SOCIETY OF NUCLEAR MEDICINE & MOLECULAR IMAGING

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USP Executive Secretariat
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA

USP Small Molecules 4 Expert Committee,

We commend the committee for their work in bringing forward this proposed chapter. We welcome this opportunity to provide comment on the proposed USP/NF PF 49(5) ⟨823⟩ "Production of Diagnostic Positron Emission Tomography Drugs for Investigational and Research Uses" draft published in September 2023.

We would like to take this opportunity to reemphasize the origin and development of this chapter in association with the origin and development of FDA cGMP requirements for PET drugs and to illustrate the original FDA position with respect to the original scope of the USP 823 as directed by 1997 Federal Modernization Act and Promulgation of FDA regulation of PET drugs under 21 CFR part 212. Of note is the inaugural FDA position as defined within the inaugural part 212 guidance document in December. 2009: PET Drugs – Current Good Manufacturing Practice (CGMP). This guidance specifically details the appropriateness of less detailed CGMP requirements for investigational and research drugs to allow flexibility during the development of these drugs under USP Chapter 823 as directed in section 212.5 (b) of the 21 CFR part 212 PET Drug regulation.

"Section 212.5(b) gives producers of investigational PET drugs and research PET drugs the option of following the CGMP regulations in part 212 or producing PET drugs in accordance with Chapter <823> of the 32nd edition of the USP (2009). We believe that it is appropriate to have less detailed CGMP requirements for investigational and research PET drugs to allow more flexibility during the development of these drugs. We also recognize that many investigational PET drugs may not have commercial potential."

This position of special consideration for research is developed further within FDA guidance, namely, Current Good Manufacturing Practice (CGMP) (Small Entity Compliance Guide), August 2011

> "Although the provisions in Chapter <823>, including those on documentation, are generally less specific and explicit than the requirements in part 212, we believe that they are adequate to ensure that investigational and research PET drugs are produced safely under appropriate conditions, consistent with section 501(a)(2)(B) of the Act, and

are appropriate CGMP requirements for the investigational and research stage of development."

We believe that the current proposed chapter has moved away from the original intent for the scope of this chapter which was deemed adequate. We recognize that there has been evolution with the establishment of Sterile (USP 797), Non-Sterile (USP 795) compounding chapters and establishment of the radiopharmaceutical compounding chapter's (USP 825) but would point out that these chapter requirements while appropriate for Pharmacy and Practice of Medicine radiopharmaceutical preparation compounding dispensing practice, they should not be unilaterally adapted to PET drug production which operates in the cGMP manufacturing paradigm. Prescriptive direction required by pharmacy and practice of medicine practice is not relevant to the research and investigational drug production where the end product undergoes validated 100% end product quality testing.

To date we know of no documented PET drug patient misadventure from an investigational or research investigational PET drug product produced under the current requirements of the current and previous existing USP 823.

As such we recommend the chapter be reviewed and re-written to a less prescriptive standard as originally envisioned by the FDA as appropriate cGMP requirements for research and investigational PET Drug production.

We also hereby provide specific comments to the proposed chapter,

Chapter Briefing

We agree the chapter title descriptive change to "Production of Diagnostic Positron Emission Tomography Drugs for investigational and Research Uses " better describes the scope of this chapter.

We express a caution to the complete replacement of should with must throughout the chapter when validity of equivalent or superior pathways or techniques may exist that satisfy the intent and goals of this chapter. This complete replacement of must for should is in direct contraposition to following chapter small scale facility allowances statements and may produce restrictive effects on Phase 0 to Phase I of PET drug development in small research-based facilities

Chapter Body

1. **Introduction:**

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)

- Premise:

Unnecessary and out of scope of this chapter, it is covered appropriately in USP 1823

Request removal of statement

1. **Introduction:**

- *Premise:*
  The fundamental challenges of PET Radiopharmaceutical production are notably absent from this introduction. Recognition of the validity of equivalent alternative or superior pathways or techniques that satisfy the intent and goals of Positron Emission Tomography Drugs for Compounding, Investigational, and Research Use is not readily evident in the chapter.

