benefit of a project are all examined prior to RDRC approval. Research studies regulated in this manner are limited to small numbers of subjects sufficient to answer proposed research hypotheses.

Clinical PET

In contrast to the innovative discovery that is the goal of research PET, clinical PET employs established PET radiopharmaceuticals and proven imaging protocols to answer a diagnostic question about a specific patient. In this regard clinical PET can be viewed as a vehicle for the routine delivery of state-of-the-art health care. As the goal of clinical PET studies is to assist in the therapy of a patient, experimental innovation does not play a role. Rather, systematic, reproducible imaging procedures are needed that allow direct comparison of the PET data from a given subject with values established for the control population.

Because clinical PET has only recently been introduced to the medical community, its regulation has not yet been fully formalized (60). There are generally two proposed approaches to the regulation of radiopharmaceuticals for clinical PET. These are the investigational new drug (IND; drug manufacturing) approach and the practice of medicine/pharmacy (dr. compounding) approach.

Drug Manufacturing

This means of regulating PET tracers requires that every tracer used for clinical studies be evaluated for safety and efficacy via an **investigational new drug application (IND)**. The evaluation process carried out under the authority of these applications is classified into three clinical investigation phases, as are those for other drugs regulated by FDA. Once clinical trials are completed, a **new drug application (NDA)** is applied for, which, when approved, allows for routine full-scale manufacturing of the drug in question. From the standpoint of PET radiopharmaceutical preparation, the NDA approach requires that all labeled drugs be prepared under **Current Good Manufacturing Practices (CGMPs)** that are similar to those required for drug manufacturing centers. Although proposed CGMPs for PET radiopharmaceuticals (61) are attenuated compared to those typically required for drug manufacturing, PET centers would be nonetheless inspected by the FDA for compliance. This regulatory approach thus considers the formulation of PET tracers to be dru manufacturing, and places PET facilities accountable t the FDA as such.

Drug Compounding

An alternative approach for the regulation of PET radiopharmaceuticals proposes that the formulation and application of these labeled drugs fall under the jurisdiction of pharmacy practice and the practice of medicine, respectively. This approach considers the formulation of a PET radiopharmaceutical pursuant to a prescription from a licensed physician for an individual patient no different than the filling of any other prescription. In this case, the activities of the pharmacists and physicians involved with PET would be regulated by pharmacy and medical boards. This regulatory approach thus differs from the drug manufacturing concept in that the FDA traditionally does not regulate the professional activities of pharmacists, so prerogatives of the licensed pharmacist are permitted in the compounding process. The American Pharmaceutical Association has drafted **APhA Guidelines for the Compounding of PET Radiopharmaceuticals** (62); these supplement the more general **APhA Nuclear Pharmacy Practice Standard** (63). These guidelines make recommendations concerning the procurement, compounding, quality control, dispensing and distribution of PET

radiopharmaceuticals by nuclear pharmacists. PET radiopharmaceuticals that are formulated under the practice of pharmacy rather than according to an IND or NDA are, nonetheless, expected to meet all standards of quality described in USP monographs for these labeled drugs.

PROFESSIONAL RESPONSIBILITIES

PET teams are of a multidisciplinary nature, requiring members with specialized talents for various aspects of the total operation. Typical teams consist of physicians, pharmacists, chemists, physicists, nurses, computer specialists, and nuclear medicine technologists. Within such a team, there is unique expertise which is supplied by the nuclear pharmacist. Most of the special contributions of nuclear pharmacists are described in the APhA draft guidelines for the compounding of PET radiopharmaceuticals (62). In addition to these unique services, there is also opportunity for overlap in some of the activities of the pharmacist and those of other members of the PET team. This latter aspect is probably most apparent in the services provided by nuclear pharmacists and chemists.

Product Release

A key role of the pharmacist is to be the quality approval member of the PET team. That is, the pharmacist should review all quality control test results for the final drug product to assure that it meets USP standards. This product release role is one that is especially important when PET radiopharmaceuticals are compounded under the practice of pharmacy, since all radiopharmaceuticals dispensed are the legal responsibility of the licensed pharmacist. This responsibility is also appropriate for pharmacists in centers where PET tracers are prepared under drug manufacturing regulations and CGMPs. In this case the special training and skills of the pharmacist supplement that of the chemist, whose major expertise is in synthesizing the radiotracer.

