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REF: 5-98-014-P

Dear Dr. Valentino:

This letter is in regard to General Chapter <823>, Radiopharmaceuticals for Positron Emission Tomography, which appeared in the Eighth Supplement to USP 23 on pages 4326-4327. Attached is a copy of our proposed changes to the text of this chapter.

As USP recognized by moving the PET compounding chapter to the mandatory portion of the General Chapters, the PET chapter has acquired considerable regulatory importance under the Food and Drug Administration Modernization Act. Until FDA adopts approval procedures and current good manufacturing practices (CGMPs) specifically for PET drugs, the Agency may not require the submission of either a new drug application or an abbreviated new drug application for a PET drug that complies with USP standards and monographs for PET compounding. Consequently, it is essential that the USP's PET compounding standards be designed to ensure the identity, strength, quality, and purity of these products. In addition, to the extent possible, the USP chapter should be consistent with the Agency's approach to approval procedures and CGMPs for PET drugs, although this approach is still under development. We are, therefore, suggesting certain revisions that we believe will clarify and enhance certain aspects of the chapter in a manner consistent with the Agency's current thinking on these matters. We will inform the USP of any further developments in our regulatory policies on PET drugs.

Although a section-by-section discussion of our suggested revisions follows, we wish to highlight certain issues that we believe are of special importance to this General Chapter. Because the preparation of a PET drug is a very complex operation, the

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General Chapter should ensure that PET centers have highly qualified and trained personnel to supervise and perform compounding and quality control activities. We also believe that the chapter should be revised to require additional documentation of the materials and processes used in the compounding, packaging, and testing of a batch of a PET drug. In addition, the chapter should require additional release testing to ensure drug product identity, purity, and quality. FDA officials observed such testing at a recent visit to a PET facility and we believe that it will not impose an unreasonable burden on PET centers.

The chapter should state that manufacturers of critical components must be qualified, which we regard as being capable of producing an item of known quality in a consistent and reliable manner. Moreover, PET drug compounders should be required to obtain certificates of analysis (COAs) demonstrating compliance with specifications from manufacturers of components, containers, closures, and materials used in compounding. As to determining the identity of components and other items, we do not believe the reaction-based testing procedure, as described, is based on sound scientific criteria. We also believe that the chapter should be revised to include additional requirements for determining the stability of components and materials used in PET compounding that are potentially susceptible to degradation.

We think it may cause confusion to refer to “routine PET compounding” (in the fourth section) because there is no clear conception of what constitutes “routine” compounding. Therefore, we suggest that the heading be changed to “PET Radiopharmaceutical Compounding for Human Use.”

We also are suggesting changes in the quality control section to clarify requirements for sterility and endotoxin testing. This section also should be revised to ensure that analytical equipment used for quality control testing of PET drugs is operated in accordance with relevant USP requirements. In addition, we recommend that “routine batches” for quality control testing be changed to “each batch” because routine can be interpreted in various ways.

Following is a section-by-section analysis of the changes that we are proposing to the General Chapter on PET compounding. The revised text also contains some minor self-explanatory revisions. Please refer to the revised text for the entire compilation of changes that we recommend.

1. Introduction

- In the second paragraph, “are then synthetically incorporated” should be changed to “may be synthetically incorporated” because some PET radiopharmaceuticals are prepared other than by incorporation of the radionuclide, e.g., those produced by in-target preparation.
- In the third paragraph, a reference to USP chapter <1211> Sterilization and Sterility Assurance of Compendial Articles should be added because this chapter contains procedures which are necessary in the aseptic preparation of PET radiopharmaceuticals.

2. Control of Components, Materials and Supplies

- The first sentence states that “The following activities are to be established or performed...” This should be changed to “established and performed...” We also urge that the second sentence be amended to ensure that all persons involved in performing and supervising the activities possess the necessary qualifications to carry out their assigned responsibilities. We suggest addition of the descriptive phrase “qualified and trained” after “designated.” Corresponding revisions should be made elsewhere in the introductory paragraphs of **Compounding Procedure Verification, PET Radiopharmaceutical Compounding for Human Use, and Quality Control.**
- Item (1) states, “Establish written specifications for the quality of components (including ingredients, reagents, target solutions, and gases), containers and closures, and other materials (e.g., transfer lines, purification devices, membrane filters) that come in contact with the final PET radiopharmaceutical...” In our opinion, the written specifications should also establish the identity and purity of components. Additionally, identity and quality criteria for containers and closures and other materials, as defined above, should be established.
- Under item (1), second bullet, identity and purity criteria should be established for analytical and other quality control supplies. While the identity may need to be established in-house, the purity and quality

criteria may be satisfied from the vendor's results provided in the supplied COA. Further, the analytical supplies may include reference materials, for which written specifications should establish identity, purity (if used in quantitative methods), and quality criteria (e.g., USP or NIST reference material).

