BRIEFING

(823) Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses. This proposal is based on the version of the chapter official prior to 2013. The Small Molecules 4 Expert Committee is proposing to update this chapter with the following key changes:

1. Revise the chapter title from “Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses” to “Production of Diagnostic Positron Emission Tomography Drugs for Investigational and Research Uses” to better describe the scope of the chapter and to support the removal of references to the compounding of positron emission tomography (PET) drugs.

2. Replace “should” with “must” throughout the chapter, as appropriate, to be consistent with the current compliance standards. Replace “preparation” and “make” with “production” and “produce”, respectively, throughout the chapter, as appropriate, to support the removal of compounding from the scope of this chapter.

3. Incorporate the relevant components of Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging (825).

4. Make the following changes to the introduction section:
   - Replace “dedicated couriers” with “appropriately trained couriers that transport radioactive materials”.
   - Limit the scope of this chapter to diagnostic PET drugs for human administration.
   - Exclude the production of PET drug products used for therapeutic purposes and the manufacturing of PET drugs under 21 CFR part 212.

5. Add a Documentation section to provide the documentation standards for PET drugs for investigational and research uses.

6. Make the following changes to the Personnel section:
   - Expand the Training Requirements subsection to include a statement regarding personnel with limited roles.
   - Limit the scope of the Aseptic Operations Training subsection to address the ISO Class 5 environmental conditions where designated. Move text regarding the evaluation of personnel involved in aseptic operations to a new subsection titled Aseptic Qualifications.
   - Add a new subsection, Reevaluation, Retraining, and Requalification, to provide standards for these activities.

7. Revise the Quality Assurance section to ensure that PET drugs have adequately defined potency (if applicable) and they are produced, tested, labeled, released, and distributed according to the facility's established procedures and practices based on investigational new drug (IND) or Radioactive Drug Research Committee (RDRC) protocols for PET drug products.

8. Make the following changes to the Facilities and Equipment section:
   - Update the Environmental Controls for Parenteral PET Drug Products by clarifying that facilities and equipment must be designed and operated to promote sterile PET drug product production. Replace many of the references to an “aseptic workstation” with references to a “PEC” (primary engineering control station). Accommodate additional concepts such as a cleanliness rating of better than ISO Class 5, a description of the PEC location applying when it is operated, details about the work area inside of the PEC, and the surface sampling frequency. The paragraph about alert and action limits is removed.
   - Expand the Cleaning Equipment and Components subsection to provide standards for appropriate working environments to be aligned with current expectations. The topics addressed include design, controls, monitoring, sampling, cleaning and disinfecting, and data evaluation and action levels.
   - Add a new subsection titled Creating Areas to Achieve Easily Cleanable Conditions.
   - Add a new subsection titled Water Sources.
   - Add a new subsection titled Placement and Movement of Materials.
   - Add a new subsection titled Remote Aseptic Processing Involving a Hot Cell.
   - Add a new subsection titled Environmental Controls.
   - Remove “reagent delivery volumes” from the Day-of-Use Checks subsection.
   - Simplify the System Suitability for QC Equipment subsection by replacing several paragraphs with a reference to the chapter Positron Emission Tomography Drugs—Information (823), which is also being revised in this issue of PF.

9. Add an Environmental Monitoring section to provide the related standards for PET drugs for investigational and research uses.

10. Add a Cleaning and Disinfecting section to provide the related standards for PET drugs for investigational and research uses.

11. Update the Control of Components, Materials and Supplies section to be consistent with the current terminology and practices.

12. Make the following changes to the Process and Operational Controls section:
• Remove the *Aseptic Techniques* subsection and provide details about the performance of sterility tests and sample timing in the *Aseptic Operations for Parenteral PET Drug Products* subsection.
• Update the *Sterility Test Inoculations* subsection to be consistent with the current terminology and practices.

13. Make the following changes to the *Controls and Acceptance Criteria for Finished PET Drug Products* section:
• Clarify that half-life measurement is one option to determine the radionuclidic identity of all dosage forms in the *Quality Control Tests* subsection.
• Remove the phrase 'rather than on a batch-to-batch basis' from the *Periodic Quality Indicating Tests* subsection.
• Remove statements about testing with regard to the first batch prepared each day and pooled samples from the *Microbiological Tests for Sterile PET Drug Products* subsection.

14. Update the section titled If a PET Drug Product Does Not Conform to Specifications to be consistent with current terminology and practices.
15. Update the *Reprocessing* section by adding an example of secondary dilution and by removing the example of a second passage through a purification column to remove an impurity.
16. Update the *Labeling* section to be consistent with current terminology and practices.
17. Update the *Glossary* to include additional definitions, to remove the entry for *compounding*, and to revise the entries for *PET drug substance*, *PET drug product*, *Specific Activity*, and *Strength*.

Additionally, minor editorial changes have been made to update the chapter to current USP style.

(SM4: G. Hsu)

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The following Briefing list includes monographs and/or chapters that both reference the General Chapter under revision and require revision to keep references to the General Chapter accurate. Other monographs and/or chapters may also be listed, even where the reference to the General Chapter remains unchanged, as additional notice to stakeholders where there is believed to be potential for the change in the general chapter itself to affect pass-fail determinations for particular monograph articles.

Show Chapter Dependencies

**Change to read:**

〈 823 〉**POSITRON EMISSION TOMOGRAPHY DRUGS FOR COMPOUNDING, INVESTIGATIONAL, AND RESEARCH USES**
**PRODUCTION OF DIAGNOSTIC POSITRON EMISSION TOMOGRAPHY DRUGS FOR INVESTIGATIONAL AND RESEARCH USES**

(USP 1-May-2025)

**Change to read:**

1. INTRODUCTION
2. PERSONNEL
   2.1 Training Requirements
   2.2 Aseptic Operations Training
3. QUALITY ASSURANCE
4. FACILITIES AND EQUIPMENT
   4.1 Environmental Controls for Parenteral PET Drug Products
   4.2 Equipment
   4.3 Cleaning Equipment and Components
   4.4 Day-of-Use Checks
   4.5 System Suitability for QC Equipment
5. CONTROL OF COMPONENTS, MATERIALS, AND SUPPLIES
6. PROCESS AND OPERATIONAL CONTROLS

6.1 Process Controls
6.2 Operational Controls
6.3 Aseptic Operations for Parenteral PET Drug Products

7. STABILITY

8. CONTROLS AND ACCEPTANCE CRITERIA FOR FINISHED PET DRUG PRODUCTS

8.1 Quality Control Tests
8.2 Periodic Quality-Indicating Tests
8.3 Microbiological Tests for Sterile PET Drug Products
8.4 Conditional Final Release Tests

9. IF A PET DRUG PRODUCT DOES NOT CONFORM TO SPECIFICATIONS

10. REPROCESSING

11. LABELING

GLOSSARY

1. INTRODUCTION

Radionuclides used in positron emission tomography (PET) typically possess short physical half-lives, \( T \) (e.g., \( T_{1/2} \) for \( ^{18}O = 2.03 \) min, \( ^{64}Cu = 9.67 \) min, \( ^{9}N = 9.96 \) min, \( ^{13}C = 20.4 \) min, \( ^{68}Ga = 67.7 \) min, \( ^{18}F = 109.9 \) 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 products 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.

2. 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.

