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⟨823⟩ ▲POSITRON EMISSION TOMOGRAPHY DRUGS FOR COMPOUNDING, INVESTIGATIONAL, AND RESEARCH USES

INTRODUCTION

Radionuclides used in positron emission tomography (PET) typically possess short physical half-lives, $T_{1/2}$ (e.g., $T_{1/2}$ of ^{15}O = 2.03 min, ^{62}Cu = 9.67 min, ^{13}N = 9.96 min, ^{11}C = 20.4 min, ^{68}Ga = 67.7 min, ^{18}F = 109.8 min, ^{64}Cu = 12.7 h). 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 product 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 drug products. This chapter describes guidelines for making and testing PET drug products based on the following constraints:

- It is not possible to complete all testing before the use of PET drug products.
- An entire batch or sub-batch of a PET drug product 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 Samples withdrawn for quality control (QC) testing are representative of the entire batch or sub-batch.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 PET drug in a PET drug product usually ranges from nanogram to microgram quantities.
- PET drug products do not enter a traditional drug distribution chain. Instead, PET drug products are used in-house or are delivered to the point of use by dedicated couriers.
- Small-scale facilities for the preparation of PET drug prodcuts have limited personnel and resources, which require the following:
  - — Allowance for multiple operations in one area with adequate controls;
  - — Allowance for the making and testing of multiple PET drug products 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 drug products 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.

Batch: A quantity of PET drug product that is intended to have uniform character and quality, within specified limits, and that is made in a single operational cycle produced according to one or more production order(s).

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 product.

PET Drug: A radioactive substance (active pharmaceutical ingredient) that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is incorporated into a PET drug product to furnish direct effect in the diagnosis or monitoring of a disease or a manifestation of a disease in humans, or monitoring treatment of disease or therapeutic procedures (e.g., tumor therapy).

PET Drug Product: A finished dosage form that contains a PET drug, whether or not in association with one or more other ingredients.

Compounding: The practice as described in the Food, Drug and Cosmetic Act (1997) Chapter II, Section 121 (a) (ii) (1) (B) of synthesizing or formulating a PET drug product, by or on the order of a practitioner who is licensed by a State to compound or order compounding for a PET drug product, and is compounded in accordance with that State's law, for a patient or for research, teaching, or quality control.

Line Clearance: The segregation and cleaning of different processing and work areas to avoid cross-contamination and mix-ups between the production and/or compounding of different PET drug products.

Manufacturer's Certification: Documentation, including, but not limited to, certificates of analysis, certificates of conformance, or certificates of quality obtained from the manufacturer, supplier, or vendor of a material or component that describes critical quality characteristics used to determine acceptability of use.

Out of Specification (OOS): A quality control test result for a PET drug product that does not conform to established acceptance criteria.

Production: The process of synthesis or formulation of a PET drug product including processing, packaging, labeling, reprocessing, and testing for investigational or research use.

Quality Assurance (QA): A planned system for ensuring that a PET drug product possesses defined identity, strength, quality, and purity required for its intended purpose by procedures, tests, and analytical methods.

Quality Control (QC): A system for testing the quality of components, materials, supplies, and PET drug products 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 PET drug in the PET drug product 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 product 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 may be required for PET drug products 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.

PERSONNEL

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

Training Requirements: Personnel should be trained before they begin to make and test PET drug products. Training can be performed by various methods, including live instruction, audio-video instruction, and study of publications. 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 drug products, and QC methods, including equipment, software, and documentation. Training must be documented.

Aseptic Operations Training: 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 aseptic simulations in which a microbiological growth medium is used to assess the quality of the aseptic operation. Aseptic simulations should provide the following:

- Include all manipulations required for the aseptic assembly of the PET drug product vial assembly (e.g., vial, filter, and syringe assembly, etc.).
- Represent worst-case scenarios for aseptic operations.
- Be performed in triplicate to qualify a new operator. Each operator should be requalified annually by conducting at least one media fill.
- 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 aseptic simulations result in microbial growth should be immediately re-instructed and re-evaluated to ensure correction of aseptic practice deficiencies.

QUALITY ASSURANCE

QA is a broad concept that covers all matters that influence identity, strength, quality, and purity of a PET drug product. QC is a subset of QA that deals with testing of materials and PET drug products 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 drug products.
- Evaluate each batch of a PET drug product to ensure the batch meets its established specifications before authorizing the final release of the batch.

The oversight functions associated with QA include the following:

- Review completed batch records for accuracy and completeness.
- Approve procedures, specifications, processes, and methods.
- Ensure that personnel are properly trained and qualified, as appropriate.
- Ensure that PET drug products have adequately defined identity, strength, quality, and purity.
- Ensure that changes to component quality, suppliers, changes to production procedures, and changes to testing procedures and specifications are appropriate and implemented properly.
- Investigate errors and ensure that appropriate corrective and preventive actions are taken to prevent their recurrence.
- Handle complaints.
- Ensure that the PET drug products are produced, tested, labeled, released, and distributed according to the facility's established procedures and practices for PET drug products.
- Conduct periodic audits to monitor compliance with established procedures and practices for PET drug products.