- Under item (2), first sentence, we recommend addition of text to state that each lot of shipment must be logged. The revised text would read, "Log in each lot of shipments of components...." Corresponding changes should be made in item (3).
- Under item (2), the second sentence states, "If no expiration date is designated by the manufacturer, an expiration date is to be assigned to the component, material or supply based on knowledge of its physical properties and prior experience with its use." We propose to add the following: "For organic substrates, reactants, and reagent materials that are potentially susceptible to degradation or change in their composition, the expiration date should be based on the component's documented evidence of stability." This is important because an organic substrate that is susceptible to hydrolysis in the presence of moisture may be more susceptible to degradation in a region of higher-than-average humidity. Also, in the enrichment of isotopic target material changes (e.g., $H_2^{16}O$ in $H_2^{18}O$), side reactions would produce more radionuclidic impurities (in the above case, contamination of F-18 with N-13).
- Under item (3), first sentence, we recommend addition of text to require that each batch of components, etc., be checked for compliance with written specifications.
- Under item (3), second sentence, we recommend that the critical component manufacturers also be required to be "qualified." Further, the incoming components must be accompanied by a supplier's COA. In our experience, manufacturers of products intended for the pharmaceutical market usually issue a COA upon request. Therefore, we urge deletion of "If possible," from the beginning of the second sentence.

- The fourth and fifth sentences of item (3) state as follows: “The identities of components, containers and closures, and materials used in the compounding of PET radiopharmaceuticals are to be verified by an appropriate, documented mechanism. In lieu of extensive analytical testing, a reaction-based analytical procedure can be established, which would capitalize on the fact that if wrong components or materials are used in the synthesis of the PET radiopharmaceutical, the next intended step would not transpire or the finished product would not meet its specifications.” We urge deletion of the latter sentence, with subsequent revision of other text to correspond to the deletion, because there is no scientific basis for this statement. Consider the following examples that would be inconsistent with the described philosophy:
 - (1) In the case of nucleophilic synthesis of fludeoxyglucose F-18 Injection (FDG), a group in place of triflate may be used in the mannose triflate raw material. The different leaving group may give the appearance of yielding pure F-18 FDG, as radiochemically identified by the test described in the USP monograph. In fact, depending on the nature of the leaving group, the proportion of reaction occurring through the SN1 and SN2 reactions may be different. In the case of the triflate, only the SN2 reaction occurs. If the SN1 reaction were to occur, F-18 fluorodeoxymannose would be produced. The USP radiochemical purity test method may not be able to tell if any mannose is present. According to the USP test, the starting material would be identified as the same, even though it is different.
 - (2) Again, in the case of FDG synthesis (which may be regarded as representative of other products), a number of organic solvents are used in the purification process. If an incorrect solvent is used, the product would still be extracted, as long as the polarities of the solvents are similar. However, as there are no provisions to test for organic solvents or impurities in the quality control section, contamination of the product would not be detected. This would lead to administration of an adulterated product. Under the approach described above, PET manufacturers would still think that they had a satisfactory product.