2.1 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.

2.2 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.

3. 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.

4. 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.

4.1-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 Control and Monitoring of Aseptic Processing 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.

4.2 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.

4.3 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.

4.4 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.
4.5 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 created 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 analyses. 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.

5. 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.

6. PROCESS AND OPERATIONAL CONTROLS

6.1 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.
6.2 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 recordkeeping 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;
   - Labelling for the PET drug product (see Labelling 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.

6.3 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.
appropriate (e.g., for pH determination of 
inspection should be performed before human administration. In certain cases, limited testing of each sub-batch before administration may be 
release of subsequent sub-batches for human administration. For subsequent sub-batches of parenteral and inhaled dosage forms, visual 
prepared in a dened operational cycle. The QC tests described in the previous paragraph should be considered for the QC sub-batch before 
8.1 Quality Control Tests 
from process studies or in-process controls should be documented. 
of some QC tests. An example of this approach is the chlorodeoxyglucose determination in the testing of 
analytical methods should be documented. Data derived from process studies or from in-process controls can be used as a basis for the omission 
use. Noncompendial test procedures used in the testing of a PET drug product should be reliable and specic. Supporting data for use of all 
8. CONTROLS AND ACCEPTANCE CRITERIA FOR FINISHED PET DRUG PRODUCTS 
Correct specifications for identity, strength, and purity should be established for each PET drug product. For PET drug products intended 
for parenteral administration, specications 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 veried 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 $[^{18}F]$ludeoxyglucose. Supporting data from 
process studies or in-process controls should be documented. 
6.1 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 specic activity of PET drug products that have mass-dependent localization or toxicity concerns; 
7. Determination of residual solvents used in the synthesis or purication processes; 
8. Determination of the chemical purity and residual compounds used in the synthesis or purication 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 deined 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 $[^{18}N]$ammonia produced by Devarda’s alloy);
8.2 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 targety associated with the particle accelerator. For PET drug products labeled with certain radionuclides (e.g., $^{90}$Y, $^{124}$Sn, $^{64}$Cu, $^{75}$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 lot-to-lot basis.

8.3 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 Endotoxin Test, USP). 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, USP). 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.

8.4 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.

9. 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.

10. 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.

11. 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.

GLOSSARY

- **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., $^{18}$F 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.

1. 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 proximity to where the diagnostic PET procedure will be conducted.

The short half-lives of PET radionuclides create unique constraints for the production and testing of PET drug products. This chapter describes standards for production and testing of diagnostic PET drug products based on the following constraints:

- It may not be possible to complete all testing before the administration 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 may be produced and used in-house, or are delivered to the point of use by appropriately trained couriers that transport radioactive materials (RAM).
- Small-scale facilities for the production of PET drug products have limited personnel and resources, which require the following:
  - Allowance for multiple operations in one area with adequate controls;
  - Allowance for the production 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 testing; and
  - Single-person oversight of production, review of batch records, and release authorization.

The scope of this chapter includes the production of diagnostic PET drug products for human administration as used according to:

1. An approved investigational new drug (IND) application [see US Code of Federal Regulations (21 CFR 312)]
2. Research uses under the supervision of a Radioactive Drug Research Committee (RDRC) (see 21 CFR Part 361)

The scope of this chapter does not include:

1. Activities as defined in Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging (825), Examples include:
   - Preparation of a PET drug product using an FDA-approved kit
   - Compounding of a PET drug product using an FDA-approved kit
   - Dispensing or repackaging of a PET drug product
   - Direct infusion systems (e.g., rubidium generator infusion system) of a PET drug product
2. Production of PET drug products used for therapeutic purposes
3. Manufacturing of approved PET drug products under 21 CFR Part 212 [e.g., new drug application (NDA), abbreviated new drug application (ANDA), biologics license applications (BLA)] in FDA-registered manufacturing establishments

2. DOCUMENTATION

Applicable records (hard-copy or electronic), including policies and SOPs, must be maintained for all activities. Such records include, but are not limited to:

- Personnel training and testing, including visual assessment of aseptic technique competency, validation, garbing, hand hygiene, equipment/environment cleaning and disinfecting, gloved fingertip and thumb sampling, and aseptic qualification evaluation initially and follow up testing at specified intervals.
- Testing and monitoring of environmental controls
3. PERSONNEL

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

3.1 Training Requirements

Personnel must be trained before they begin to produce and test PET drug products. For personnel with limited roles, training may be limited to operations performed in those limited roles. 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 produce PET drug products, and QC methods, including equipment, software, and documentation. Training must be documented.

3.2 Aseptic Operations Training

Training must address aseptic manipulations as well as the techniques and equipment used to achieve and maintain International Organization for Standardization (ISO) Class 5 environmental conditions where designated. Training also must address all aseptic operations, including the assembly of sterile components and product sterility filtration. Manipulations of sterile solutions must be performed by operators who are qualified to use aseptic techniques.

3.3 Aseptic Qualifications

Personnel involved in aseptic operations must be evaluated as indicated by aseptic simulations, also referred to as media-simulation testing, in which a microbiological growth medium is used to assess the quality of the aseptic operation. This testing must be reflective of the actual manipulations to be carried out by the individual and must simulate the most challenging and stressful conditions to be encountered in the worker's duties. Media-simulation tests must be documented as defined by the facility's procedures. The certificate of analysis (CoA) for the media should include documentation of growth promotion testing (GPT) for each lot of media used. Alternatively, if the CoA does not include documentation of growth promotion testing, the facility must perform GPT internally or using an external vendor.

Media-simulation testing must:

- Include all manipulations required for the aseptic assembly of the PET drug product vial assembly (e.g., vial, filter, syringe assembly, QC sampling, etc.)
- Include final drug product filtration, quality control sampling, and any other aseptic manipulations performed on the final drug product, as applicable.
- Represent worst-case scenarios for aseptic operations.
- Be performed in triplicate to qualify a new operator. Each operator must be requalified annually by conducting at least one aseptic simulation.
- Be performed any time procedures or aseptic processes are changed significantly (i.e., no longer represent worse-case scenario).
- Use general microbial growth media [e.g., trypticase soy agar (TSA)].

Personnel must successfully complete an initial aseptic simulation evaluation for each aseptic process a minimum of three separate times on 3 separate days (see **Box 1**). The three successful completions must be in succession—failure of any of the three initial aseptic simulation evaluations requires repeat testing until personnel successfully complete three evaluations in a row. Once the media-simulation is completed and the final containers are filled with the test medium, incubate media-simulation containers and environmental monitoring plates in an incubator as outlined in facility standard operating procedures, for example between 20°–35°, with the range ±2.5°. Containers filled with media must be incubated no less than 14 days. Media plates must be incubated no less than 7 days.

One unopened container of media must be incubated as a negative control. Positive control testing must also be performed following media simulation testing. The positive and negative controls should be incubated under the same conditions as the media simulation. One positive and one negative control may be used when multiple media simulations are being completed within a week and use the same lot of growth medium.

Failure of the media simulation is indicated by visible turbidity or other visual manifestations of growth in the medium in 1 or more container–closure unit(s) on or before 14 days or by reaching action-level growth on the environmental monitoring plates used during the media simulation process.