Procurement

An important role for the pharmacist is to maintain records of all components used for the preparation of PET radiopharmaceuticals. A record should be kept of the date of receipt, quantity, manufacturer, lot number and expiration date of all drug ingredients. This allows complete traceability of all components used for a given radiopharmaceutical, which is especially important for PET tracers with their multistep preparation protocols. All materials should be maintained in a limited access area, so that only personnel approved for clinical drug preparation are allowed entrance.

Dispensing

Dispensing patient doses with appropriate recordkeeping is also a traditional role for the pharmacist. These activities are described in the APhA Nuclear Pharmacy Practice Standards, and are designed to assure that the correct PET radiopharmaceutical, in the prescribed dosage and dosage form, is received by the correct patient at the desired time via the prescribed route of administration.

Product labeling is another aspect of recordkeeping which is a special concern for the pharmacist. Like conventional radiopharmaceuticals, the final container label should include the identity of the PET radiopharmaceutical, the assigned batch or lot number, and required regulatory (state board of pharmacy, IND, NDA, RDRC) and/or warning ("radioactive") statements and symbols.

Clinical Monitoring

In traditional pharmacy practice, there is increasing responsibility of the pharmacist in the clinical monitoring of drug use to promote rational pharmacotherapy. Although such professional activity is not yet taking place with the monitoring of PET radiopharmaceuticals, there is a clear opportunity for pharmacists with expertise in this area. Correlations between imaging artifacts in patients, drug use and/or clinical laboratory data may give insight into the interpretation of PET scans and improve the accuracy of diagnostic information.

Research

The emphasis on drug action, pharmacokinetics, and pharmaceutics in pharmacy education creates opportunities for the involvement of pharmacists in research projects. The integration of nuclear pharmacists with research activities is especially favored at sites which combine research PET with clinical PET. Pharmacists can contribute to research projects at a variety of levels, ranging from radiopharmaceutical stability studies to evaluation of tracer kinetics and interpretation of iatrogenic effects on PET imaging data. Such research activities promote the image of the profession among non-pharmacist colleagues, and maintain practice standards for PET nuclear pharmacy at a high level.

CONCLUSIONS

PET is a sophisticated imaging modality that permits physiologic measurements to be made in human subjects in a noninvasive manner. Cardiovascular and metabolic parameters that assist in therapeutic decision-making can be measured by PET using positron-emitting radiopharmaceuticals. Labeled drugs for clinical PET

are formulated from accelerator-produced or generator-eluted nuclides using multistep compounding devices, and are subjected to quality control tests to assure safety and efficacy to the patient. In this exciting new field of radiology, there is a special need for the expertise of nuclear pharmacists in the preparation, quality control, and application of PET radiopharmaceuticals.

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QUESTIONS

1. An advantage of positron emission tomography over computerized axial tomography or magnetic resonance imaging is

   a. human anatomy is imaged with superior resolution.
   b. anatomical structures are imaged at reduced cost.
   c. human physiology can be assessed noninvasively.
   d. imaging intervals are shorter.

2. Which of the following is not an advantage of PET over conventional nuclear medicine imaging?

   a. Superior image resolution
   b. More physiological processes can be studied
   c. Improved sensitivity
   d. Decreased cost

3. PET scanners function by detection of

   a. positrons.
   b. negatrons.
   c. annihilation radiation.
   d. random coincidences.

4. The scintillation crystal used in most clinical PET scanners is

   a. sodium iodide.
   b. bismuth germanate.
   c. barium fluoride.
   d. cesium fluoride.

5. Blood volume is measured using

   a. [^{15}O]water.
   b. [^{15}O]carbon dioxide.
   c. [^{15}O]oxygen.
   d. [^{15}O]carbon monoxide.

6. The drug of choice for assessment of regional cerebral blood flow is

   a. [^{15}O]water.
   b. Ammonia N 13 Injection, USP.
   c. Rubidium Rb 82 Injection.
   d. Fludeoxyglucose F 18 Injection, USP.

7. A PET tracer commonly used for sequential perfusi imaging is

   a. Ammonia N 13 Injection, USP.
   b. Rubidium Rb 82 Injection.
   c. [^{15}O]oxygen.
   d. [^{68}Ga]gallium citrate.