3. **Compounding Procedure Verification**

- Item (1) includes the phrase “Written minimum acceptance criteria....” We believe that “minimum” should be deleted because it is redundant. Acceptance criteria (i.e., limits) are the minimum standards that a product should meet. Corresponding deletions should be made elsewhere in Item (4), in the second sentence under **Stability Testing and Expiration Dating**, and under **Quality Control** in Items (1) and (5).
- Under Item (2), introductory phrase, “verified” should be added after “Written” to indicate that the procedures used for compounding must be verified before they can be used.
- Under Item (2), bullet 3, we recommend editorial changes to clarify the requirements for documentation of compounding procedures.
- Under Item (3), software available “for use” should be changed to software available “and used.” Only current versions of software should be used in compounding procedures. “For use” could be interpreted to mean that the current version has to be available but previous versions may be used in compounding procedures.
- Under Item (4), bullet 1, the verification studies also should include, where appropriate, the evaluation of radiochemical identity, stereoisomeric purity, optical purity, osmolality, organic volatile impurities, other toxic chemicals that may have been used in the synthetic and/or purification procedures, and equivalency of sub-batches for PET radiopharmaceuticals with nuclides having a half-life ($T_{1/2}$) of less than 20 minutes. For $T_{1/2} < 20$ minutes, only the first daily batch is normally tested as part of the compounding procedure quality control, and the equivalency of the first and last sub-batch produced during the day must be verified. We also recommend that “absence of” be deleted from “absence of bacterial endotoxins” because their absence or presence cannot be ascertained until the product has been evaluated.

- Under Item (4), bullet 2, the certification that the product meets established acceptance criteria must be available for subsequent review. To indicate this, “and retained” should be inserted after “dated.”
- In the last paragraph, the text should be revised to clarify that verification studies must be performed on consecutive batches. “Consecutive verification studies” could be interpreted to mean that studies could be done on other than consecutive batches.

4. Stability Testing and Expiration Dating

A sentence should be added to specify that stability testing must be performed on product which has been stored in the container/closure system specified for storing the product.

5. Routine PET Radiopharmaceutical Compounding

- In the title, “Routine” can be interpreted in various ways. We recommend that the title be changed to “PET Radiopharmaceutical Compounding for Human Use.”
- In the introduction, the phrase “and documented according to established written procedures” should be added at the end of the first sentence to ensure adequate documentation.
- Under item (1), first sentence, “and suitability” should be added after “cleanliness.” Criteria other than cleanliness (e.g., configuration of materials, components, and equipment) are necessary to ensure the proper functioning of the compounding and dispensing area and all equipment.
- Under item (1), last sentence, “in an appropriately controlled environment (see <1211> Sterilization and Sterility Assurance of Compendial Articles)” should be added after “using aseptic technique.” This would be consistent with procedures in this chapter.

- Under item (2), first sentence, the “Adopt strategies” phrase should be changed to “Document the procedures used.”
- Under item (3), “for identity and traceability” should be inserted after “components” to clarify the intent of the labeling.
- Under item (4), second sentence, the expiry and radioactive concentration should also appear on the label. We recommend insertion of “the expiration date and time, the radioactivity concentration at the time of calibration” prior to “an assigned batch.”
- Under item (5), second bullet, “to be” should be deleted. The written record should contain what actually occurred, not what was supposed to occur.
- Under item (5), the fifth bullet regarding “ad-hoc deviations” should be deleted because it would allow excessive latitude for unverified changes in established procedures.
- Under item (5), sixth bullet, unplanned deviations in established procedures are generally not acceptable. The text should be revised to indicate that deviations must be investigated and the investigation, including its outcome, must be documented. We suggest adding “of the investigation” after “documentation,” changing “unexpected outcomes” to “unexpected results,” changing “processes and” to “processes including,” and deleting “respective event.”
- Under item (5), the following should be added as a bullet between bullets 6 and 7:

the percent yield calculated on the basis of the decay-corrected amount of starting radionuclide that is synthetically incorporated into the final radiopharmaceutical

This language requires the calculation of the yield of the PET radiopharmaceutical when the radionuclide is incorporated in a molecule. It exempts from this requirement methods where the radiopharmaceutical is prepared either (1) in-target or (2) by a

continuous flow method where the flow does not stop outside of the target body.

- Under item (5), the written record also should include the raw data for each batch of the PET radiopharmaceutical.