Request change to introduction to include the following statement:

US federal and state radiation regulatory authorities require limiting radiation exposure to personnel who handle radiopharmaceuticals, which necessitates special provisions for radiation protection. The principles of radiation safety involve time, distance, shielding, and radioactive contamination control. Moreover, the use of radiation detection and measuring devices is a necessary component of radiopharmaceutical production procedures. Strict adherence to all typical aseptic handling practices is not possible in many scenarios where radiopharmaceuticals are handled. Thus, it is necessary to balance aseptic handling practices with radiation protection practices (worker safety). This chapter describes appropriate strategies that provide assurance of ensuring the safety of individuals performing these activities. Because radiopharmaceuticals represent a unique class of drugs, the use of techniques, materials, and procedures other than those described in this chapter are not prohibited so long as they are documented to be equivalent or superior to those described herein. USP 823

Introduction:

"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

- *Premise:*
  FDA kit is term is not adequately defined within the chapter remove and redefine as FDA approved drug product.

  Change to:
  - *Preparation of a PET drug product using an FDA-approved radiopharmaceutical drug product*
  - *Compounding of a PET drug product using an FDA- approved radiopharmaceutical drug product*
  - *Dispensing or repackaging of a PET drug product*

2. DOCUMENTATION

"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."

- *Premise:*
  Documentation for visual training could be mis-interpreted to require video recording which is an unnecessary documentation requirement burden.

Change to read:
Personnel training and testing, to include written documentation of 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.

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 purify cation 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."

- *Premise: Incomplete direction, chapter should direct to supporting USP associated chapters and associated references. Training must include review of relevant USP chapters and associated references as called out in this chapter*

Change to:
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 This training should include review of relevant USP chapters such as USP 1823.

3.3 Aseptic Qualification

"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.

- Premise:
  List order is not appropriate. Each skill level is dependent on achieving prior competency.

Change to:

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

3.3 Aseptic Qualification

"Personnel must successfully complete an initial aseptic simulation evaluation for each aseptic process a minimum of three separate times on 3 separate days (see Box1)."

- *Premise = Appropriate requirements for aseptic operations for small scale facilities.*
  For IND / RDRC production sites the 3 separate successive day requirement is burdensome. Allowing more than 1 media fill per day per operator is appropriate considering the burden on small facilities with limited staff.

Change to:
Personnel must successfully complete an initial aseptic simulation evaluation for each aseptic process a minimum of three separate times. (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.

Media-simulation testing must represent worst-case scenarios for aseptic operations.
(Repeats several times throughout the chapter)

- P*remise: Incomplete and unclear direction*
  Include descriptive and include "as appropriate"
  (The term "worst-case scenarios" is subjective and open for interpretation, change all "worst –case scenarios" statements throughout the chapter)

Change to:
Media fill studies should closely simulate aseptic manufacturing operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations.

3.3.1 Gloved Fingertip and Thumb Sampling

- *Premise: Section is poorly written and misleading.*

Change requested: Section should be written to clearly identify aseptic process glove garbing sampling is designated to take place inside the ISO-5 aseptic work area immediately prior to start of aseptic processing and at completion of media-fill simulation testing.

- *Premise: Mandating sterile gloves is a burdensome requirement. Use of certified particulate free clean gloves with sanitization using 70% sterile alcohol is a prior USP 823 accepted practice with qualification and validation through this gloved fingertip and thumb sampling process.*

Change requested:
Add option of sanitized particulate free gloves with validation.

3.4.2 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.

- *Premise = Appropriate requirements for aseptic operations for small scale facilities. For IND / RDRC production sites this retesting schedule is burdensome. Yearly requalification including pauses is appropriate considering the burden on small facilities with limited staff.*

Change to:
After a pause in sterile radiopharmaceutical processing: Personnel who have not performed aseptic operations in more than 12 months must be requalified in media simulation before resuming aseptic operation duties.

4. Quality Assurance

"QC functions include the following:

- Evaluate each lot of incoming material that it meets its established specifications before use in the production or testing of PET drug products."

- *Premise: PET Production facilities are not required to perform testing on each lot of incoming material, use of a certificate of analysis from a trusted vendor is sufficient. The use of the term "Evaluate" is subjective and will lead to incorrect interpretation.*

Change to:

Inspect each lot of incoming material for appropriateness of use through predefined, site specific, metrics. Including the use of Certificates of Analysis/Acceptance or equivalent paperwork from trusted vendors.

