BRIEFING

⟨823⟩ Radiopharmaceuticals for Positron Emission Tomography—Compounding, *USP 32* page 365. Since the original publication of this chapter, technological, marketplace, and regulatory changes have necessitated revision. This general chapter is being revised in its entirety to represent current compendial thinking about the preparation of positron emission tomography (PET) drugs as well as the recent announcement by the Food and Drug Administration (FDA) recognizing the standards in ⟨823⟩ in *USP 32* as an alternative standard for current good manufacturing practice (CGMP) for investigational and research PET drugs. The proposed revision incorporates the concepts and rationale outlined in a *Stimuli* article, ''Revision of *USP* General Chapter *Radiopharmaceuticals for Positron Emission Tomography—Compounding* ⟨823⟩'' in this issue of *Pharmacopeial Forum*.

This revised general chapter provides a framework for the preparation of PET drugs for human administration as required according to (1) state-regulated practice of medicine and compounding pharmacy, (2) an approved investigational new drug (IND) application (see 21 CFR 312), and (3) research uses with the approval of a Radioactive Drug Research Committee (RDRC; see 21 CFR 361.1).

The primary goal of the revision is to provide more flexibility in the production of PET drugs for investigational and research uses. Appropriate provisions have been proposed in the revised ⟨823⟩ to ensure drug identity, strength, quality, purity, and patient safety are not compromised.

It is proposed to revise the current title *Radiopharmaceuticals for Positron Emission Tomography—Compounding* to *Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses*. The proposed revision is organized into twelve sections that mirror the final PET CGMP rule and guidance issued by the FDA. The revision of this general chapter will be supplemented by a future informational general chapter that will provide additional descriptions of certain concepts, technologies, and procedures related to PET drugs. The changes will serve the needs of patients, research subjects, medical institutions, clinical researchers, pharmaceutical companies, commercial PET drug producers, and all members of the PET community.

(GC PA: R. Ravichandran) RTS—C88390

Change to read:

⟨823⟩ ~~RADIOPHARMACEUTICALS FOR POSITRON EMISSION TOMOGRAPHY—COMPOUNDING~~

▲POSITRON EMISSION TOMOGRAPHY DRUGS FOR COMPOUNDING, INVESTIGATIONAL, AND RESEARCH USES▲*USP35*

Change to read:

~~Physicians frequently prescribe special formulations of noncommercially available drugs for patient care. Upon receipt of a prescription for such a preparation, pharmacists (or other qualified individuals working under the authority and supervision of a physician) compound the drug formulation and dispense it to the patient. For convenience, a limited bulk quantity of the special formulation may be compounded in anticipation of future dispensing requirements. Such medical and pharmacy practices are regulated by state boards of medicine and pharmacy. Physicians who prescribe a drug that must be compounded extemporaneously bear the professional responsibility to base its use on sound scientific and medical evidence. Pharmacists and physicians who compound (or oversee the compounding of) drug preparations on prescription orders, bear the professional responsibility to ensure that the preparation meets prescribed and appropriate standards of strength, quality, and purity.~~

~~Radiopharmaceuticals administered for positron emission tomography (PET) procedures typically incorporate radionuclides that possess very short physical half-lives, *T*~~ (e.g., ~~*T* of ^{18}F = 109.7 minutes, of ^{11}C = 20.4 minutes, of ^{13}N = 9.96 minutes, and of ^{15}O = 2.03 minutes~~). ~~As a result, these radionuclides are usually produced using particle acceleration techniques (e.g., cyclotron) at or within close proximity to the site where the PET procedure will be conducted. The radionuclides may then be synthetically incorporated into the final PET radiopharmaceutical for subsequent patient administration.~~

~~The following requirements address the compounding of PET radiopharmaceuticals for human use (see also *Automated Radiochemical Synthesis Apparatus* ⟨1015⟩).~~

~~Control of Components, Materials, and Supplies~~

~~The following activities are to be established and performed. A designated person shall be responsible for ensuring that these activities are carried out and completed properly.~~

~~(1) Establish written specifications for~~

- ~~the identity, purity, and quality of components (including ingredients, reagents, target solutions, and gases); the identity and quality of containers and closures, and other materials (e.g., transfer lines, purification devices, membrane filters) that come into contact with the final PET radiopharmaceutical; and the identity, purity, and quality of analytical supplies (e.g., solvents, chromatography columns, and reference materials), sterility test media, endotoxin test reagents, and other supplies intended for use in PET radiopharmaceutical quality control procedures; and~~
- ~~the appropriate storage (i.e., based on heat, light, and humidity considerations) of components, containers and closures, materials and supplies used for the compounding of PET radiopharmaceuticals.~~

~~(2) Log in each lot of shipments of components, containers and closures, materials, and supplies used for the compounding of PET radiopharmaceuticals, and record the date of receipt, quantity received, manufacturer, lot number, and expiration date. If no expiration date is designated by the manufacturer, an expiration date is to be assigned to the component, material, or supply based on knowledge of its physical and chemical properties and prior experience with its use. For organic substrates, reactants, and reagent materials that are potentially susceptible to degradation or to a change in composition, the expiration date is based on the component's documented evidence of stability.~~

~~(3) Determine that each batch of components, containers and closures, materials, and supplies used for the compounding of PET radiopharmaceuticals are in compliance with established written specifications. A reliable manufacturer is routinely used as the source of a given product. Certification of compliance with the specifications for containers, closures, and materials marketed commercially for the intended purpose(s) may be ac-~~

complished by inspection of the product labeling and/or inspection of the certificate of analysis provided by the manufacturer. Certification of compliance with the specifications for other components and materials used in the compounding of PET radiopharmaceuticals may be accomplished by inspection of the certificate of analysis provided by the manufacturer. The identities of each lot of components, containers and closures, and materials used in the compounding of PET radiopharmaceuticals are to be verified by defined procedures, tests, and/or documented certificates of analysis, as appropriate.

(4) Store components, containers and closures, materials, and supplies used for the compounding of PET radiopharmaceuticals in a controlled access area according to established storage conditions.

Compounding Procedure Verification

The following activities are to be established or performed. A designated, qualified, and trained person shall be responsible for ensuring that these activities are carried out and properly completed by qualified and trained personnel.

(1) Written acceptance criteria for the identity, purity, and quality of each PET radiopharmaceutical being compounded. If a USP monograph exists for a particular PET, then these standards are the minimum acceptance criteria (see *Official and Official Articles* under the *General Notices and Requirements*).

(2) Written and verified procedures for the compounding of each PET radiopharmaceutical that

- incorporate, for each PET radiopharmaceutical intended for parenteral administration, sterile membrane filtration (0.22 μm);
- incorporate, for each PET radiopharmaceutical intended for inhalation, particulate filtration (0.45 μm); and
- are routinely updated and verified as changes in the compounding procedures are implemented or are reviewed and verified at a minimum of once a year to ensure that they are current. A master file of written compounding procedures currently used for each PET radiopharmaceutical is to be maintained within the PET facility. Copies of outdated compounding procedures shall also be retained, separate from the master file, for review purposes.

(3) Appropriate controls over computer and related automated equipment to ensure that changes in compounding software are instituted only by authorized personnel, that such changes are documented and verified, and that only current versions of the software are available and used in PET radiopharmaceutical compounding procedures. A diskette copy and printout of current computer software programs used in the compounding of each PET radiopharmaceutical is to be maintained within a master file located in the PET facility. Copies of outdated computer software programs shall also be retained, separate from the master file, for review purposes.