6. Quality Control

- Under Item (1), for PET radiopharmaceuticals labeled with a nuclide that has a half life of ≥ 20 minutes, routine testing performed on each batch prior to release should also include, where applicable, measurement of stereoisomeric purity, organic volatile impurities, and presence of toxic chemicals (kryptofix, mercury, etc.). We recommend that “batch” be defined here as “the material produced during a single synthesis and purification operation.” When a PET drug is manufactured by an in-target preparation procedure (e.g., F-18 sodium fluoride), the radionuclidic purity should be determined on each batch prior to release.
- Under Item (1), for PET radiopharmaceuticals labeled with a nuclide that has a half life of < 20 minutes, the definition of a batch should state that the compounding of the batch should occur “without any changes to the equipment setup.” Tests for organic volatile impurities, toxic materials, and (where applicable) stereoisomeric purity should be performed prior to the release of a batch. Additionally, when a PET drug is manufactured by an in-target preparation procedure, the radionuclidic purity should be determined for each batch prior to release.
- Membrane filter integrity testing (bullet 3) should be done on the sterilizing filter at each filter change, and filters should be changed with each patient dose because membrane filtration is the critical step for removing microbial contaminants. We recommend that bubble point tests, or equivalent, be required prior to installing each filter. If the filter is defective, the product will require filtration with a different membrane filter. Whether or not the filter is tested before filtration,

membrane filter testing must be performed after filter removal and if the filter fails, the product must be refiltered.

- The sections for sterility and endotoxin testing are confusing and need to be simplified. The recommendations for the testing of batches prior to release are highly complex in that some PET drugs may be tested batch-by-batch while others are tested only as the “Quality Control” sub-batches. The tests themselves change similarly; for example, some LAL tests are read at 20 minutes and some at 60 minutes (Item (1), bullets 4, 5, and 6). Although the separation of criteria for product release testing based on the product’s half-life appears to make sense initially, it becomes very difficult to understand in the text of the document. We recommend deleting bullet 4.
- We believe that LAL tests (bullet 5) should be standardized to 60 minutes for batch release (or QC sub-batches when the radionuclide half-life is <20 minutes). The Agency has no objection to 20-minute readings of the LAL result after data validating the procedure are generated, but the Agency has not seen such data. However, we believe that quality control sub-batches may be tested fully (60-minute reading for LAL) without delaying the release of product for patient administration.
- For sterility testing (bullet 6), the first daily batch (or QC sub-batch) of each PET radiopharmaceutical should be tested. The provision for testing according to a defined periodic interval should be deleted in bullets 5 and 6 because the qualifying phrase “after extensive documentation” is not an objective criterion. Bullet 6 should be revised to state that sterility testing should be performed on the first daily batch of each PET radiopharmaceutical. This amount of testing is suitable because of the special characteristics of these drugs and the safety afforded by appropriate testing of the sterilizing filter integrity (bullet 3).

A limit for delay in sterility testing of product batches should be added to assure that these tests are begun within 24 hours. Some PET facilities have stored sterility samples for a time sufficient to cause potential microbial contaminants to die in some products, which would yield a false satisfactory sterility result. A requirement that the tests be

conducted on individual batches rather than pooled batches also should be added.

- Item (3) states, “Using internal or external standards, the correct operation of the analytical equipment (e.g., gas chromatography or high performance liquid chromatography) must be confirmed upon installation, change of columns, or solvent systems, or upon major repairs.” We do not believe this is adequate to ensure optimal operation of the analytical equipment. The following phrase should be added as the third sentence: “Correct operation of analytical equipment also must be checked and maintenance performed according to appropriate written scheduled procedures.”

We also recommend addition of a reference to <621> **Chromatography (System Suitability)** which specifies that appropriate system suitability tests and acceptance criteria should be established for each analytical procedure. The system suitability test should be performed prior to performance of each analytical procedure to ensure optimal functioning of the equipment. This approach would be consistent with the USP recommendations in chapter <621>, which states, “To ascertain the effectiveness of the final operating system, it should be subjected to a suitability test prior to use and during testing, whenever there is a significant change in equipment, or in a critical reagent, or when a malfunction is suspected.”

- Under item (4), “routine batches” should be changed to “each batch.” Batches for PET radiopharmaceuticals with $T_{1/2} \geq 20$ minutes or ≤ 20 minutes are defined under **Quality Control**, item (1), bullets 1 and 2. Use of the word “routine” would allow excessive latitude in the interpretation of which batches to test.

<823> RADIOPHARMACEUTICALS FOR POSITRON EMISSION TOMOGRAPHY - COMPOUNDING

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

Radiopharmaceuticals administered for positron emission tomography (PET) procedures typically incorporate radionuclides that possess very short physical half-lives, $T_{1/2}$ (e.g., $T_{1/2}$ of ^{18}F = 110 minutes, of ^{11}C = 20 minutes, of ^{13}N = 10 minutes, and of ^{15}O = 2 minutes). As a result, these radionuclides are usually produced using particle acceleration techniques (e.g., cyclotron) at or within close proximity to the site where the PET procedure will be conducted. The radionuclides are ~~may~~ then ~~be~~ synthetically incorporated into the final PET radiopharmaceutical for subsequent patient ~~adrtation~~ ~~administration~~.