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

Environmental Controls for Parenteral PET Drug Products: Because the sterility test results for parenteral PET drug products are obtained after release, facilities and equipment should ensure a sterile PET drug product.

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. These requirements supersede those in other USP general information chapters (e.g., *Microbiological Evaluation of Clean Rooms and Other Controlled Environments* ⟨1116⟩).

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 certification.

Microbiological Testing—Microbiological testing of the environment should be performed to assess air quality and surface disinfection of the aseptic areas. 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. For microbiological testing of the aseptic workstation, the air should be tested as part of the workstation qualification (e.g., every six months) and the surface (using swab or contact plates) should be assessed after use, each day of use. 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 drug products 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 drug products at an appropriate level of detail based on complexity. All qualification activities should be properly documented, including the date and the name of the person who performed the qualification. For more complex equipment, 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 drug products 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*—Analytical equipment calibration should be performed before use, as appropriate. A schedule should be developed for 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 drug products includes automated, computer-controlled devices, as well as manually operated apparatus. Before it is used in making PET drug products, equipment should be properly cleaned to ensure that the resulting PET drug product meets established specifications for identity, strength, quality, and purity (see *Controls and Acceptance Criteria for Finished PET Drug Products* 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 drug products. 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. Written procedures for line clearance between batches of different PET drug products should describe routine execution of cleaning processes.

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 prior to using the equipment according to established procedures. 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 a known concentration is necessary for these determinations. Standards should be prepared from well-characterized materials or from materials that have a manufacturer's certification. Two acceptable approaches that may be used for chromatographic methods are the following:

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. The calibration curve should be used over a suitably specified period of time (e.g., six months), after which time a new one should be created. A new calibration curve should be created each time an alteration is made to the chromatographic system. 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 demonstrates 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, and limit of quantitation 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 use 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 drug products 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 product 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 drug products.
4. Establish appropriate storage conditions (based on heat, light, humidity, and other factors) for components, materials, and supplies used to make and test PET drug products.
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 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 manufacturer's certification. The identity of each lot of components, materials, and supplies should be verified by defined procedures, tests, or documented manufacturer's certification, as appropriate. Perform an identity test for precursors (e.g., melting point determination or other appropriate tests). Alternatively, the manufacturer's certification can be used as the only acceptance criterion for a precursor if final testing of the PET drug product ensures that the correct precursor has been used. Reference standards used in chromatographic procedures should have suitable documentation of identity and purity. Other components can be accepted on the basis of a manufacturer's certification only.
8. Membrane filters used with parenteral PET drug products should have a manufacturer's certification. Examine the manufacturer's certification for each lot to ensure compliance with written specifications.
9. Media used in the sterility testing of PET drug products may be obtained from commercial sources. If the media is obtained from commercial sources, then growth-promotion testing that uses a suitable single species of organism should be performed on initial qualification of the supplier and periodically (e.g., quarterly) thereafter.

PROCESS AND OPERATIONAL CONTROLS

Process Controls: The following process controls should be established and summarized in a master formula for the PET drug product. 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 product should be established. For PET drug products intended for parenteral administration, specifications should include sterility and bacterial endotoxins. If a *USP* monograph exists or if there are specifications that have been previously accepted by the appropriate regulatory agency (e.g., FDA), then these standards, if applicable, may be applied as the minimum acceptance criteria.
2. Written procedures for the preparation of each PET drug product should provide the following:
   - Incorporate, for each PET drug product intended for parenteral administration, sterile membrane filtration (0.22 μm) or steam sterilization;
   - Incorporate, for each PET drug product 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 drug products, including precursors, standards, reagents, stock solutions, and related items;
   - Describe the process and the steps used to make the PET drug product;
   - Describe the formulation process, including the use of stabilizers, buffers, and other agents;
   - Describe calculations performed for quantitative parameters associated with making and QC testing

the PET drug product (e.g., including radiochemical yield, radiochemical purity, specific activity, solvent amounts, etc.);
- Describe QC tests for the final PET drug product (see *Controls and Acceptance Criteria for Finished PET Drug Products* 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. The quality of each batch of a PET drug product should be verified by full finished product testing prior to use to ensure the product meets all specifications.
4. In cases where testing as described in the previous paragraph is not possible or impractical, the quality of a PET drug product may also be ensured by documented validation studies in lieu of prerelease tests. Such studies should provide the following:
   - Demonstrate a consistent process that is suitable for the intended preparation of the PET drug product;
   - 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 drug products), bacterial endotoxins (for parenteral PET drug products), 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 product, 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 product;
5. The processes and steps described in the master formula should be updated as needed and should be reviewed annually to ensure they are current. Prior to the implementation of updates, appropriate validation and/or verification should be approved and performed.

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 product. The batch record should adequately document the routine process for making the PET drug product. A designated person should be responsible for ensuring that these activities are carried out and completed properly. Completed batch records and associated documentation should be maintained for one year after batch release.