**Box 1. Media-Simulation Testing Procedures**
If all of the starting components are sterile, manipulate them in a manner that simulates sterile-to-sterile handling activities, and transfer media into the same types of container–closure systems commonly used at the facility. Do not further dilute the media unless specified by the manufacturer.

If some of the starting components are nonsterile, prepare a commercially available nonsterile media (e.g., soybean–casein digest powder in nonbacteriostatic water to make a 3% nonsterile solution). Manipulate it in a manner that simulates nonsterile-to-sterile handling activities. Prepare at least 1 container as the positive control to demonstrate growth promotion, which is indicated by visible turbidity upon incubation.

Once the simulation is completed and the final containers are filled with the test media, perform a gloved fingertip and thumb sample on each hand and surface sample, if applicable. Take the samples prior to disinfecting gloves and primary engineering control (PEC). Incubate the final containers in an incubator and evaluate as previously detailed.

In the event of failure, results of the evaluation and corrective actions must be documented. Documentation must include the name of the person evaluated, evaluation date/time, media and components used, including manufacturer, expiration date and lot number, starting temperature for each interval of incubation, dates of incubation, and growth results, as applicable.

These qualifications must be completed and documented initially, and then successfully repeated at intervals described in 3.4.2 Timing of Reevaluation and Requalification. Qualifications should include the following:

- Aseptic technique
- Garbing and hand hygiene
- PEC cleaning and disinfecting
- Gloved fingertip and thumb sampling
- Aseptic simulation testing

The aseptic qualifications must be observed. The observer should be a knowledgeable person with training, education, and experience in the above areas.

3.3.1 Gloved Fingertip and Thumb Sampling

Appropriate garbing, including sterile gloves, is necessary for personnel who enter and perform tasks in an ISO Class 5 PEC (e.g., aseptic manipulations, cleaning the PEC). Personnel who perform such functions must prove their competency in this process. Gloved fingertip and thumb sampling must be performed as detailed in Box 2, initially on both hands, immediately following hand-hygiene and garbing. Successful completion of initial gloved fingertip and thumb sampling is defined as 0 colony-forming units (cfu) and subsequent gloved fingertip and thumb sampling after media-simulation testing is defined as ≤3 cfu (total for both hands).

The plates must be incubated in an incubator at 30°–35° for no less than 48 h, and then at 20°–25° for no less than 5 additional days.

Box 2. Gloved Fingertip and Thumb Sampling Procedures

- Use one sampling device (e.g., plate, paddle, or slide) per hand, where growth media has been supplemented with neutralizing additives (e.g., lecithin and polysorbate 80).
- Label each sampling device with a personnel identifier, right or left hand, and the date of sampling.
- If manually manipulating, do not apply sterile 70% isopropyl alcohol (IPA) to gloves immediately before touching the sampling device because this could cause a false-negative result. Using a separate sampling device for each hand, collect samples from all gloved fingertips and thumb from both hands by rolling fingertip pads and thumb pad over the agar surface.
- Incubate the sampling device and evaluate as previously detailed. Store media devices appropriately to prevent condensate from dropping onto the media during incubation and affecting the accuracy of the cfu reading (e.g., invert plates).

3.4 Reevaluation, Retraining, and Requalification

3.4.1 Requalification after Failure

Personnel who fail visual observation of hand hygiene, garbing, and aseptic technique, gloved fingertip and thumb sampling, or media-simulation testing must successfully pass reevaluations in the deficient area(s) before they can resume production. All failures, retraining, and reevaluations must be documented.

3.4.2 Timing of Reevaluation and Requalification

Visual observation: Personnel must be visually observed while performing hand hygiene and aseptic technique procedures initially.

Media-simulation testing: After initial qualification, conduct a media-simulation test of all personnel engaged in sterile production at least every 12 months (in conjunction with gloved fingertip and thumb sampling, as applicable).

After a pause in sterile radiopharmaceutical processing: Personnel who have not performed aseptic operations in more than 6 months must be requalified in media simulation before resuming aseptic operation duties.

4. QUALITY ASSURANCE
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 relates to the execution of the applicable activities.

QC functions include the following:
- Evaluate each lot of incoming material to ensure that it meets its established specifications before use in the production 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, purity, and potency (if applicable).
- 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 based on IND or RDRC protocols 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.

5. FACILITIES AND EQUIPMENT

Facilities must be adequate for the production 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 must be regularly cleaned, and procedures must be documented.

5.1 Environmental Controls for Parenteral PET Drug Products

Because the sterility test results for parenteral PET drug products are obtained after release, facilities and equipment must be designed and operated to promote sterile PET drug production.

5.1.1 Aseptic Primary Engineering Control

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 or better. This can be achieved with a laminar airflow aseptic workstation, biological safety cabinet, or other suitable primary engineering control (PEC) station. The PEC must be protected from sources of microbial contamination and be located in an area where personnel traffic is limited when operated (e.g., within a hot cell enclosure). The area around the PEC must not be used for storage of materials that shed large quantities of particulate matter (e.g., corrugated boxes).

The proper operation of the PEC must be certified by measurement of airborne particles, HEPA filter integrity testing, and pressure differential testing. The specific tests may depend on the type of PEC. Certification should be performed at the inception of operation and at least every 6 months thereafter, or after repair or replacement of the HEPA filter or relocation of the PEC. These requirements supersede those in other USP general information chapters (e.g., Microbiological Control and Monitoring of Aseptic Processing Environments (1116)).

The work area inside the PEC must be cleaned and disinfected, at minimum, prior to the first manipulation of the day. The internal surfaces should allow easy cleaning and disinfection. The internal surfaces must be cleaned and disinfected with appropriate disinfectants that are sterile filtered or certified sterile with a manufacturer’s certification.

5.1.2 Microbiological Testing

Microbiological testing of the environment must be performed to assess air quality and surface disinfection of the aseptic areas. For microbiological testing of the aseptic workstation, the viable air samples must be tested as part of the PEC certification (e.g., every 6 months). Surface sampling frequency of the ISO class 5 environment must be performed according to written procedures and be documented.

5.1.3 Engineering Controls and Design

Due to the interdependence of the various areas that make up a sterile radiopharmaceutical processing facility, it is essential to define and control the dynamic interactions permitted between areas. When designing doors, consider the placement of door closures, door surfaces, and the movement of the door, all of which can affect airflow. Tacky surfaces must not be used in ISO-classified areas.

The PEC must be located in a manner that minimizes conditions that could increase the risk of microbial contamination. For example, strong air currents from opened doors, personnel traffic, or air streams from the HVAC system(s) can disrupt the unidirectional airflow of an open-faced PEC such as a workstation, laminar airflow workbench (LAFW) or biological safety cabinet (BSC).

A PEC may be located in ambient air (e.g., within an unclassified area), without an anteroom or buffer area. The PEC must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow that may adversely affect the air quality in the PEC. The impact of activities
that will be conducted around or adjacent to the PEC must be considered carefully when arranging such an area. Access to the PEC must be restricted to authorized personnel and necessary materials/equipment.

It is also critical to control materials (e.g., supplies and equipment) as they move from ambient air into areas of higher quality air (e.g., ISO Class 5 PEC) to prevent the influx of contaminants.

5.1.4 The PET Drug Product Production Environment

The general production environment does not need to be ISO-classified space. The PEC, including those within a hot cell, must be certified to meet ISO Class 5 or better conditions (see Table 1) and must be designed to minimize microbial contamination during processing of radiopharmaceuticals under dynamic operating conditions.