The following requirements address the compounding of PET radiopharmaceuticals for human use (see also *Automated Radiochemical Synthesis Apparatus* <1015> ~~and~~ ~~Sterilization and Sterility Assurance of Compendial Articles~~ <1211>).

Control of Components, Materials and Supplies

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

- (1) Establish written specifications for
 - the ~~identity, purity, and~~ quality of components (including ingredients, reagents, target solutions, and gases), ~~identity and quality of~~ containers and closures, and other materials (e.g., transfer lines, purification devices, membrane filters) that come into contact with the final PET radiopharmaceutical;

- the ~~identity, purity, and~~ quality of analytical supplies (e.g., solvents, chromatography columns, ~~reference materials~~), sterility test media, endotoxin test reagents, and other supplies intended for use in PET radiopharmaceutical quality control procedures; and
 - the appropriate storage (i.e, based on heat, light, and humidity considerations) of components, containers and closures, materials and supplies used for the compounding of PET radiopharmaceuticals.
- (2) Log in ~~each lot of~~ shipments of components, containers and closures, materials, and supplies used for the compounding of PET radiopharmaceuticals, and record the date of receipt, quantity received, manufacturer, lot number, and expiration date. If no expiration date is designated by the manufacturer, an expiration date is to be assigned to the component, material, or supply based on knowledge of its physical and chemical properties and prior experience with its use. ~~For organic substrates, reagents and reagent materials that are potentially susceptible to degradation or a change in the composition, the expiration date should be based on the component's documented evidence of stability.~~
- (3) Determine that ~~each lot of~~ components, containers and closures, materials, and supplies used for the compounding of PET radiopharmaceuticals are in compliance with established written specifications. For critical components, a single ~~qualified~~ manufacturer should be routinely used as the source of a given product. ~~If possible, certification~~ ~~Certification~~ of ~~compliance with~~ the specifications of components, containers and closures, and materials used in the compounding of PET radiopharmaceuticals are obtained from the respective manufacturer. The identities of ~~each lot of~~ components, containers and closures, and materials used in the compounding of PET radiopharmaceuticals are to be verified by an appropriate, ~~tests and / or~~ documented mechanisms ~~as appropriate~~. ~~In lieu of extensive analytical testing, a reaction-based testing procedure can be established, which would capitalize on the fact that if the wrong components or materials are used in the synthesis of the PET radiopharmaceutical, the next intended step would not transpire or the finished product would not meet its specifications.~~
- (4) Store components, containers and closures, materials, and supplies used for the compounding of PET radiopharmaceuticals in a controlled access area according to established storage conditions.

Compounding Procedure Verification

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

- (1) Written ~~minimum~~ acceptance criteria for the identity, purity, and quality of each PET radiopharmaceutical being compounded. If a USP monograph exists for a particular PET ~~radiopharmaceutical~~, then these standards are the ~~minimum~~ acceptance criteria (see *Official and Official Articles* under the *General Notices*).
- (2) Written ~~verified~~ procedures for the compounding of each PET radiopharmaceutical that
 - incorporate, for each PET radiopharmaceutical intended for parenteral administration, sterile membrane filtration (0.22 μm);
 - incorporate, for each PET radiopharmaceutical intended for inhalation, particulate filtration (0.45 μm); and
 - are routinely updated and verified as changes in the compounding procedures are implemented or are reviewed and verified at a minimum of once a year to ensure that they are current. A master file of ~~current~~ written compounding procedures ~~currently used~~ for each PET radiopharmaceutical is to be maintained within the PET facility. ~~Outdated~~ Copies of written ~~outdated~~ compounding procedures shall also be retained, separate from the master file, for review purposes.
- (3) Appropriate controls over computer and related automated equipment to ensure that changes in compounding software are instituted only by authorized personnel, that such changes are documented and verified, and that only current versions of the software are available for use ~~and used~~ in PET radiopharmaceutical compounding procedures. A diskette copy and printout of current computer software programs used in the compounding of each PET radiopharmaceutical is to be maintained within a master file located in the PET facility. Outdated copies of computer software programs shall also be retained, separate from the master file, for review purposes.
- (4) Verification studies to ensure that the written compounding procedures, computer software program, equipment, and facilities result in a PET radiopharmaceutical that meets established ~~minimum~~ acceptance criteria. Such verification studies must