(4) Verification studies to ensure that the written compounding procedures, computer software program, equipment, and facilities result in a PET radiopharmaceutical that meets established acceptance criteria. Such verification studies must

- include documented evaluations of the radiochemical identity and purity, radionuclidic identity and purity, specific activity, sterility (for parenteral agents), bacterial endotoxins (for parenteral agents), pH, osmolality (for parenteral agents), if appropriate, appearance, stereochemical purity (for applicable compounds), potential organic volatile impurities, other toxic chemicals that may have been used during the synthesis or purification procedure, effective concentration of a stabilizer (if any), chemical purity of the PET radiopharmaceutical [NOTE—Evaluations for chemical purity must include analyses for the presence of starting materials, known intermediates, by-products, and known degradation products], and equivalency of initial and final sub-batches (for PET radiopharmaceuticals with radionuclides having a $T_{\frac{1}{2}} < 20.0$ minutes). For purposes of this chapter, "sub-batch" is defined as a quantity of PET drug product having uniform character and quality, within specified limits, that is produced during one succession of multiple irradiations, using a given synthesis and/or purification operation; and
- be signed, and dated, and retained as an indication that the compounding procedures, equipment, and facilities have resulted in a PET radiopharmaceutical that meets established acceptance criteria.

Whenever there is a change in the compounding procedures, computer software program, or component specifications that has the potential to alter the identity, quality, or purity of the drug product, verification procedures and studies must be conducted. Verification studies on a minimum of three consecutive batches, which show that the product meets acceptance criteria, are to be performed prior to the approval, for human use, of new or revised compounding procedures for a given PET radiopharmaceutical. For routine verified processes that are being used with consistent success, a minimum of one verification study that shows the product meets acceptance criteria must be conducted on an annual basis.

Stability Testing and Expiration Dating

Written specifications for the expiration dating and storage conditions of each PET radiopharmaceutical are to be established based on the results of stability testing and specific activity considerations. The stability test specimen must be taken from the product stored in the container and closure system specified for storing the product. The PET radiopharmaceutical must meet all acceptance criteria at expiry. Whenever there is a change in the compounding procedures, computer software program, or component specifications that has the potential to affect the stability of the drug product, stability testing must be conducted.

PET Radiopharmaceutical Compounding for Human Use

The following are to be performed according to established written procedures and documented. A designated, qualified, and trained person shall be responsible for ensuring that these activities are carried out and completed properly by qualified and trained personnel.

(1) Inspect the compounding and dispensing area and all equipment for cleanliness and suitability immediately before use. Before initiating compounding and dispensing activities, extraneous materials and labels must be removed from involved areas and equipment. For PET radiopharmaceuticals intended for parenteral administration, all manipulations of components, containers and closures, and materials distal to sterile membrane filtration must be performed using an appropriate aseptic technique in an appropriately controlled environment.

(2) Ensure the correct identity, quantity, and suitability of components, containers and closures, and other materials used in compounding the PET radiopharmaceutical.

(3) Label all subdivided components used in the compounding procedure for identity and traceability.

(4) Label the final PET radiopharmaceutical container or dispensing administration assembly prior to initiating the compounding procedure. The following information must appear on the label or labeling attached to the final container or dispensing administration assembly: the identity of the PET radiopharmaceutical, and added substances (e.g., stabilizers and preservatives), an assigned batch or lot number, and the required warning (e.g., radioactive) statements or symbols. The final PET radiopharmaceutical shall also be labeled to include the total radioactivity and radioactive concentration at the stated time of calibration, the expiration time and date, and any required or applicable warning statements (e.g., "Caution Radioactive Material", "Do not use if cloudy or contains particulate matter") and/or the radioactivity symbol.

(5) Compound the PET radiopharmaceutical according to current, verified procedures. A written record must be maintained for each batch (i.e., the material produced during a single synthesis and purification) of the compounded PET radiopharmaceutical. This written record includes

- lot numbers, manufacturer identities, expiration dates, and quantities of all components, containers and closures, and materials used in the compounding procedure;
- a description of the individual compounding procedures to be followed;
- the initials of the responsible individual indicating that the compounding procedure for the batch is an accurate reproduction of the current, verified compounding procedure;
- the initials of the responsible individual indicating that critical steps and processes in the compounding procedure were completed [NOTE—Critical steps in automated compounding processes shall be monitored through direct observation (if possible, considering visual or radiation exposure constraints) or via computer or other feedback mechanisms];
- documentation of the investigation of any unplanned deviations in, or unexpected results of, verified compounding procedures or processes, including documentation of the outcome of the investigation;
- the percent yield calculated on the basis of the known or expected decay-corrected amount of the starting radionuclide that is synthetically incorporated into the final radiopharmaceutical;
- raw analytical data on each batch of compounded PET radiopharmaceutical; and
- the date and the signature of the individual assuming overall responsibility for, and adherence to, the verified compounding procedure.

Quality Control

The following are to be performed according to established, written procedures and documented. A designated, qualified, and trained person shall be responsible for ensuring that these activities are carried out and completed properly by qualified and trained personnel.

(1) Establish, in writing, the quality control tests to be performed on individual batches of the PET radiopharmaceutical, the analytical procedures, and the corresponding acceptance criteria.

- For PET radiopharmaceuticals labeled with a nuclide having a $T_{\frac{1}{2}} \geq 20.0$ minutes, the following quality control procedures are to be performed on each batch (i.e., the material produced during a single synthesis and purification operation) prior to release: measurement of the pH of parenteral and oral dosage forms; visual inspection of parenteral and oral dosage forms; determination of the radiochemical purity and identity of all dosage forms; determination of the radionuclidic identity of all dosage forms; and assessment of the specific activity of PET radiopharmaceuticals with mass-dependent localization or toxicity concerns; and evidence of compliance with the established acceptance criteria for residual solvents and other toxic chemicals used during the synthesis or purification procedures.
- For PET radiopharmaceuticals labeled with a nuclide having a $T_{\frac{1}{2}} < 20.0$ minutes, a batch is defined as all related sub-batches of the PET radiopharmaceutical compounded during a given day. The following quality control procedures are to be performed on an initial quality control sub-batch of each such PET radiopharmaceutical prior to release for human use of subsequent sub-batches: measurement of the pH of parenteral and oral dosage forms; visual inspection of parenteral and oral dosage forms; determination of the radiochemical purity and identity of all dosage forms; determination of radionuclidic identity of all dosage forms; and assessment of the specific activity of PET radiopharmaceuticals with mass-dependent localization or toxicity concerns; and evidence of compliance with the established acceptance criteria for residual solvents and other toxic chemicals used or produced during the synthesis or purification procedures.
- For each batch of PET radiopharmaceutical intended for parenteral administration, perform a membrane filter integrity test immediately after completion of product filtration. This post filtration integrity test is to be completed prior to release of the batch for human use, except in the case of ^{15}O water, where it may be necessary to release the batch prior to completion of the post filtration integrity test. In this case, the test is completed as soon as possible after release of the batch.
- For PET radiopharmaceuticals intended for parenteral administration, perform an in-process 20-minute endotoxin "limit test" (i.e., incorporating positive controls in the range of 5 EU per mL to 175 EU/*V*, where *V* is the maximum volume of injection) on each batch ($T_{\frac{1}{2}} \geq 20.0$ minutes) or quality control sub-batch ($T_{\frac{1}{2}} < 20.0$ minutes) of the radiopharmaceutical prior to release, for human use, of the batch or subsequent sub-batches.
- For PET radiopharmaceuticals intended for parenteral administration, a standard 60-minute bacterial endotoxin test must be performed on each batch ($T_{\frac{1}{2}} \geq 20.0$ minutes) or quality control sub-batch ($T_{\frac{1}{2}} < 20.0$ minutes) of the radiopharmaceutical. Endotoxin testing may also be performed using other recognized procedures (see *Bacterial Endotoxins Test* ⟨85⟩). Regardless of which test is utilized, an assessment of the bacterial endotoxins should be performed prior to release of each batch ($T_{\frac{1}{2}} \geq 20.0$ minutes) or quality control sub-batch ($T_{\frac{1}{2}} < 20.0$ minutes) of the radiopharmaceutical before release for human use of the batch or subsequent sub-batches.
- Sterility tests for each PET radiopharmaceutical intended for parenteral administration are performed on each batch ($T_{\frac{1}{2}} \geq 20.0$ minutes) or quality control sub-batch ($T_{\frac{1}{2}} < 20.0$ minutes). Sterility tests are also performed following the replacement of system components. Sterility tests are initiated within 24 hours of sterile filtration. Product samples are tested individually and are not pooled.