The airflow in the PEC must be unidirectional (laminar flow), and because of the particle collection efficiency of the filter, the “first air” at the face of the filter is, for the purpose of aseptic processing, free from airborne particulate contamination. HEPA-filtered air must be supplied in the PEC (ISO Class 5; see Table 1) at a velocity sufficient to sweep particles away from aseptic processing areas and maintain unidirectional airflow as much as possible during operations, given the limitations added from the radiation shielding and other necessary production supplies that may be necessary in the PEC. Proper design and control prevent turbulence and stagnant air in the PEC. In situ air pattern analysis via smoke studies must be conducted at the critical area to demonstrate unidirectional airflow and sweeping action under dynamic conditions as part of the 6-month certification.

### Table 1. ISO Classification of Particulate Matter in Area Air

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>Particle Count ( \times 10^3 )/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>35.2</td>
</tr>
<tr>
<td>4</td>
<td>352</td>
</tr>
<tr>
<td>5</td>
<td>3520</td>
</tr>
<tr>
<td>6</td>
<td>35,200</td>
</tr>
<tr>
<td>7</td>
<td>352,000</td>
</tr>
<tr>
<td>8</td>
<td>3,520,000</td>
</tr>
</tbody>
</table>

\( ^a \) Adapted from ISO 14644-1, Clean areas and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration.

\( ^b \) Limits for number of particles \( \geq 0.5 \) µm measured under dynamic operating conditions.

5.1.5 Types of PECS and Placement

Placement of the PEC must allow for cleaning around the PEC. A PEC provides an ISO Class 5 or better environment for reagents and sterile products. The unidirectional airflow within the PEC helps protect the critical zone from process-generated contamination (e.g., opening wrappings of sterile containers, worker movement, etc.) as well as from outside sources.

Laminar airflow workbench (LAFW): An LAFW used for producing radiopharmaceuticals must provide vertical unidirectional HEPA-filtered airflow. In cases where the LAFW is located within the segregated containment area of a hot-cell, it is acceptable for a horizontal unidirectional HEPA-filtered airflow pattern to be utilized.

Biological safety cabinet (BSC) Class II: A Class II BSC is a cabinet with an open front, inward airflow, downward unidirectional HEPA-filtered airflow, and HEPA-filtered exhaust. The BSC is designed to provide worker protection from exposure to biohazardous material and to provide an ISO Class 5 or better environment for preparing sterile radiopharmaceuticals.

Placement of PEC: The PEC must be located out of traffic patterns and away from area air currents that could disrupt the intended airflow patterns inside the PEC. A dynamic airflow smoke pattern test must be performed initially and at least every 6 months to ensure that the PEC is properly placed into the facility and that workers understand how to utilize the unidirectional airflow to maintain first air as much as possible given the limitations added from the radiation shielding in the critical area.

Hot cell: A device used for the shielding and containment of radioactive materials. The shielding material(s) (e.g., lead) is generally incorporated into the structure of the unit itself. Radiopharmaceutical personnel carry out the majority of the tasks within the hot cell from the exterior of the unit. This is accomplished by the use of remote manipulation systems (e.g., manipulator arms, automated dispensing system) of various designs. Numerous air quality configurations of the hot cell may exist, including integrated HEPA filtration systems to render all or a specified portion (e.g., critical zone) of the device capable of certifying to a classified ISO Class 5 environment. In other situations, the hot cell offers only radiation protection, and a laminar flow PEC, capable of achieving an ISO Class 5 environment, placed within the enclosure to allow for safe aseptic
A hot cell may also be referred to by other designations (e.g., shielded isolator with laminar flow, PET dispensing station, manipulator hot cell, shielded isolators for dispensing, radiopharmaceutical dispensing isolator).

5.2 Equipment

Equipment used to produce and test PET drug products must be appropriate for its intended purpose and must be installed, cleaned, and maintained in an appropriate manner. Equipment must be capable of producing consistent results.

The following requirements must be described in written procedures, and performance of these procedures must be documented.

1. Installation of New Equipment—Newly installed equipment must be qualified before it is used to produce or test PET drug products at an appropriate level of detail based on complexity. All qualification activities must 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 produce 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 must 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 must 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 must 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 must be properly documented, including the date of such performance and the name of the person who performed them.

5.3 Cleaning Equipment and Components

Equipment used in the production of PET drug products includes automated, computer-controlled devices, as well as manually operated apparatus. Before use, equipment should be properly cleaned to ensure the resulting PET drug product meets established specifications for identity, strength, quality, and purity (see 11. Controls and Acceptance Criteria for Finished PET Drug Products). Once cleaned, equipment should be maintained in a state of cleanliness before use.

Equipment may be used to produce multiple batches of one or more PET drug products. The effectiveness of the cleaning process between batches must be documented. 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 the routine execution of cleaning processes.

Facilities should be arranged and controlled to provide an appropriate working environment. The temperature should be maintained below 25°C and must be monitored in the production areas each production day, either manually or by a continuous recording device. Temperature results must be documented and/or readily retrievable, and must be reviewed as described by the facility’s procedures. Temperature monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.

5.4 Creating Areas to Achieve Easily Cleanable Conditions

The production facility (e.g., walls, floors, counters, equipment) must be clean and uncluttered. Surfaces should be resistant to damage by cleaning agents, disinfectants, and tools used to clean.

5.5 Water Sources

The water sources must be arranged so that activities such as hand hygiene and garbing do not adversely affect the ability of the PEC to function as designed.

5.6 Placement and Movement of Materials

Only furniture, equipment, and other materials necessary for production should be within the areas. All materials should be easily cleaned. The number, design, location, and manner of installation of materials and/or fixtures must not adversely impact effective cleaning of equipment as specified in production processes. No shipping carton(s) or other corrugated or uncoated cardboard are allowed in the production areas.

5.7 Remote Aseptic Processing Involving a Hot Cell

A hot cell device provides an inherent physical segregation for the ISO Class 5 aseptic processing area. If the hot cell is located in an ISO-classified space, personnel must garb. In settings where tasks are carried out within the hot cell enclosure, not within an ISO-classified space by remote means (i.e., no direct intervention by personnel into the ISO Class 5 space), it is not necessary for personnel to don the garbing to carry out
these aseptic manipulations or to perform other routine tasks in the general area where the hot cell is located. If hand and arm incursions into the interior of the hot cell might be necessary for personnel to stage the required materials and supplies, the personnel must garb in relation to the contamination risk associated with the individual hot cell/ISO Class 5 relationship.

For situations where a PEC device is located within a hot cell, dynamic airflow smoke pattern tests must show that the staging of supplies and materials in the demarcated PEC area does not allow the influx of unclassified air into the PEC. Personnel may be garbed in nonsterile gloves and a low-particulate lab coat for interventions that are outside of the PEC. A failure of the airflow smoke pattern test requires personnel to garb for all incursions into the hot cell.