8. A PET radiopharmaceutical that can be used for assessment of both cardiovascular and metabolic parameters is

   a. [^{15}O]water.
   b. Ammonia N 13 Injection, USP.
   c. [^{11}C]acetate.
   d. Fludeoxyglucose F 18 Injection, USP.

9. PET measurement of pulmonary function uses

   a. [^{11}C]acetate.
   b. Fludeoxyglucose F 18 Injection, USP.
   c. Rubidium Rb 82 Injection.
   d. [^{68}Ga]gallium citrate.

10. The tracer most widely used in clinical PET is

    a. [^{15}O]water.
    b. Ammonia N 13 Injection, USP.
    c. Fludeoxyglucose F 18 Injection, USP.
    d. Rubidium Rb 82 Injection.

11. A PET radiopharmaceutical that is not used for both brain and heart imaging is

    a. [^{11}C]acetate.
    b. Rubidium Rb 82 Injection.
    c. Fludeoxyglucose F 18 Injection, USP.
    d. Ammonia N 13 Injection, USP.

12. The longest/shortest-lived nuclides used in clinical PET are

    a. fluorine-18 / oxygen-15.
    b. fluorine-18 / rubidium-82.
    c. gallium-68 / oxygen-15.
    d. gallium-68 / rubidium-82.

13. An advantage of generator nuclides compared to cyclotron-produced nuclides is

    a. lower positron energy.
    b. improved image resolution.
    c. decreased cost.
    d. ease of attachment to drug structures.

14. A disadvantage of gallium-68 compared to rubidium-82 is

    a. generator lifetime.
    b. potential for labeling substrates.
    c. utility for rapid sequential imaging.
    d. positron energy.

15. The devices most appropriate for compounding oxygen-15 labeled drugs are

    a. on-line systems.
    b. remotely-operated systems.
    c. automated systems.
    d. robotic systems.

16. The chemical form of oxygen-15 produced in the cyclotron target is

    a. oxygen.
    b. carbon monoxide.
    c. carbon dioxide.
    d. water.

17. A reaction step used in the compounding of Ammonia N 13 Injection, USP, is

    a. hydrolysis.
    b. oxidation.
    c. reduction.
    d. electrolysis.

18. A Grignard reagent is used in the compounding of

    a. Ammonia N 13 Injection, USP.
    b. [^{11}C]acetate.
    c. Fludeoxyglucose F 18 Injection, USP.
    d. [^{15}O]water.

19. Resolubilization is a step in the compounding of

    a. [^{68}Ga]gallium citrate.
    b. Ammonia N 13 Injection, USP.
    c. [^{11}C]acetate.
    d. Fludeoxyglucose F 18 Injection, USP.

20. Which of the following PET tracers cannot be prepared in multi-dose batches?

    a. Fludeoxyglucose F 18 Injection, USP
    b. [^{11}C]Acetate
    c. [^{68}Ga]Gallium citrate
    d. Ammonia N 13 Injection, USP

21. Gas chromatography is commonly used for quality control of

    a. [^{15}O]carbon monoxide.
    b. Ammonia N 13 Injection, USP.
    c. [^{11}C]acetate.
    d. Fludeoxyglucose F 18 Injection, USP.

22. Radiochemical purity is not routinely tested for

    a. [^{15}O]carbon monoxide.
    b. Rubidium Rb 82 Injection.
    c. [^{11}C]acetate.
    d. Fludeoxyglucose F 18 Injection, USP.

23. Which of the following QC tests are not done on a pre-release basis with PET tracers?

    a. Radiochemical purity
    b. Apyrogenicity
    c. Sterility
    d. pH

24. Radiopharmaceuticals for research PET are regulated by

    a. Radioactive Drug Research Committees (RDRC).
    b. Nuclear Regulatory Commission (NRC).
    c. Department of Energy (DOE).
    d. National Institutes of Health (NIH).

25. Which of the following drugs is not tested for radiochemical purity by the analytical method noted?

    a. [^{15}O]carbon monoxide : GC
    b. Ammonia N 13 Injection, USP : HPLC
    c. [^{68}Ga]gallium citrate : HPLC
    d. Fludeoxyglucose F 18 Injection, USP : TLC