(2) Establish written procedures for the performance of quality control tests on batches of PET radiopharmaceuticals intended for human use.

(3) Conduct verification testing of equipment and procedures used for the quality control testing of PET radiopharmaceuticals. Using internal or external standards, the correct operation of analytical equipment, such as gas chromatography or high-performance liquid chromatography (see *System Suitability* under *Chromatography* ⟨621⟩) must be confirmed upon initial installation or upon major repair. Correct operation of analytical equipment must also be checked (i.e., a system suitability test must be performed) on a scheduled basis, and maintenance must be performed according to appropriate, written, scheduled procedures. Dose calibrators used in measuring the bulk radioactivity and the radioactivity of dispensed dosages of PET radiopharmaceuticals should be tested in accordance with applicable state regulations governing the medical use of radioactive materials.

(4) Perform quality control tests on batches of PET radiopharmaceuticals according to written procedures, and initial the results of such testing.

(5) Accept or reject the individual batch of the PET radiopharmaceutical based on the conformity of quality control test results with established acceptance criteria. If the individual batch of the PET radiopharmaceutical is acceptable, sign and date the batch.

(6) Investigate unacceptable quality control test results and document the outcome of such investigations.

Sterilization and Sterility Assurance

A complete system of process controls is required to assure sterility of PET radiopharmaceuticals. Sterilization activities for the following elements of the process are to be established, documented, and performed.

Compounding Equipment and Components— Equipment used to prepare PET radiopharmaceuticals must be properly cleaned and kept in sanitary condition. Equipment in contact with a PET drug solution may be processed to remove endotoxin and may be sterilized to eliminate bioburden. Prepared equipment is stored and protected to maintain cleanliness and, if necessary, sterility. It is recommended that components for PET products be obtained from qualified suppliers after verifying that the components meet specifications for sterile drug products. It is further recommended that sterile vials, syringes, transfer sets, and filters be obtained from commercial sources. If components are sterilized by the PET facility, the sterilization processes and asepsis of assembly components must be verified. Verification of sterilizer performance must be repeated periodically. Solutions for parenteral administration must be filter sterilized and aseptically transferred to a sterile, nonpyrogenic, multiple-dose vial. Certain finished dosage forms of PET products may not be transferred to a vial and require special consideration.

Environmental Controls— The work area used for compounding the finished dosage form must be clean. The aseptic hood is protected from sources of microbial contamination and is located in an area where surrounding personnel traffic is controlled and limited. Appropriate clean laboratory clothing shall be worn when performing functions in the aseptic hood. Components, materials, and equipment are transferred to the aseptic area in protective wrapping or containers. Aseptic techniques are used whenever a sterile solution dosage form is handled. The containers, filter assembly, vent filters, and needles for the final dosage form must be sterile, disposable, and for single use only. After the filter and the product container are assembled, the sterility of this assembly must be preserved. If the sterility of any component is compromised, the component or set must be replaced. Before penetrating the finished product container, the septum of the product vial must be thoroughly swabbed with a disinfectant solution (i.e., freshly filtered or certified sterile 70% alcohol) and allowed to air dry in the aseptic hood.

Aseptic Hood— Assemble the product filter and the container and closure system for the finished product in an aseptic hood. Sterile (aseptic) operations should be conducted within an aseptic workstation with an air cleanliness rating of class 100 (e.g., Laminar flow hood or isolator). The aseptic hood surfaces and equipment surfaces allow easy cleaning and disinfecting. Disinfectants are filtered or certified sterile with a manufacturer's certificate of analysis, and the hood's internal surfaces are cleaned and disinfected daily before use and after new equipment is brought in. Microbiological testing of the aseptic hood is performed periodically (e.g., weekly). This may be done by swab or contact plate for surfaces and settle plate or dynamic air sampler. Airborne, nonviable particle counting may be performed less frequently.

Aseptic Technique— All aseptic operations, including the assembly of sterile components, compounding, filtration, and manipulations of sterile solutions must be performed by operators qualified to work with aseptic techniques. Aseptic manipulations shall be performed using sterile items sealed in protective covering and opened within the aseptic hood. Any sterile equipment or component that is compromised by contact with a nonsterile surface must be replaced. Sterile components shall be transferred from the hood with closures in place. Aseptic operations are performed by operators wearing laboratory clothing appropriate for pharmaceutical compounding. Gloved hands are disinfected immediately before reaching into the aseptic hood.

Aseptic area operators are trained and evaluated periodically through observation as well as through microbiological tests. Aseptic techniques used to make sterile products are evaluated by simulations, in which a microbiological growth medium is substituted for the PET radiopharmaceutical solution. Process simulations include manipulations such as connecting vents and filtration. Verification of the medium's growth-promotion capability in the PET drug container is an essential control for process simulations. After completing the simulation process, the final product container is gently shaken to permit the medium to contact all surfaces, and the container and the medium are incubated (at 30° to 35°, 20° to 25°, or another suitable temperature) for 14 days with periodic examination for evidence of growth: the absence of growth in the containers is necessary for an acceptable test result. Simulations are performed in triplicate to qualify a new operator. Each operator repeats one simulation about once a year or any time procedures are changed.

Qualification of the Filtration Process— Sterilizing filtration is the final safeguard in removing microorganisms from solutions of PET radiopharmaceuticals. This critical procedure requires that microbial retention by membrane filters be demonstrated under specified conditions. Filters must not release particles or soluble compounds, bind product ingredients, or lose integrity during use. When the filters are prepared and sterilized by a commercial filter manufacturer, the filter manufacturer generally provides filtration conditions (i.e., pressure and flow rate); these conditions are not to be exceeded when preparing a PET drug product. For most aqueous solutions of near neutral pH, certification regarding microbial retention challenges to the selected filter may be obtained from the filter manufacturer. Certification of conformance to specifications must be examined and maintained for each filter lot.