For situations where the hot cell is an integrated HEPA filtration system with a demarcated area that is a critical zone in the PEC, dynamic airflow smoke pattern tests must show that the staging of supplies and materials into the demarcated PEC area does not allow the influx of less than ISO Class 5 quality air into the PEC. A failure of the airflow smoke pattern test requires personnel to garb for all incursions into the PEC. Since other hot cell/PEC configurations and technologies may exist, verification (either by airflow smoke pattern tests or other manufacturer specified methods) must ensure, upon each certification, that the staging of materials and supplies does not allow for the intrusion of less than ISO Class 5 air into the designated ISO Class 5 space. A failure of the airflow smoke pattern test requires personnel to garb for all incursions into the hot cell.

5.8 Environmental Controls
Environmental controls must comply with the conditions specified in approved RAM license applications and regulations, and RAM license conditions may supersede the requirements for environmental controls described in this section.

5.9 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, 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.

5.10 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 must be established and followed for system suitability tests, and the test results must be documented. See Positron Emission Tomography Drugs—Information (1823) for more information on system suitability used for PET drug products.

6. ENVIRONMENTAL MONITORING
An effective air and surface monitoring program provides information on the environmental quality of the ISO classified areas where PET drug products are produced. The program identifies environmental quality trends over time, potential routes of microbiological contamination, and allows for implementation of corrective actions to prevent microbiological contamination.

6.1 General Monitoring Requirements
The goals of an air and surface monitoring program are to determine whether microbiological contamination is present at unacceptable levels within ISO classified spaces and to assess whether proper personnel practices are being followed, cleaning and disinfecting agents are effective, and environmental quality is maintained. The microbiological air and surface monitoring program must include viable airborne and surface sampling.

Air and surface sampling must be conducted during actual or simulated dynamic operating conditions within ISO classified environments to confirm that the required environmental quality in ISO classified areas is maintained. In addition to the specific sampling frequencies described in this section, sampling must be performed in any of the following circumstances of an ISO classified space:

- In conjunction with the certification of new facilities and equipment
- In conjunction with relocation of the PEC
- After any modification of facilities or equipment
- In response to identified problems (e.g., positive growth in sterility tests)
- In response to identified trends (e.g., repeated positive gloved fingertip sampling results or failed media-simulation testing involving more than one operator where a review of the operator technique shows no reasonable flaws in process; repeated observations of air or surface contamination)
- In response to changes that could impact the controlled area environments (e.g., significant change in cleaning process or the agents involved)

To obtain an air and surface sample that is representative of the typical aseptic operating conditions at the facility, air and surface sampling must be conducted under dynamic or simulated dynamic operating conditions in all PECs.

The air and surface monitoring program must be clearly described in the facility's procedures and must include a diagram of the sampling locations, SOPs for collecting samples, frequency of sampling, number of samples, and action levels that will trigger corrective action. The locations of sampling should be carefully selected based on their relationship to the activities performed in the area. It is important to obtain
samples from locations that pose the highest possible contamination risk to the operation's processes and that are likely to be representative of the conditions throughout the area.

Evaluating results collected over a period of time can be useful in identifying trends or determining that a significant change has occurred, even when the results fall within the specified limits.

If using air-sampling devices to perform this monitoring, it is important that personnel who operate the equipment be trained in the proper operation of the air and surface sampling equipment to ensure accurate and reproducible sampling. All air sampling devices must be serviced and calibrated as recommended by the manufacturer.

6.2 Monitoring Air Quality for Viable Airborne Particles

A monitoring program for viable airborne particles must be developed and implemented to assess microbiological air quality in all ISO classified areas.

6.2.1 Viable Air Sampling: Timing and Locations

Volumetric active air sampling of all classified areas (e.g., ISO Class 5 PEC) using an impaction device must be conducted during dynamic operating or simulated operating conditions at least every 6 months. Unless validated otherwise, viable air sampling must include:

- Follow the manufacturer’s instructions for operation of the air sampling device, including placement of media.
- Using the sampling device, test at least 1 m³ or 1000 L of air from each location sampled.
- At the end of the sampling, retrieve the media plates/devices and cover.
- Invert the media and incubate at 30°–35° for no less than 48 h. Examine for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu/m³ of air on an environmental sampling form based on sample type (i.e., viable air). Include sample location and date.
- Incubate the inverted media at 20°–25° for no less than 5 additional days. Examine the media plates for growth. Record the total number of discrete colonies of microorganisms on each plate as cfu/m³ of air on an environmental sampling form based on sample type (i.e., viable air). Include sample location and date.

Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location and incubated concurrently. Both samples could be TSA or one sample could be TSA and the other fungal media [e.g., Malt Extract Agar (MEA) or Sabouraud Dextrose Agar (SDA)]. Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 h, and incubate the other sample at 20°–25° for no less than 5 days. Fungal media samples must be incubated at 20°–25° for no less than 5 days. Count the total number of discrete colonies of microorganisms on each and record these results as cfu per sample.

Record the results of the sampling on an environmental sampling form based on sample type (i.e., viable air) and include the sample location, and sample date. CoA(s) from the manufacturer must verify that the medium meets the expected growth promotion, pH, and sterilization requirements. Samples must be incubated in a temperature monitored incubator with a calibrated measuring device. The incubator temperature must be monitored during incubation, either manually or by a continuous recording device, and the results must be reviewed and documented. All sampling activities must be performed by trained individuals.

6.2.2 Data Evaluation and Action Levels

Evaluate cfu counts against the action levels in Table 2 and in relation to previous data to identify adverse results and/or trends. If two pieces of media were collected at a single location, all recovered growth on each must be documented and action levels are applied individually to each plate/device (i.e., results from each cubic meter of air sampled must be compared to the action level for that area). Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective. If levels measured during the viable air monitoring program exceed the levels in Table 2 for the ISO classification levels of the area sampled, the cause must be investigated and corrective action must be taken. The corrective action plan must consider the cfu count and the microorganism recovered. Some examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair. The extent of the investigation should be consistent with the excursion and should include an evaluation of trends. The corrective action plan must be documented. If levels measured during viable air sampling exceed the levels in Table 2, an attempt must be made to identify any microorganism recovered to the genus level (see Microbial Characterization, Identification, and Strain Typing (1113)) with the assistance of a qualified individual (e.g., microbiologist or industrial hygienist).

Table 2. Action Levels for Viable Airborne Particle Air Sampling

<table>
<thead>
<tr>
<th>ISO Class</th>
<th>Air Sampling Action Levels [cfu/m³ (1000 L) of air per plate]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>&gt;1</td>
</tr>
<tr>
<td>7</td>
<td>&gt;10</td>
</tr>
<tr>
<td>8</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location and incubated concurrently.

**7.2 Reusable Cleaning Tools**

Reusable cleaning tools must be made of cleanable material. If used, contact plates must have a raised surface. Sterile swabs wetted with sterile water, or a sterile neutralizing buffer, may be used when sampling irregular surfaces and difficult-to-reach locations, such as crevices, corners, and spaces between surfaces. After sampling, the sampled area must be thoroughly cleaned and disinfected. All sampling processes must be appropriate for the surfaces involved.

Use the following procedures for surface sampling on flat surfaces:

1. Incubate the surface sampling devices at 30°–35° for no less than 48 h. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu/sample on an environmental sampling form based on sample type (i.e., surface). Include sample location and date.
2. Incubate the device at 20°–25° for no less than 5 additional days. Examine the media plates for growth. Record the total number of discrete colonies of microorganisms (cfu/sample) on the environmental sampling record based on sample type (i.e., surface). Include sample location and date.

Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location and incubated concurrently.

1. Both samples could be TSA or one sample could be TSA and the other fungal media (e.g., MEA or SDA).
2. Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 h and incubate the other sample at 20°–25° for no less than 5 days.
3. If fungal media are used as one of the samples, incubate the fungal media sample at 20°–25° for no less than 5 days.
4. Count the total number of discrete colonies of microorganisms on each sample, and record these results as cfu per sample.
5. Record the results of the sampling on an environmental sampling form based on sample type (i.e., surface sample), and include the sample location, and sample date.

**6.3.3 Data Evaluation and Action Levels for Monitoring Surfaces**

Evaluate cfu counts against the action levels described in approved procedures and examine counts to identify adverse results or trends. If levels measured during surface sampling exceed the levels described in approved procedures, an attempt must be made to identify any microorganism recovered to the genus level (see [1113]) with the assistance of a qualified individual (e.g., microbiologist or industrial hygienist). The cause must be investigated, and corrective action must be taken. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective. The corrective action plan must consider the cfu count and the microorganism recovered. Examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair. The extent of the investigation should be consistent with the excursion and should include an evaluation of trends. The corrective action plan must be documented.

**6.4 Corrective Action Planning**

Examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair. The extent of the investigation should be consistent with the excursion and should include an evaluation of trends. The corrective action plan must be documented.

**6.5 Corrective Action Planning**

Use the following procedures for surface sampling on flat surfaces:

1. Incubate the surface sampling devices at 30°–35° for no less than 48 h. Examine for growth. Record the total number of discrete colonies of microorganisms on each media device as cfu/sample on an environmental sampling form based on sample type (i.e., surface). Include sample location and date.
2. Incubate the device at 20°–25° for no less than 5 additional days. Examine the media plates for growth. Record the total number of discrete colonies of microorganisms (cfu/sample) on the environmental sampling record based on sample type (i.e., surface). Include sample location and date.

Alternatively, to shorten the overall incubation period, two samples may be collected for each sample location and incubated concurrently.

1. Both samples could be TSA or one sample could be TSA and the other fungal media (e.g., MEA or SDA).
2. Incubate each sample in a separate incubator. Incubate one sample at 30°–35° for no less than 48 h and incubate the other sample at 20°–25° for no less than 5 days.
3. If fungal media are used as one of the samples, incubate the fungal media sample at 20°–25° for no less than 5 days.
4. Count the total number of discrete colonies of microorganisms on each sample, and record these results as cfu per sample.
5. Record the results of the sampling on an environmental sampling form based on sample type (i.e., surface sample), and include the sample location, and sample date.

**6.6 Corrective Action Planning**

Evaluate cfu counts against the action levels described in approved procedures and examine counts to identify adverse results or trends. If levels measured during surface sampling exceed the levels described in approved procedures, an attempt must be made to identify any microorganism recovered to the genus level (see [1113]) with the assistance of a qualified individual (e.g., microbiologist or industrial hygienist). The cause must be investigated, and corrective action must be taken. Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective. The corrective action plan must consider the cfu count and the microorganism recovered. Examples of corrective action include process or facility improvements, personnel training, cleaning and disinfecting, or HEPA filter replacement and/or repair. The extent of the investigation should be consistent with the excursion and should include an evaluation of trends. The corrective action plan must be documented.

**7. CLEANING AND DISINFECTING**

PECs and any other ISO classified areas must be cleaned/disinfected in accordance with the facility’s procedures. At a minimum, PECs must be cleaned/disinfected each day prior to use and the process must include sterile 70% IPA. Sterile 70% IPA must be allowed to dry prior to initiating aseptic processing activities. A sporicidal agent must be used in the PEC and all classified areas at least monthly. Contact time must align with the manufacturer’s recommendations or other validated time. All cleaning and disinfecting processes must be documented according to facility procedures.

**7.1 Cleaning Supplies**

All cleaning supplies (e.g., wipers and mop heads), with the exception of tool handles and holders, must be low-lint and should be disposable. If disposable cleaning supplies are used, they must be discarded after each cleaning activity. Reusable cleaning tools must be made of cleanable

materials (e.g., no wooden handles) and must be cleaned and disinfected before each use, and if applicable, after each use. Reusable cleaning tools must be dedicated for use in the classified areas and must not be removed from these areas except for disposal. They must be discarded after an appropriate amount of time, to be determined based on the condition of the tools. Cleaning supplies and solutions used should be monitored for radioactive contamination after use and prior to disposal, as per facility SOPs.

### 7.2 Disinfecting Supplies for ISO Classified Areas

No shipping carton(s) or other corrugated or uncoated cardboard are allowed within the ISO classified areas. Before items are introduced into an ISO classified area, they must be wiped with a sporicidal agent, EPA-registered (or equivalent) one-step disinfectant cleaner, or sterile 70% IPA using low-lint wiper. After the sporicidal or sterile disinfectant is applied onto the surface, the agent must be allowed to dwell on the surface for the minimum contact time specified by the manufacturer. If sterile 70% IPA is used, it must be allowed to dry. In the case of radiopharmaceuticals being processed by remote means in a hot cell, the opening of sterile packages (e.g., syringes, Luer lock caps) may not be possible by remote means within the ISO Class 5 area. In this case, the items may be opened and appropriately labeled outside of the ISO Class 5 environment and placed in disinfected shielding, immediately prior to the forthcoming production activities.

### 7.3 Disinfecting Critical Sites

Critical sites (e.g., vial stoppers) must be wiped with sterile 70% IPA. The critical site must be wiped ensuring that both chemical and mechanical actions are used to remove contaminants. The sterile 70% IPA must be allowed to dry before piercing critical sites.

### 7.4 Cleaning and Disinfecting Items from Patient Care and Procedural Areas

Radiation shielding and equipment used in the production process that is exposed to patient care areas during the process of administration must be cleaned and disinfected before returning to any production area in accordance with the Centers for Disease Control and Prevention guidelines as noncritical equipment requiring low-risk disinfection. Dosage containers (e.g., syringes) that have been used in a patient care area must not be brought back into the processing area unless the container is sealed inside an impervious barrier (e.g., sealed plastic bag) that is disinfected prior to entry in the classified area. Equipment that has been exposed to needles and syringes contaminated with blood-borne pathogens and radioactive materials are considered mixed waste (e.g., syringe shields and syringe carrying containers). This equipment must be cleaned and disinfected through actions regulated by the facilities’ procedures.

### 8. CONTROL OF COMPONENTS, MATERIALS, AND SUPPLIES

Components, materials, and supplies that are used in the production 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/or tests for components, materials, and supplies should be maintained for 1 year after their expiration or for 1 year thereafter. Compliance with written specifications can be demonstrated by inspection of the labeling or inspection of the manufacturer's certificate. 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.

- 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 certificate. 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.

- Membrane filters used with parenteral PET drug products must have a manufacturer's CoA. Examine the CoA for each lot to ensure compliance with written specifications.