- include evaluations of the radiochemical ~~identity and~~ purity, radionuclidic identity and purity, specific activity, sterility (for parenteral agents), ~~absence of bacterial endotoxins (for parenteral agents), pH, osmolality (for parenteral agents), appearance, stereoisomeric purity (for stereoisomeric compounds), optical purity, organic volatile impurities, other toxic chemicals that may have been used during the synthetic or purification procedure,~~ and chemical purity of the PET radiopharmaceutical [NOTE - Evaluations for chemical purity must include analyses for the presence of starting materials, known intermediates, and known degradation products], ~~and equivalency of sub-batches (for PET radiopharmaceuticals with radionuclides having a $T_{1/2} < 20$ minutes)~~
- be signed and dated ~~and retained~~ as an indication that the compounding procedures, equipment, and facilities have resulted in a PET radiopharmaceutical that meets established ~~minimum~~ acceptance criteria.

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

Stability Testing and Expiration Dating

Written specifications for the expiration dating and storage conditions of each PET radiopharmaceutical are to be established based on the results of stability testing and specific activity considerations. ~~the stability test specimen must be taken from product stored in the same container/closure system specified for storing the product.~~ The PET radiopharmaceutical must meet all ~~minimum~~ acceptance criteria at expiry.

Routine PET Radiopharmaceutical Compounding ~~for Human Use~~

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

(1) Inspect the compounding and dispensing area and all equipment for cleanliness and suitability immediately before use. Before initiating compounding and dispensing activities, extraneous materials and labels must be removed from involved areas and equipment. For PET radiopharmaceuticals intended for parenteral administration, all manipulations of components, containers and closures, and materials distal to sterile membrane filtration must be performed using aseptic technique in an appropriately controlled environment (see <1211> Sterilization and Sterility Assurance of Compendial Articles).

(2) Adopt strategies Document the procedures used to ensure the correct identity, quantity, and suitability of components, containers and closures, and other materials used in compounding the PET radiopharmaceutical.

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

(4) Label the final PET radiopharmaceutical containers or dispensing-administration assembly prior to initiating the compounding procedure. The following information must appear on the label attached to the final container or dispensing-administration assembly; the identity of the PET radiopharmaceutical, the expiration date and time, the radioactivity concentration at time of calibration, an assigned batch or lot number, and the required warning (e.g., radioactive) statements or symbols.

(5) Compound the PET radiopharmaceutical according to current, verified procedures. A written record must be maintained for each batch of the compounded PET radiopharmaceutical. This written record includes

- lot numbers, manufacturer identities, expiration dates, and quantities of all components, containers and closures, and materials used in the compounding procedure;
- a description of the individual compounding procedures to be followed;
- the initials of the responsible individual indicating that the compounding procedure for the batch is an accurate reproduction of the current, verified compounding procedure;
- the initials of the responsible individual indicating that critical steps and processes in the compounding procedure were completed [NOTE - Critical steps in automated compounding processes shall be monitored through direct observation (if possible, considering visual or radiation exposure constraints) or via computer or other feedback mechanisms];

- documentation of any ad-hoc deviations from the current, verified compounding procedure, including the rationale for such deviations;
- documentation of the investigation of any unplanned deviations in, or unexpected outcomes results of, verified compounding procedures or processes and including the outcome of respective event the investigations; and
- the percent yield calculated on the basis of the decay-corrected amount of starting radionuclide that is synthetically incorporated into the final radiopharmaceutical;
- raw analytical data on each batch of compounded PET radiopharmaceutical; and
- the date and the signature of the individual assuming overall responsibility for, and adherence to, the verified compounding procedure.

Quality Control

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

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

- For PET radiopharmaceuticals labeled with a nuclide having a $T_{1/2} \geq 20$ minutes, the following quality control procedures are to be performed on each batch of the material produced during a single synthesis and purification operation prior to release: measurement of the pH of parenteral and oral dosage forms; visual inspection of the parenteral and oral dosage forms; determination of the radiochemical purity and identity of all dosage forms; determination of the radionuclidic identity (all radiopharmaceuticals) radionuclidic purity (for final radiopharmaceuticals prepared by in-target procedures) of all dosage forms, stereoisomeric purity (for stereoisomeric compounds), organic volatile impurities and other toxic chemicals that may have been used during the synthetic or purification procedure for all dosage forms, and assessment of the specific activity of PET radiopharmaceuticals with mass-dependent localization or toxicity concerns.