Before using filters from a particular lot, a sample is tested for integrity to demonstrate that the membrane and housing have not lost the ability to retain microorganisms. The manufacturer's recommended method or an alternative method, if demonstrated to be acceptable, may be used.

The sterilizing membrane filter must also be tested for integrity after filtering the compounded PET radiopharmaceutical but before the product is released. An example of a simple test is the "Bubble Point" test, which uses a pressure gauge and a source of air pressure connected to the transfer set attached to the filter. The filter disk is placed in a beaker of water with the filter outlet below the water surface, and air pressure is applied gently to the nonsterile side of the filter assembly. The air pressure is increased until the validated bubble point is reached, at which point the pressure is maintained briefly to allow equilibration. Filter integrity is demonstrated to be acceptable in the absence of a steady stream of bubbles.

Microbiological Testing of Finished Products— PET radiopharmaceuticals for parenteral administration must be sterile and free of endotoxins, as demonstrated by sterility and endotoxin tests. Endotoxin tests are initiated promptly after compounding, and sterility tests are started no later than 24 hours after compounding. Each lot shall be assayed individually and not pooled with other lots. If a microbiological test fails, an investigation shall be undertaken to identify the cause, and corrections shall be undertaken. After a record of successful sterility tests is established for a particular PET drug, only the first lot prepared each day shall be subject to a sterility test using cultivation methods. However, when a different PET drug is made at the facility or a new lot of sterile components (for example, filter or final product container) is substituted, then the first daily lot of that PET drug is tested for sterility.

▲INTRODUCTION

Radionuclides used in positron emission tomography (PET) typically possess short physical half-lives, $T_{1/2}$ (e.g., $T_{1/2}$ of ^{18}F = 109.8 min, ^{68}Ga = 67.7 min, ^{11}C = 20.4 min, ^{13}N = 9.96 min, and ^{15}O = 2.03 min). As a result, these radionuclides usually are produced using particle acceleration techniques (e.g., cyclotrons) or from

generators, and then are processed into the final PET drug in close proximity to the site where the PET procedure will be conducted.

The short half-lives of PET radionuclides create unique constraints for the preparation and testing of PET drugs. This chapter describes guidelines for making and testing PET drugs based on the following constraints:

- It is not possible to complete all testing before the use of PET drugs.
- An entire batch or sub-batch of a PET drug may be contained in a single vial. Samples withdrawn for quality control (QC) testing are representative of the entire batch or sub-batch.
- An entire batch or sub-batch may be administered to a single patient.
- The mass of the active pharmaceutical ingredient in a PET drug usually ranges from nanogram to microgram quantities.
- PET drugs do not enter a traditional drug distribution chain. Instead, PET drugs are used in-house or are delivered to the point of use by dedicated couriers.
- Small-scale PET facilities have limited personnel and resources, which require:
  - Allowance for multiple operations in one area with adequate controls;
  - Allowance for the making and testing of multiple PET drugs using shared equipment;
  - Appropriate requirements for aseptic operations;
  - Appropriate requirements for system suitability and other day-of-use activities;
  - QC requirements for components, materials, and supplies;
  - Self-verification of significant steps in radionuclide production, PET drug production, or compounding and testing; and
  - Single-person oversight of production and compounding, review of batch records, and release authorization.

The scope of this chapter includes the production and compounding of PET drugs for human administration as used (a) according to state-regulated practice of medicine and pharmacy, (b) according to an approved investigational new drug (IND) application (see 21 CFR 312), and (c) according to research uses under the supervision of a Radioactive Drug Research Committee (RDRC; see 21 CFR 361). The scope of this chapter does not include dispensing activities as defined in other USP general chapters.

DEFINITIONS

The following definitions apply to words and phrases as they are used in this chapter:

Active Pharmaceutical Ingredient—a substance that is incorporated into a finished PET drug and is intended to furnish direct effect in the diagnosis or monitoring of a disease or a manifestation of a disease in humans, or treatment of disease for therapeutic procedures (e.g., tumor therapy).

Batch—a quantity of PET drug that is intended to have uniform character and quality, within specified limits, and that is made in a single operational cycle.

Conditional Final Release—a final release for patient administration before completion of required tests because of a malfunction of analytical equipment.

Lot—a quantity of materials (e.g., reagents, solvents, gases, purification columns, and other auxiliary materials) that have uniform character and quality within specified limits and are used to make a PET drug.

PET Drug—a finished form of a radioactive drug that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is intended for human administration in diagnosis or therapy.

PET Drug Product—a finished dosage form that contains a PET drug.

Compounding—the process of synthesis or formulation of a PET drug for use under the practice of pharmacy and medicine.

Production—the process of synthesis or formulation of a PET drug for investigational or research uses.

Quality Assurance (QA)—a planned and systematic program to ensure that a PET drug possesses defined identity, strength, quality, and purity required for its intended purpose.

Quality Control (QC)—a system for testing the quality of components, materials, supplies, and PET drugs by procedures, tests, analytical methods, and acceptance criteria.

Specific Activity—the radioactivity of a radionuclide per unit mass of the element or compound. The unit of specific activity is radioactivity per mass expressed on a gram or mole basis (e.g., mCi/μg [MBq/μg], Ci/mmol [GBq/mmol]).

Strength—the radioactivity concentration of the active pharmaceutical ingredient on a volume basis at the time of calibration. The unit of strength is the amount of radioactivity per volume at the time of calibration (e.g., mCi/mL [MBq/mL]).

Sub-batch—a quantity of PET drug having uniform character and quality, within specified limits, that is produced during one succession of multiple irradiations using a given synthesis or purification operation. A group of sub-batches collectively form a batch that is intended to have uniform character and quality, within specified limits. Sub-batches are required for PET drugs with very short-lived radionuclides (e.g., ^{13}N and ^{15}O) because QC tests cannot be completed before use.

Validation—establishment of documented evidence that a method, process, or system meets its intended requirements.

Verification—confirmation that an established method, process, or system meets predetermined acceptance criteria.

ADEQUATE PERSONNEL AND RESOURCES

Sufficient numbers of personnel with the appropriate education, training, and experience are needed for the preparation and testing of PET drugs. The number depends on the size and complexity of the operations executed at each facility.

Personnel should be trained before they begin to make and test PET drugs. Training can be performed by various methods, including live instruction, audio-video instruction, and study of publications. Personnel should pass written assessments.

Personnel Requirements—Training should address but is not limited to radionuclide production techniques, synthetic and purification methods, materials, components, reagents, stock solutions, automated and manual apparatus used to make PET drugs, and QC methods, including equipment, software, and documentation.

Personnel Requirements for Aseptic Operations—Training should address aseptic manipulations as well as the techniques and equipment used to achieve and maintain International Organization for Standardization (ISO) Class 5 environmental conditions. Training also should address all aseptic operations, including the assembly of sterile components, compounding, and filtration. Manipulations of sterile solutions should be performed by operators who are qualified to use aseptic techniques (see *Facilities and Equipment*, below).

Personnel involved in aseptic operations should be evaluated periodically by observation and microbiological tests (media simulations) in which a microbiological growth medium is substituted for the PET drug. Media simulations should include all manipulations required for the assembly of the PET drug vial. Simulations should be representative of worst-case scenarios for aseptic op-

erations. Media fill simulations should be performed in triplicate to qualify a new operator. Each operator should be reviewed annually to determine the need for a repeat annual simulation test. Simulations also should be performed any time procedures are changed significantly. After the simulation process, the media should show the absence of contamination after incubation at a suitable temperature for 14 days. An operator who fails written assessments or whose media simulations result in microbial growth should be immediately re-instructed and re-evaluated to ensure correction of aseptic practice deficiencies.