- 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 on a defined basis thereafter.
9. PROCESS AND OPERATIONAL CONTROLS

9.1 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 must be established. For PET drug products intended for parenteral administration, specifications must 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 production of each PET drug product must provide the following, as applicable:
   - Incorporate, for each PET drug product intended for parenteral administration, procedure to ensure sterility, including sterile membrane filtration (0.22 µm) or other suitable means of 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 produce PET drug products (e.g., precursors, standards, reagents, stock solutions, etc.)
   - Describe the process and the steps used to produce 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 producing 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 11. Controls and Acceptance Criteria for Finished PET Drug Products), 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 must 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 pre-release tests. Such studies should provide the following:
   - Demonstrate a consistent process that is suitable for the intended production 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 products), 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 the Glossary).
   - 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 must be reviewed periodically (e.g., annually), to ensure they are current. Prior to the implementation of updates, appropriate validation and/or verification must 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 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.

9.2 Operational Controls

The following operational controls must be established and should be summarized in a batch record that is a subset of the master formula for the PET drug product. The batch record should document the routine process and controls for making the PET drug product. A designated person should be responsible for ensuring that these activities are carried out and completed properly. Finalized 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 produce 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 production of the PET drug product. Label components as appropriate for identity and traceability purposes.

3. Execute routine cleaning procedures for equipment and facilities.

4. Manufacture 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 recordkeeping tools should be
verified to ensure traceability, data integrity, accuracy of results for calculations, and so on. The batch record must include the following:

- Lot numbers or other unique identifiers for all components, materials, and supplies used to produce the PET drug product;
- A description of the individual procedures that were followed;
- The initials, signature, or other identifier of the individual indicating that critical steps and processes used to produce 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, as applicable;
- Raw analytical data on each batch of the PET drug product;
- Labeling for the PET drug product (see §4. Labeling);
- 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, signature, or other identifier of the individual 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 initials, signature, or other identifier of the individual who assumes overall responsibility for, and adherence to, the procedures used to produce 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.

9.3 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 must ensure a sterile PET drug product. All aseptically manufactured PET drug products for parenteral administration must be filtered through a sterile membrane filter of 0.22-µm or finer pore size into a closed sterile container or sterilized using other suitable means. 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, endotoxin (i.e., pyrogen)-free, and commercially available components using aseptic technique in a PEC.

9.3.1 Components

The sterile, single-use components used in the aseptically assembled apparatus typically consist of an empty vial, needles, membrane filters, vent needles, syringes, tubing, stopcocks, and perhaps others. If all components are not commercially available presterilized items, then these components must be sterilized by the PET facility and the sterilization processes must be validated. 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 into 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.

9.3.2 Pet Drug Product Vial Assembly

Aseptic techniques must be used in the assembling the PET drug product vial assembly. These operations must be performed in an ISO Class 5 or better environment (see §5.1 Environmental Controls for Parenteral PET Drug Products).

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 non ISO-controlled ambient 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 must be discarded.

9.3.3 Sterility Test Inoculations

Sterility tests must be performed to assess the quality of PET drug products intended for parenteral administration for each batch or QC sub-batch as described in procedures and master production records. 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 containers with a screw-cap opening, the inoculation should be performed in the aseptic workstation. Media containers with a septum cap can be inoculated in a shielded area that does not contain a HEPA filter but must be sampled within 30 h of inoculation.

10. STABILITY

Written specifications for the expiration time and storage conditions must be established for each PET drug product. The expiration time must be based on the results of stability testing (and specific activity requirements, as appropriate). Stability testing of the PET drug product must 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 must be examined after a time period equal to the shelf life under defined storage conditions. In addition, the PET drug product must 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 must 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 the stability testing must be documented.

11. CONTROLS AND ACCEPTANCE CRITERIA FOR FINISHED PET DRUG PRODUCTS

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

Written procedures must be developed for QC tests. QC and documentation requirements must be established for each batch or sub-batch of a PET drug product (see 9, Process and Operational Controls). All QC tests must be executed by qualified and trained personnel according to written procedures.

The short half-life of some PET radionuclides frequently precludes the completion of all QC tests before shipment of the PET drug product. This is acceptable as long as the QC tests required for release of the PET drug product for human administration (see 11.1 Quality Control Tests) are completed before administration. The controls used in the release for distribution must be previously established in writing and 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 must be verified to demonstrate that the test works under the conditions of actual use. Non-compendial test procedures used in the testing of a PET drug product must be reliable and specific. Supporting data for use in all analytical methods must 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 must be documented.

11.1 Quality Control Tests

The QC tests used for each PET drug product must be established prior to batch release for administration. The following QC tests may be considered, as appropriate:

1. Appearance by visual inspection for color and clarity (absence of particulate matter) 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 (e.g., half-life measurement or gamma spectrometry).
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, manufacture an initial QC sub-batch that is representative of successive sub-batches manufactured 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.

11.2 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., $^{124}$I, $^{64}$Cu, $^{76}$Br, $^{89}$Zr), consider the measurement of radionuclidic purity by gamma spectrometry. Periodic quality indicating tests for PET drug products may be considered for low-level nontoxic impurities. The periodic testing should be performed at pre-established intervals.

11.3 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 must 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 must 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 must 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.
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 h 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 h before inoculation. It is acceptable to exceed the 30-h 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 the USP–NF (see Sterility Tests (71)). Samples must be tested individually.

11.4 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:

- 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.
- Confirm that the acceptance criteria are met for all other QC tests for the batch.
- Retain a sample of the conditionally released batch.
- Promptly correct the malfunction of the testing equipment.
- 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.
- If the sample fails the omitted QC test, immediately notify the physician or facility that received the PET drug product.
- 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.

12. 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 product failure, the batch must be rejected and cannot be released for human administration. Segregate the failed 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 established written procedures (see 13. Reprocessing).

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.

13. REPROCESSING

If a PET drug product is rejected as a true product 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;
- Secondary dilution; and
- A second passage through a membrane filter in the event of a failed filter integrity test.

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.

14. LABELING

The labeling of the immediate container for the PET drug product must include:

- The name of the PET drug product, including the dosage form;
- The assigned lot or batch number; and
- Any required caution statements [e.g., for investigational drug, “Caution: New Drug—Limited by Federal (or United States) law to investigational use”] or symbols (e.g., radioactive).

The labeling of the outer shielding for the immediate PET drug container must include:

- The name of the PET drug product, including the dosage form;
• The assigned lot or batch number;
• The date and time of calibration;
• Any required caution statements [e.g., for investigational drug, “Caution: New Drug—Limited by Federal (or United States) law to investigational use”] 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 inactive ingredients);
• The name of the producer where the PET drug product was made or the name of the distributor, and
• Other pertinent information [e.g., “Do not use if cloudy or if it contains particulate matter”; storage condition(s)].

GLOSSARY

Anteroom: An ISO Class 8 or cleaner area with fixed walls and doors where personnel hand hygiene, garbing procedures, and other activities that generate high particulate levels are performed. The anteroom is the transition area between the unclassified area in a facility and the classified buffer area.

Aseptic technique: Methods utilized during the processing of radiopharmaceuticals to keep objects and areas free of microorganisms and thereby minimize infection risk to the patient. It is accomplished through practices that maintain the microbial count at a near irreducible number.

Aseptic workstation: See Primary Engineering Control (PEC).

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).

Biological safety cabinet (BSC) Class II: A Class II BSC is a cabinet with an open front, inward airflow, downward unidirectional HEPA-filtered airflow, and HEPA-filtered exhaust. The BSC is designed to provide worker protection from exposure to biohazardous material and to provide an ISO Class 5 or better environment for preparing sterile radiopharmaceuticals.