1. Execute suitable line clearance procedures to avoid mix-ups and cross-contamination, including the inspection of areas used to make and test PET drug products, and the inspection of 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 product. Label components as appropriate for identity and traceability purposes.
3. Execute routine cleaning procedures for equipment and facilities.
4. Prepare the PET drug product 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 the following:
   - 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 product 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 product;
   - Raw analytical data on each batch of the PET drug product;
   - Labeling for the PET drug product (see *Labeling* below);
   - Calculations for key parameters defined in the master formula;
   - Results obtained from QC tests of the PET drug product, 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 Drug Products: Because the sterility test results for parenteral PET drug products are obtained after release for human administration, aseptic operations and procedures should adequately ensure a sterile PET drug product. All aseptically prepared PET drug products 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 or sterilized by steam sterilization. Although the chemical synthesis of a parenteral PET drug product may take place in an open or closed apparatus, the membrane filtration of the PET drug product should be a closed system downstream of the membrane filter. This system should be 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 facility, the sterilization processes should be verified. The exact configuration of the PET drug product 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 Product Vial Assembly—Aseptic techniques should be used in the preparation of the PET drug product 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 product 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 product vial assembly is not compromised during the process. Any PET drug product 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 product 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 product vial assemblies can be prepared in a single aseptic operational cycle. The storage conditions and time for assembled vials should be based on data from aseptic simulations.

Sterility Test Inoculations—Sterility tests should be performed to assess the quality of PET drug products 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 product. The expiration time should be based on the results of stability testing (and specific activity requirements, as appropriate). Stability testing of the PET drug product should be performed at the highest strength of the PET drug product and in the intended final vial or container. At least three batches of the PET drug product 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 product should meet acceptance criteria for radiochemical purity, appearance (color and clarity), pH, and stabilizer effectiveness (as appropriate) and chemical purity 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 DRUG PRODUCTS

Written specifications for identity, strength, quality, and purity should be established for each PET drug product. For PET drug products 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 product (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 product. 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 product 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 drug products.

If a *USP* compendial test procedure is used, the procedure should be verified to demonstrate that the test works under the conditions of actual use. Noncompendial test procedures used in the testing of a PET drug product 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.

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

1. Appearance by visual inspection for color and clarity (absence of particulate matter) for parenteral dosage forms.
2. Measurement of the pH for parenteral dosage forms.
3. Determination of the radiochemical purity and identity of all dosage forms.
4. Determination of the radionuclidic identity of all dosage forms by half-life measurement.
5. Determination of the strength.
6. Determination of the specific activity of PET drug products that have mass-dependent localization or toxicity concerns.
7. Determination of residual solvents used in the synthesis or purification processes.
8. Determination of the chemical purity and residual compounds used in the synthesis or purification processes (e.g., cryptand [2.2.2]).
9. Determination of preservative or stabilizer, if present.

For PET drug products 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).

Periodic Quality Indicating Tests: For all PET drug products, periodically measure the radionuclidic purity of decayed samples of the PET drug product to assess the presence of long-lived radionuclides that are produced in targetry associated with the particle accelerator. For PET drug products 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 quality indicating tests for PET drug products also include low-level nontoxic impurities (e.g., Class 3 residual solvents). The periodic testing should be performed at predetermined intervals rather than on a batch-to-batch basis.

Microbiological Tests for Sterile PET Drug Products: For PET drug products 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 drug products should be subjected to manufacturers' recommended integrity tests such as the bubble point test. Perform the filter integrity test after completion of filtration and before release of the PET drug product for human administration. In the case of PET drug products with $T_{1/2} < 10$ min, the PET drug product can be released for human administration 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 product. 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 drug products 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 product, it is necessary only to test the first batch prepared each day for that PET drug product.
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 suitable indicator organism 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 product, it is only necessary to test the first batch prepared each day for that PET drug product.

Conditional Final Release Tests: When a required QC test for a PET drug product cannot be completed because of a malfunction of testing equipment, it may be appropriate to conditionally release the batch. PET drug products 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.
4. Promptly correct the malfunction of the testing equipment.
5. 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 product.
6. If the sample fails the omitted QC test, immediately notify the physician or receiving facility that ordered the PET drug product.
7. Document all actions regarding the conditional release of the PET drug product, including the justification for the release, results of completed testing, and any notifications and corrective and preventive actions resulting from the incident.

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 product.

IF A PET DRUG PRODUCT DOES NOT CONFORM TO SPECIFICATIONS

When the result of a QC test for a PET drug product does not meet established acceptance criteria, the result is OOS. An OOS result does not necessarily mean that the final PET drug product 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 product may be reprocessed according to pre-established written procedures (see *Reprocessing* below).

When a sterility test for a PET drug product shows signs of microbial growth, the test result is OOS and should be investigated. Upon completion of the investigation, immediately notify all receiving facilities if the product fails to meet the criterion for sterility, including the microbiological findings from the investigation.

REPROCESSING

If a PET drug product 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 the following:

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

LABELING

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

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

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

- The name of the PET drug product, including the dosage form;
- The assigned batch number;
- The date and time of calibration;
- Any required warning statements or symbols (e.g., investigational use, 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 inactive ingredients);
- The name of the producer where the PET drug product was made or the name of the distributor;
- 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.▲*USP35*