QUALITY ASSURANCE

QA and QC are important elements in the process of making PET drugs. QA is a broad concept that covers all matters that influence identity, strength, quality, and purity of a PET drug. QC is a subset of QA that deals with testing of materials and PET drugs to determine if they meet acceptance criteria. The QA function typically consists of oversight activities, and the QC function consists of execution activities.

QC functions include the following:

- Evaluate each lot of incoming material to ensure that it meets its established specifications before use in the preparation or testing of PET drugs.
- Evaluate each batch of a PET drug to ensure the batch meets its established specifications before authorizing the final release or rejection of the batch.

The oversight functions associated with QA include the following:

- Review completed batch records for accuracy and completeness.
- Validate and approve procedures, specifications, processes, and methods.
- Ensure that personnel are properly trained and qualified, as appropriate.
- Ensure that PET drugs have adequately defined identity, strength, quality, and purity.
- Investigate errors and ensure that appropriate corrective action is taken to prevent their recurrence.
- Handle complaints.
- Ensure that the PET drugs are distributed according to the established procedures and practices for PET drugs.
- Conduct periodic audits to monitor compliance with established procedures and practices for PET drugs.

Personnel at the facility may perform both QA and QC functions.

FACILITIES AND EQUIPMENT

Facilities should be adequate for the production, compounding, and testing of PET drugs. Work areas should be organized to prevent cross-contamination, mix-ups, and errors, especially in areas used for making multiple PET drugs. Work areas should be periodically cleaned to prevent the contamination of equipment, materials, components, or PET drugs by personnel or environmental conditions that could reasonably be expected to adversely affect PET drug quality. These requirements should be described in written procedures, and their routine execution should be documented.

Environmental Controls for Parenteral PET Drugs—Because the sterility test results for parenteral PET drugs are obtained after release, facilities and equipment should ensure a sterile PET drug.

Aseptic Workstation—The primary environmental control for aseptic operations is a high-efficiency particulate air (HEPA) filter that is capable of producing air with a cleanliness rating of ISO Class 5. This can be achieved with a laminar airflow workstation, aseptic isolator, biological safety cabinet, or other suitable device (generically, aseptic workstations). The aseptic workstation should be protected from sources of microbial contamination and

should be located in an area where personnel traffic is limited. The area around the aseptic workstation should not be used for storage of materials that shed large quantities of particulate matter (e.g., corrugated boxes).

The proper operation of the aseptic workstation must be certified by measurement of airborne particles, HEPA filter integrity testing, pressure differential testing, or other means. The specific tests depend on the type of aseptic workstation. Certification should be performed at the inception of operation and at least annually thereafter or after repair or replacement of the HEPA filter.

The work area inside the aseptic workstation should be clean. The internal surfaces should allow easy cleaning and disinfection. The internal surfaces should be cleaned and disinfected with appropriate disinfectants that are sterile filtered or certified sterile with a manufacturer's certificate of analysis (COA).

Microbiological Testing—Microbiological testing of the environment should be performed to assess air quality and surface disinfection. This can be achieved by either settling plates or active air-sampling plates. Surface disinfection of critical surfaces (e.g., the work surface of the aseptic workstation or operators' fingers) should be assessed with swab or contact plates. Microbiological testing of the aseptic workstation should be performed periodically (e.g., weekly). Nonviable particle counts may be determined less frequently following certification of the aseptic workstation (see above).

Alert and action limits should be established for samples obtained during microbiological testing. Typical alert levels are set at less than three colony-forming units (CFU) per plate. More than three CFU require corrective actions that may include operator retraining, recertification of the aseptic workstation, or other actions. The results of microbiological testing also should be used in the investigation of positive sterility tests.

Equipment—Equipment used to make and test PET drugs should be appropriate for its intended purpose and should be installed, cleaned, and maintained in an appropriate manner. Equipment should be capable of producing consistent results.

The following requirements should be described in written procedures, and performance of these procedures should be documented:

1. *Installation of New Equipment*—Newly installed equipment should be qualified before it is used to make or test PET drugs. All qualification activities should be properly documented, including the date and the name of the person who performed the qualification. Qualification consists of three phases:
   - Installation Qualification (IQ)—IQ is a check of items required for proper installation of the equipment, including physical location, required utilities and supplies, communications, and environmental conditions. IQ should describe the installation procedure for the equipment.
   - Operational Qualification (OQ)—OQ is a check of operational specifications for the equipment, including equipment set-up, functional testing of subsystems, and proper overall operation. OQ should describe operational procedures for the equipment.
   - Performance Qualification (PQ)—PQ demonstrates that the equipment is capable of performing tasks required to make and test PET drugs in the operating environment and that the equipment provides the intended results. PQ should describe the required performance tasks for the equipment.
2. *Calibration of Equipment*—As necessary, equipment calibration should be performed before use. A schedule should be developed for the recalibration and should have a sufficient frequency to ensure accurate

results. Calibration activities should be properly documented, including the date and the name of the person who performed the calibration.

3. *Preventive Maintenance of Equipment*—A preventive maintenance schedule should be developed for major production and testing equipment, including automated chemistry modules, gas chromatographs, high-performance liquid chromatographs, and others. The schedule should have a sufficient frequency to minimize equipment downtime. Major repairs may require recalibration and requalification. Preventative maintenance activities should be properly documented, including the date of such performance and the name of the person who performed them.

Cleaning Equipment and Components—Equipment used in production or compounding of PET drugs includes automated, computer-controlled devices, as well as manually operated apparatus. Before it is used in making PET drugs, equipment should be properly cleaned to ensure that the resulting PET drug meets established specifications for identity, strength, quality, and purity (see *Controls and Acceptance Criteria for Finished PET Drugs*, below). Once cleaned, equipment should be maintained in a state of cleanliness before use.

Equipment may be used to make multiple batches of one or more PET drugs. Documented studies should demonstrate the effectiveness of the cleaning process between batches. All impurities should be controlled at levels that conform to established specifications for identity, strength, quality, and purity.

Day-of-Use Checks—Day-of-use checks are necessary for processing equipment to ensure proper function. Written procedures for the day-of-use checks should be established and followed. These procedures should be designed to check key parameters at the beginning of each operational cycle (e.g., temperature, pressure integrity, gas supply, vacuum supply, proper delivery line selection, reagent delivery volumes, gas flow rates, radiation monitors, and other process sensors). Some parameters may be periodically checked as part of the calibration and preventive maintenance schedules as described above.

System Suitability for QC Equipment—System suitability tests are necessary for QC equipment to ensure that the equipment, components, and personnel (i.e., the system) function as a whole to execute the desired analytical method. System suitability tests should be performed according to a predetermined schedule before the testing of a different PET drug. Written procedures should be established and followed for system suitability tests, and the test results should be documented.