Buffer area: An ISO Class 8 or cleaner area with fixed walls and doors where PEC(s) that generate and maintain an ISO Class 5 environment are physically located. The buffer area may only be accessed through the anteroom.

Chemical purity: The fraction of the total chemical species present in the radiopharmaceutical as the specified chemical component(s). A chemical impurity is the presence of an unwanted nonradioactive chemical.

Classified area: An area that maintains an air quality classification based on the ISO guidelines (i.e., anteroom, buffer area). See ISO class.

Cleaning agent: A material for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.

Conditional final release: A final release for patient administration before completion of required tests because of a malfunction of analytical equipment.

Container–closure system: The packaging components that contain or come in contact with the radiopharmaceutical and maintain the integrity of the radiopharmaceutical contained within. Examples include (but are not limited to) vials and syringes.

Critical site: A location that includes any component or fluid pathway surface (e.g., vial septa, injection ports) or openings (e.g., needle hubs) that, when exposed, is at risk for contamination by direct contact with air (e.g., ambient area or HEPA-filtered), moisture (e.g., oral and mucosal secretions), or touch.

Critical zone: A critical area within the ISO Class 5 PEC where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.

Designated person: One or more individuals assigned to be responsible and accountable for the performance and operation of the radiopharmaceutical processing facility, and for personnel who manufacture, dispense, and repackage radiopharmaceuticals.

Disinfectant: A chemical or physical agent used on inanimate surfaces and objects to destroy microbiological contamination (e.g., fungi, viruses, and bacteria) when used in the appropriate concentrations and for the appropriate contact times. Sporicidal disinfectant agents are considered a special class of disinfectants that also are effective against bacterial endospores and fungal spores.

Dynamic operating conditions: Conditions in the classified area in which operating personnel are present and performing actual or simulated activities. The PEC should contain equipment and materials regularly used for radiopharmaceutical processing (e.g., low-lint absorbent pads, dose calibrator, syringe shields).

Expiration date: The specified date and time beyond which the product must not be administered.

First air: The air exiting the HEPA filter in a unidirectional air stream.

Garb: Gloves, gowns, shoe covers, head (covers ears and all hair) and facial hair covers, masks, and other items designed to reduce particle shedding from personnel, and minimize the risk of microbiological contamination to radiopharmaceuticals.

Hot cell: A device used for the shielding and containment of radioactive materials. The shielding material(s) (e.g., lead) is generally incorporated into the structure of the unit itself. Radiopharmaceutical personnel carry out the majority of the tasks within the hot cell from the exterior of the unit. This is accomplished by the use of remote manipulation systems (e.g., manipulator arms, automated dispensing system) of various designs. Numerous air quality configurations of the hot cell may exist, including integrated HEPA filtration systems to render all or a specified portion (direct processing area) of the device capable of certifying to a controlled ISO Class 5 environment. In other situations, the hot cell offers only radiation protection, and a laminar flow PEC, capable of achieving an ISO Class 5 environment, is placed within the...
enclosure to allow for safe aseptic manipulations. A hot cell may also be referred to by other designations (e.g., shielded isolator with laminar flow, PET dispensing station, manipulator hot cell, shielded isolators for dispensing, radiopharmaceutical dispensing isolator).

**Immediate PET drug container:** A vial, syringe, or other container-closure system that contains the PET drug product.

**ISO class:** A quality classification from the International Organization for Standardization based on quantity and size of particles per unit of air.

**Laminar airflow workbench (LAFW):** An LAFW used for producing radiopharmaceuticals must provide vertical unidirectional HEPA-filtered airflow. In cases where the LAFW is located within the segregated containment area of a hot cell, it is acceptable for a horizontal unidirectional HEPA-filtered airflow pattern to be utilized.

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

**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 produce a PET drug product.

**Low-lint wiper:** A wiper exhibiting few, if any, fibers or other particulates, visible without magnification, which are separate from or easily removed from the wiper material in a dry condition.

**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.

**Media-simulation test:** A simulation used to qualify processes and personnel engaged in sterile radiopharmaceutical manufacturing to ensure that the processes and personnel are able to manufacture PET drug products without microbiological contamination.

**One-step disinfectant cleaner:** A product with an EPA-registered claim (or equivalent) that it can clean and disinfect a nonporous surface in the presence of light to moderate organic soiling without a separate cleaning step.

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

**PET drug substance:** A radioactive substance that exhibits spontaneous disintegration of unstable nuclei by the emission of a positron. The radioactive molecule in a PET drug substance, including nonradioactive carrier, is typically not isolated but is generated in solution as part of the manufacturing process. The radioactive molecule, including nonradioactive carrier, may also be known as the active pharmaceutical ingredient (API). The PET drug substance is typically converted into a PET drug product by membrane filtration and/or the addition of inactive ingredients and excipients.

**PET drug product:** A finished dosage form as described in the approved product documentation (IND, or RDRC, or other approval documentation) that contains a PET drug substance. The purpose of this product is to provide a direct effect in the diagnosis or monitoring of a disease or a manifestation of a disease in humans, as well as monitor the treatment of disease. It may include one or more other inactive ingredients or excipients (e.g., buffers, isotonicity agents, preservatives).

**Potency:** The quantitative measurement of the biological activity of a given product.

**Primary Engineering Control (PEC):** A device or zone that provides an ISO Class 5 air quality environment for sterile processing.

**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.

**Radiochemical purity:** The ratio, expressed as a percentage, of the radioactivity of the intended active radiopharmaceutical ingredient to the total radioactivity of all radioactive ingredients and impurities present in the radiopharmaceutical (see Radioactivity (821)).

**Radionuclidic purity:** The ratio, expressed as a percentage, of the radioactivity of the intended radionuclide to the total radioactivity of all radionuclides in the radiopharmaceutical (see 821).

**Radiopharmaceutical:** See (821). A finished dosage form that contains a radioactive substance in association with one or more other ingredients and that is intended to diagnose, stage a disease, monitor treatment, or provide therapy. A radiopharmaceutical includes any nonradioactive reagent kit or radionuclide generator that is intended to be used in the preparation of any such substance. The terms “radiopharmaceutical” and “radioactive drug” are commonly used interchangeably.

**Shielding:** Barriers of appropriate radiation attenuating material, used for radiopharmaceuticals, to protect the personnel. These barriers can be general in nature (e.g., L-block, hot-cell), as to afford protection from a radiation field, or specific to a container used to hold a particular radiopharmaceutical (e.g., syringe shield, vial shields, “pigs”).

**Specific activity:** The radioactivity of a radionuclide per unit mass of the compound involved with the radionuclide (see Radioactivity—Theory and Practice (821)). The units of specific activity involve those for the activity (e.g., mCi, MBq, Ci, GBq) and those for the unit of mass (e.g., µg, mmol); expressed on an activity per mass basis (e.g., mCi/µg, MBq/µg, Ci/mmol, GBq/mmol).

**Sporicidal agent:** A chemical or physical agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.
Sterility: The absence of viable microorganisms.

Strength: The radioactivity concentration of the radiopharmaceutical at the calibration time (see (821)). Strength is expressed as the quantity of radioactivity on a volume basis (e.g., mCi/mL or 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., $^{15}$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\(^\text{a}\) (USP 1-May-2025)

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