- For PET radiopharmaceuticals labeled with a nuclide having a $T_{1/2} < 20$ minutes, a batch is defined as all preparations (i.e., sub-batches) of the PET radiopharmaceutical compounded during a given day ~~without any changes to the equipment setup~~. The following quality control procedures are to be performed on an initial quality control sub-batch of each such PET radiopharmaceutical: measurement of the pH of parenteral and oral dosage forms; visual inspection of parenteral and oral dosage forms; determination of the radiochemical purity and identity of all dosage forms; determination of radionuclidic identity ~~[all radiopharmaceuticals) and radionuclidic purity (for final radiopharmaceuticals prepared by in-target procedures) of all dosage forms; stereoisomeric purity (for stereoisomeric compounds), organic volatile impurities and other toxic chemicals that may have been used during the synthetic or purification procedure~~ of all dosage forms and assessment of the specific activity of PET radiopharmaceuticals with mass-dependent localization or toxicity concerns.
- For ^{18}F and ^{11}C -labeled ~~each batch of PET~~ radiopharmaceuticals intended for parenteral administration, perform a sterile filter membrane ~~filter~~ integrity test prior to installing the sterilizing filter and ~~immediately~~ after each filter is removed from the processing system on each batch of radiopharmaceutical prior to release of the batch for human use ~~completion of product filtration~~. For ^{13}N -labeled radiopharmaceuticals intended for parenteral administration, perform a sterile membrane integrity test on each sub-batch of the radiopharmaceutical prior to release of the sub-batch for human use. For ^{15}O -labeled radiopharmaceuticals intended for parenteral administration, perform a sterile membrane integrity test after the final sub-batch of the radiopharmaceutical has been prepared for a given patient or research subject.
- For PET radiopharmaceuticals intended for parenteral administration, perform a 20-minute endotoxin test must be performed "limit test" (i.e., incorporating positive controls in the range of 5 EU per mL to 175 EU/V, where V is the maximum volume of injection) on each batch ($T_{1/2} \geq T_{1/2} \geq 20$ minutes) or quality control sub-batch ($T_{1/2} < 20$ minutes) of the radiopharmaceutical prior to release, for human use, of the batch or subsequent sub-batches.
- For PET radiopharmaceuticals intended for parenteral administration, a standard 60-minute bacterial endotoxin test must be performed on each batch ($T_{1/2} \geq 20$ minutes) or quality control sub-batch ($T_{1/2} < 20$ minutes) of the radiopharmaceutical. If, after extensive documentation, the compounding procedure results in a consistently negative outcome, the frequency of

performing the standard bacterial endotoxins test may be reduced to a defined periodic interval.

- ~~Sterility tests for each~~ For PET radiopharmaceuticals intended for parenteral administration should be performed on the first batch of each day, ~~sterility testing must be performed on each batch ($T_{1/2} \geq 20$ minutes) or quality control sub-batch ($T_{1/2} < 20$ minutes) of the radiopharmaceutical. If, after extensive documentation, the compounding procedure results in a consistently negative outcome, the frequency of sterility testing may be reduced to a defined periodic interval. Sterility tests should also be done following replacement of system components. Sterility samples should be tested within 24 hours after preparation. Product samples should be tested individually and should not be pooled.~~

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

(3) Conduct verification testing of equipment and procedures used for the quality control testing of PET radiopharmaceuticals. Using internal or external standards, the correct operation of analytical equipment [(e.g., gas chromatography or high-performance liquid chromatography ~~see USP chapter <621> Chromatography (System Suitability))]] must be confirmed upon initial installation, change of columns or solvent systems, or upon major repair. ~~Correct operation of analytical equipment also must be checked and maintenance performed according to appropriate written scheduled procedures.~~ Dose calibrators used in measuring the bulk radioactivity and the radioactivity of dispensed dosages of PET radiopharmaceuticals should be tested in accordance with applicable state regulations governing the medical use of radioactive materials.~~

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

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

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