The system suitability tests required for chromatographic methods include tailing factor, replicate injections, and resolution. When the test chromatogram used for system suitability contains only a single peak, then tailing factor, replicate injections, and column efficiency (theoretical plates) are adequate. The use of internal or external standards with known concentration is necessary for these determinations. Standards should be prepared from well-characterized materials or from materials that have a manufacturer's COA. Two acceptable approaches that may be used for chromatographic methods are:

1. Create a calibration curve from a range of standards with known concentrations. The concentrations of the standards should bracket the conditions of use for the chromatographic method. Use the calibration curve over an extended period of time (e.g., six months). Routine system suitability for replicate injections consists of a single injection of a known standard and a measurement of the concentration based on the calibration curve. If the measured concentration agrees with the known concentration within a predefined range (e.g., 10% for manual injections and 5% for automated injections), this dem-

onstrates the suitability of the system for replicate injections and ensures that the calibration curve is appropriate for use in subsequent sample injections. The tailing factor and resolution (or column efficiency, as appropriate) should be determined from the same chromatogram.

2. At the beginning of each testing cycle, create a single-point calibration from two injections of a known standard. The measured area of the peaks for these injections should agree within a predefined range (e.g., 10% for manual injections and 5% for automated injections). Then the results are averaged and used with the standard concentration to provide a calibration factor that is used in subsequent sample injections for that day. The tailing factor and resolution (or column efficiency as appropriate) should be determined from one of the two chromatograms.

Other chromatographic parameters such as signal-to-noise ratio, limit of detection (LOD), and limit of quantitation (LOQ) can be determined as part of routine system suitability testing.

System suitability tests also may be appropriate for other QC equipment, including dose calibrators, scanners for radio–thin layer chromatography (radio–TLC), and multichannel analyzers. When used, these tests should be performed at installation, relocation, and appropriate intervals thereafter. These tests should employ known standards to demonstrate the proper function of the equipment, for example:

1. *Dose Calibrator*—Accuracy, geometry, and linearity should be assessed at installation and at appropriate intervals thereafter. The instrument should be calibrated in accordance with nationally recognized standards or the manufacturer's instructions. Routine system suitability testing should include a constancy check with a suitable high-energy radionuclide source.
2. *Radio–TLC Scanner*—Uniformity, positional accuracy, detector linearity, and resolution should be assessed with a suitable radionuclide source. Routine system suitability testing should include checks for these parameters.
3. *Multichannel Analyzer*—Sensitivity and resolution should be assessed at installation and at appropriate intervals thereafter. Routine system suitability testing should include a constancy check with a suitable high-energy radionuclide source.

CONTROL OF COMPONENTS, MATERIALS, AND SUPPLIES

Components, materials, and supplies that are used in the preparation of PET drugs should be controlled to avoid contamination, mix-ups, and errors. A designated person should be responsible for ensuring that these activities are carried out and completed properly. Records of completed examinations and tests for components, materials, and supplies should be maintained for one year after their expiration or for one year after batch release, whichever is longer. The following activities should be established and performed:

1. Establish written specifications for the identity, strength, quality, and purity of ingredients, reagents, target materials, and gases.
2. Establish written specifications for the identity and quality of sterile empty vials, transfer lines, sterile stopcocks, sterile needles, sterile membrane filters, and other components used in the PET drug vial assembly.
3. Establish written specifications for the identity, strength, quality, and purity of analytical supplies (e.g., solvents, chromatography columns, and authentic standards), sterility test media, and endotoxin test reagents used in the testing of PET drugs.

4. Establish appropriate storage conditions (based on heat, light, humidity, and other factors) for components, materials, and supplies used to make and test PET drugs.
5. Store components, materials, and supplies in a controlled-access area according to established storage conditions. Segregate components, materials, and supplies as appropriate to avoid mix-ups and errors.
6. Log each lot of shipment of components, materials, and supplies, and record the date of receipt, quantity received, manufacturer, manufacturer's lot number, and expiration date. If no expiration date is designated by the manufacturer, assign one based on knowledge of its physical and chemical properties and previous experience with its use. For organic substrates and reagents that are potentially susceptible to degradation or to a change in composition, the expiration date should be based on the material's documented evidence of stability.
7. Determine that each lot of components, materials, and supplies complies with established written specifications. Compliance with specifications can be demonstrated by inspection of the labeling or inspection of the COA provided by the manufacturer. The identity of each lot of components, materials, and supplies should be verified by defined procedures, tests, or documented COAs, as appropriate. Perform an identity test for precursors (e.g., melting point determination or other appropriate tests). Alternatively, the COA can be used as the only acceptance criterion for a precursor if final testing of the PET drug ensures that the correct precursor has been used. Other components can be accepted on the basis of a COA only.
8. Membrane filters used with parenteral PET drugs should have a certificate of conformance (COC) from the manufacturer. Examine the COC for each lot to ensure compliance with written specifications.
9. Media used in the sterility testing of PET drugs should be commercially available. To ensure the viability of media, perform growth-promotion testing. A simplified growth-promotion test that employs a single organism is adequate to demonstrate the suitability of media. Alternatively, a positive control can be performed during the execution of each sterility test inoculation.

PROCESS AND OPERATIONAL CONTROLS

Process Controls—The following process controls should be established and summarized in a master formula for the PET drug. A designated person should be responsible for ensuring that these activities are carried out and completed properly.

1. Written acceptance criteria for the identity, strength, quality, and purity of each PET drug should be established. For PET drugs intended for parenteral administration, specifications should include sterility and bacterial endotoxins. If a *USP* monograph exists or there are QC specifications approved by FDA, then these standards should be applied as the minimum acceptance criteria.
2. Written procedures for the preparation of each PET drug should:
   - Incorporate, for each PET drug intended for parenteral administration, sterile membrane filtration (0.22 μm);
   - Incorporate, for each PET drug intended for inhalation, particulate filtration (0.45 μm);
   - Describe routine cleaning procedures for equipment and facilities;
   - Describe components, materials, and supplies used to make PET drugs, including precursors, standards, reagents, stock solutions, and related items;
   - Describe the process and the steps used to make the PET drug;

- Describe the formulation process, including the use of stabilizers, buffers, and other agents;
- Describe calculations used to determine key parameters associated with making and QC testing, including radiochemical yield, radiochemical purity, and so on;
- Describe QC tests for the final PET drug (see *Controls and Acceptance Criteria for Finished PET Drugs*, below), including a schedule that defines whether or not each test should be performed on each batch and that states if the test results should be complete at the time of release.

3. Documented studies should ensure that the processes and steps described in the master formula yield a PET drug that meets established acceptance criteria. Such studies should:
   - Demonstrate a consistent process that is suitable for the intended use of the PET drug.
   - Be completed on three batches made according to the master formula, and all three batches should meet all acceptance criteria.
   - Include evaluation of radiochemical identity and purity, radionuclidic identity and purity, specific activity, sterility (for parenteral PET drugs), bacterial endotoxins (for parenteral PET drugs), pH, appearance, stereochemical purity (for applicable compounds), residual solvents, other toxic chemicals that may have been used during the synthesis or purification procedure, effective concentration of a stabilizer (if any), chemical purity of the PET drug, and equivalence of initial and final sub-batches (see *Definitions*, above).
   - Be repeated if the process and steps described in the master formula have been altered in a way that could change the identity, strength, quality, or purity of the PET drug.
4. The processes and steps described in the master formula should be updated as needed and should be reviewed annually to ensure they are current.

Appropriate controls of computer-controlled equipment should ensure that process changes are instituted only by authorized personnel and that such changes are documented and verified. Production, compounding, and test methods should be backed up and controlled to avoid accidental use of outdated methods. In the case of processes or test methods from a vendor that are used without alteration, it is acceptable to rely on vendor certification for software verification and proper operation.

Operational Controls—The following operational controls should be established and summarized in a batch record that is a subset of the master formula for the PET drug. The batch record should adequately document the routine process for making the PET drug. A designated person should be responsible for ensuring that these activities are carried out and completed properly. Maintain completed batch records and associated documentation for one year after batch release.

1. Inspect areas used to make and test PET drugs, and inspect all equipment for cleanliness and suitability before use. Remove extraneous materials and labels from these areas and equipment.
2. Ensure the correct identity, strength, quality, and purity of components, materials, and supplies used in the preparation of the PET drug. Label components as appropriate for identity and traceability purposes.
3. Execute routine cleaning procedures for equipment and facilities.
4. Prepare the PET drug according to the current master formula, and for each batch maintain a batch record. Batch records may consist of paper documents, electronic records, or combinations thereof. Spreadsheets and other electronic record-

keeping tools should be verified to ensure traceability, data integrity, accuracy of results for calculations, and so on. The batch record should include:

- Lot numbers or other unique identifiers for all components, materials, and supplies used to make the PET drug product;
- A description of the individual procedures that were followed;
- The initials, signature, or other identifier of the responsible individual indicating that critical steps and processes used to make and test the PET drug were completed;
- The percent yield calculated on the basis of the known or expected amount of the starting radionuclide that is synthetically incorporated into the PET drug;
- Raw analytical data on each batch of the PET drug;
- Labeling for the PET drug (see *Labeling and Packaging*, below);
- Calculations for key parameters defined in the master formula;
- Results obtained from QC tests of the PET drug, including chromatograms, print-outs, and other test data;
- The initials of the analyst who performed each QC test;
- A notation of the result for each QC test and whether or not the result meets the acceptance criteria;
- The date and time of release and the signature of the individual who assumes overall responsibility for, and adherence to, the procedures used to make the batch and authorizes the release of the batch for human administration; and
- Documentation on the batch record of process deviations, when applicable.

Entries in batch records should be made immediately after the activity is performed and should include the initials, signature, or other identifier for the person making the entry. Corrections to paper entries should be dated and initialed, signed, or noted with an identifier of the person making the corrections but leaving the original entry still readable.

Aseptic Operations for Parenteral PET Drugs—Because the sterility test results for parenteral PET drugs are obtained after release for human administration, aseptic operations and procedures should adequately ensure a sterile PET drug. All aseptically prepared PET drugs for parenteral administration should be filtered through a sterile membrane filter of 0.22-μm or finer pore size into a closed sterile vial or container. Although the chemical synthesis of a parenteral PET drug may take place in an open or closed apparatus, the membrane filtration of the PET drug should take place in a closed apparatus that is aseptically assembled from presterilized, commercially available components.

Components—The sterile components used in the aseptically assembled apparatus typically consist of an empty vial, needles, membrane filters, vent needles, syringes, tubing, stopcocks, and perhaps others. All components should be single-use, commercially available, presterilized items. If components in the aseptically assembled apparatus are sterilized by the PET drug facility, the sterilization processes should be verified. The exact configuration of the PET drug vial assembly is process dependent. A typical example is a sterile, empty vial with a membrane filter of 0.22-μm pore size attached to a needle that is inserted through the vial septum for filtration, a membrane filter of 0.22-μm pore size attached to a needle that is inserted through the vial septum for venting the vial during filtration, and a syringe with needle inserted through the vial septum for removal of the QC sample after filtration is complete.

PET Drug Vial Assembly—Aseptic techniques should be used in the preparation of the PET drug vial assembly, especially the assembly of all components downstream from the membrane sterilizing filter. These operations should be performed in an ISO Class 5 environment (see *Facilities and Equipment*, above).

Following the creation of the PET drug vial assembly in the ISO Class 5 environment, the assembly can be removed to another location for filtration. The location can be a noncontrolled environment as long as the integrity of the PET drug vial assembly is not compromised during the process. Any PET drug vial assembly that is compromised during this process should be discarded.

Aseptic Techniques—Any sterile component downstream from the membrane filter that contacts the PET drug should be handled using suitable aseptic techniques inside the aseptic workstation. During aseptic operations, operators should wear proper attire, including a clean laboratory jacket, forearm sleeves, hair cover, sanitized gloves that cover the wrist, and beard/moustache covers (as appropriate). Multiple PET drug vial assemblies can be prepared in a single aseptic operational cycle. The storage time for assembled vials should be based on data from aseptic media fills.

Sterility Test Inoculations—Sterility tests should be performed to assess the quality of PET drugs intended for parenteral administration. The inoculation of sterility test media should be performed in a manner that is consistent with personnel radiation exposure requirements but that also minimizes the risk of false positives caused by adventitious contamination during the inoculation process. For media tubes with a screw-cap opening, the inoculation should be performed in the aseptic workstation. Media tubes with a septum cap can be inoculated in a shielded area that does not contain a HEPA filter.

STABILITY

Written specifications for the expiration time and storage conditions should be established for each PET drug. The expiration time should be based on the results of stability testing (and specific activity requirements, as appropriate). Stability testing of the PET drug should be performed at the highest strength of the PET drug and in the intended final vial or container. At least three batches of the PET drug should be stored according to proposed conditions and should be examined after a time period equal to the proposed shelf life. In addition, the PET drug should meet acceptance criteria for radiochemical purity, appearance, pH, and stabilizer or preservative effectiveness (as appropriate) at expiry. Analytical methods should be reliable, meaningful, and specific. Stability studies should be repeated if there is a change in strength, stabilizer (or preservative) content that has the potential to affect the stability, the final vial or container, storage conditions, or expiration time. The results of stability testing should be documented.

CONTROLS AND ACCEPTANCE CRITERIA FOR FINISHED PET DRUGS

Written specifications for identity, strength, quality, and purity should be established for each PET drug. For PET drugs intended for parenteral administration, specifications should be included for sterility and bacterial endotoxins.

Written procedures should be developed for QC tests. QC and documentation requirements should be established for each batch or sub-batch of a PET drug (see *Process and Operational Controls*, above). All QC tests should be executed by qualified and trained personnel according to written procedures.

The short half-life of PET radionuclides frequently precludes the completion of all QC tests before shipment of the PET drug. This effectively creates two levels of release,

one for distribution and the other for human administration. This is acceptable as long as the QC tests required for release of the PET drug for human administration (see below) are completed before administration. The controls used in the release for distribution should be previously established in writing and should be documented in routine practice. It is not necessary to retain reserve samples of PET drugs.

If a *USP* compendial test procedure is employed, the procedure should be verified to demonstrate that the test works under the conditions of actual use. Noncompendial test procedures employed in the testing of a PET drug should be reliable and specific. Supporting data for use of all analytical methods should be documented. Data derived from process studies or from in-process controls can be used as a basis for the omission of some QC tests. An example of this approach is the chlorodeoxyglucose determination in the testing of [^{18}F]fludeoxyglucose. Supporting data from process studies or in-process controls should be documented.

The following QC tests should be performed on each batch before release for administration:

1. Measure the pH of parenteral dosage forms.
2. Determine the radiochemical purity and identity of all dosage forms.

In addition, the following QC tests should be considered on each batch before release for administration:

1. Visually inspect parenteral dosage forms.
2. Determine the radionuclidic identity of all dosage forms by half-life measurement.
3. Determine the strength.
4. Determine the specific activity of PET drugs that have mass-dependent localization or toxicity concerns.
5. Determine the residual solvents used in the synthesis or purification processes.
6. Determine the chemical purity and residual compounds used in the synthesis or purification processes (e.g., cryptand[2.2.2]).

For PET drugs with very short-lived radionuclides, prepare an initial QC sub-batch that is representative of successive sub-batches prepared in a defined operational cycle. The QC tests described in the previous paragraph should be considered for the QC sub-batch before release of subsequent sub-batches for human administration. For subsequent sub-batches of parenteral and inhaled dosage forms, visual inspection should be performed before human administration. In certain cases, limited testing of each sub-batch before administration may be appropriate (e.g., for pH determination of [^{13}N]ammonia produced by Devarda's alloy).

For all PET drugs, periodically measure the radionuclidic purity of decayed samples of the PET drug to assess the presence of long-lived radionuclides that are produced in targetry associated with the particle accelerator. For PET drugs labeled with certain radionuclides (e.g., ^{94m}Tc, ^{124}I, ^{64}Cu, ^{76}Br, and others), consider the measurement of radionuclidic purity by gamma spectrometry.

Periodic QC tests for PET drugs also include low-level nontoxic impurities and Class 3 residual solvents. The periodic QC testing should be performed at predetermined intervals rather than on a batch-to-batch basis.

For PET drugs intended for parenteral administration, perform the following QC tests in addition to those described previously:

1. Determine the integrity of the membrane filter. Filter units used to sterilize PET drugs should be subjected to manufacturers' recommended integrity tests such as the bubble point test. Although it is not strictly a QC test on the final PET drug, this test is important to ensure the preparation of a sterile solution. Perform the filter integrity test after completion of filtration and before release of the PET drug for human administration. In the case of PET drugs with $T_{1/2} < 10$ min, the PET drug can be released for human administra-

tion before completion of the filter integrity test. In this case, the test should be completed as soon as possible after release.

2. Perform a test for bacterial endotoxins on each batch or QC sub-batch of a PET drug. The test can be performed using recognized procedures in *USP* (see *Bacterial Endotoxins Test* ⟨85⟩). Regardless of which test is used, it should be initiated before release of each batch for human administration. For PET drugs with very short-lived radionuclides, complete the test on the QC sub-batch before the release of subsequent sub-batches for human administration. After a record of successful bacterial endotoxin tests is established for a particular PET drug, it is necessary only to test the first batch prepared each day for that PET drug.
3. Perform a test for sterility on each batch or QC sub-batch. The sterility test consists of the inoculation and incubation of a sample into each of two media: tryptic soy broth and fluid thioglycollate. The inoculated volume may be adjusted to avoid excessive losses because of sterility testing (e.g., 0.1 mL inoculated into 10 mL of media). The incubation period for sterility tests should begin within 30 hours of the membrane filtration. The samples can be inoculated immediately after completion of the membrane filtration, or they can be allowed to decay in a shielded area for as long as 30 hours before inoculation. It is acceptable to exceed the 30-hour period because of weekends or holidays provided it is shown that the extended period does not significantly reduce the viability of a *USP* indicator organism (e.g., *E. coli*) in the sample. The sterility test may be performed using other recognized procedures in *USP* (see *Sterility Tests* ⟨71⟩). Samples should be tested individually and may not be pooled. After a record of successful sterility tests is established for a particular PET drug, it is only necessary to test the first batch prepared each day for that PET drug.

When a required QC test for a PET drug cannot be completed because of a malfunction of testing equipment, it may be appropriate to conditionally release the batch. PET drugs may not be released without determination of radiochemical identity and purity. The batch may be released if the following conditions are met:

1. Review historical QC data to assess the frequency of out-of-specification (OOS) results or failures associated with the QC test. A conditional release is appropriate only if the historical data reveal a record of successful completion of the QC test.
2. Confirm that the acceptance criteria are met for all other QC tests for the batch.
3. Retain a sample of the conditionally released batch, and complete the omitted QC test on the sample as soon as possible after the malfunction has been corrected. This is not necessary if the omitted QC result is meaningless after decay of the PET drug.
4. If the sample fails the omitted QC test, notify the physician or receiving facility that ordered the PET drug.
5. Document all actions regarding the conditional release of the PET drug, including the justification for the release, results of completed testing, and any notifications and corrective actions resulting from the incident.
6. Promptly correct any malfunction of the testing equipment.

In addition to the finished QC testing, other appropriate laboratory determinations could involve in-process testing of an attribute that is equivalent to finished-product testing of that attribute; continuous statistical process monitoring; or some combination of these approaches with finished testing of each PET drug.

IF A PET DRUG DOES NOT CONFORM TO SPECIFICATIONS

When the result of a QC test for a PET drug does not meet established acceptance criteria, the result is OOS. An OOS result does not necessarily mean that the final PET drug is a failure and should be rejected. Instead, an OOS investigation should be performed to determine if the OOS result indicates a true failure or an analytical error.

If an OOS investigation concludes that the OOS result was caused by an analytical error, invalidate the original test. If a printout is associated with this test, mark the printout *invalid*, retain it for the batch record, and repeat the test.

If an OOS investigation concludes that the OOS result was a true failure, the batch should be rejected and cannot be released for human administration. Segregate the batch to avoid its potential use. Investigate all failures and document the results according to written procedures. The investigation should include, but is not limited to, the examination of processes, operations, and records from previous batches, as well as complaints and other relevant sources of information. If possible, assign an actual or probable cause to the failure, and document corrective actions undertaken as a result of the investigation. Depending on the nature of the failure, the PET drug may be reprocessed according to pre-established written procedures (see *Reprocessing*, below).

When a sterility test for a PET drug shows signs of microbial growth, the test result is OOS and should be investigated. If the outcome of the investigation concludes that the OOS result was a true failure, notify the physician or receiving facility that ordered the PET drug. In addition, identify and correct the source of the contamination. The process should be revalidated and operators should be retrained as necessary to demonstrate the effectiveness of the corrective actions.

REPROCESSING

If a PET drug is rejected as a true failure, the batch may be reprocessed according to established procedures. It is not possible to describe all possible reprocessing operations, but some examples could include:

- pH adjustment;
- A second passage through a membrane filter in the event of a failed filter integrity test; and
- A second passage through a purification column to remove an impurity.

If a PET drug is reprocessed, the reprocessed batch should be tested to ensure it meets the established acceptance criteria for the PET drug before release for human administration.

LABELING AND PACKAGING

The following information should appear on the label attached to the final PET drug container:

- The name of the PET drug;
- The assigned batch number; and
- Any required warning statements or symbols (e.g., radioactive).

The following information should appear on the shielding for the PET drug:

- The name of the PET drug;
- The assigned batch number;
- The date and time of calibration;
- Any required warning statements or symbols (e.g., radioactive);
- As appropriate, the total radioactivity in MBq (or mCi) or the strength in MBq/mL (or mCi/mL) at time of calibration;
- Expiration time and date;
- Added substance(s) (e.g., stabilizer or preservative);
- Other applicable warning statement(s) (e.g., ''Do not use if cloudy or if it contains particulate matter'' or investigational use labeling); and

- Other pertinent information (if required), such as storage condition(s), half-life, and name and place of business where the PET drug was made or distributed.▲*USP35*