5.1.1 Aseptic Primary Engineering Control
"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)."

- *Premise:*
  Unnecessary and potentially confusing direction for addressing potential immediate local area environmental disturbances of an operating PEC. If necessary, a separate direction can identify the location of a PEC within a HOT Cell. It should be noted that the location of a PEC within a Hot Cell effectively satisfies the definition of an isolator.

Suggest Change:

"The PEC must be protected from sources of microbial contamination and be located in an area where personnel traffic is limited when operated. The common configuration of a PEC operating within a Hot Cell provides physical protection against microbial contamination and immediate area personnel traffic while effectively operating as an isolator."

"The proper operation of the PEC must be certified by measurement of airborne particles, HEPA filter integrity testing, and pressure differential testing."

- *Premise = Testing should be specific to type of PEC, Open-faced PEC such as a workstation, laminar airflow workbench (LAFW) or biological safety cabinet (BSC) do not require PD for maintaining an ISO 5 environment.*

Requested Change:
The proper operation of the PEC must be certified according to the specific type of PEC according to the manufacturer recommendations. Certification testing includes measurement of airborne particles, HEPA filter integrity testing, and pressure differential testing as required by specific type of PEC.

5.12 Microbiological testing

"For microbiological testing of the aseptic workstation, the viable air samples must be tested as part of the PEC certification"

- *Premise: Unclear reference to aseptic workstation*

Requested Change:
Change aseptic workstation to ISO Class 5 PEC aseptic processing work area.

"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).

- *Premise = Appropriate requirements for aseptic operations for small scale facilities. For IND / RDRC production sites this retesting schedule is burdensome. Yearly requalification including pauses is appropriate considering the burden on small facilities with limited staff.*

Change to:
For microbiological evaluation of ISO class 5 aseptic processing areas, viable air samples must be tested annually as part of the PEC certification or more frequently in response to documented evidence of recoverable ISO-5 CFU alert levels detected as part of established production environmental monitoring trending.

5.1.4
"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 <u>part of the 6-month certification."</u>

- *Premise:*
  Appropriate requirements for aseptic operations for small scale facilities. For IND / RDRC production sites this retesting schedule is burdensome, and a burden on small facilities with limited staff. Most manufacturers of ISO Class 5 PECs recommend initial dynamic air flow testing and retest only after significant repairs, significant changes to facility air handlers, or after they are moved to a new location.

Requested change:
For the scope of this chapter, initial testing and retest following significant repair, facility air handler changes, or move to a new location is sufficient

5.1.5 Types of PECS and Placement

PEC

- *Premise:*
  Provide a clearer definition for the PEC

Change to: A PEC provides an ISO Class 5 or better environment for aseptic processing of components, and sterile products.

BSC

- *Premise: Change description to include aseptic processing*

Change Requested:
The BSC is designed to provide worker protection from exposure to biohazardous material and to provide an ISO Class 5 or better environment for aseptic processing and preparing sterile radiopharmaceuticals. **Placement of 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."

- *Premise:*
  Appropriate requirements for aseptic operations for small scale facilities. For IND / RDRC production sites this retesting schedule is burdensome, and a burden on small facilities with limited staff. Most manufacturers of ISO Class 5 PECs recommend initial dynamic air flow testing and retest only after significant repairs, significant changes to facility air handlers, or after they are moved to a new location.

Requested change:
For the scope of this chapter, initial testing and retest following significant repair, facility air handler changes, or move to a new location is sufficient.

HOTCELL

" 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 manipulations."

- *Premise:*
  *add - **is***

Requested Change:
*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 Hot Cell enclosure to allow for aseptic processing.*

5.3 Cleaning Equipment and Components

- *Premise:*
  This section should be renamed and separated into 2 sections

Suggested change:

5.3 Equipment

5.3.1 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.

5.3.2 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.

5.4 Facility

Facilities should be arranged and controlled to provide an appropriate working environment. The temperature should be maintained below 25° and must be monitored in the production areas each production day, either manually or by a continuous recording device. Temperature results must be documented, retrievable and reviewed on a routine basis 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.

5.4.1 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.

5.4.2 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.

5.4.3 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.

6.1 General Monitoring Requirements

“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.”

Premise: This statement reads as advice rather than an enforceable regulation.Change to:

Remove this line from the document. This is better suited in a guidance document.

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:

- *Premise = Appropriate requirements for aseptic operations for small scale facilities. For IND / RDRC production sites this retesting schedule is burdensome. Yearly requalification including pauses is appropriate considering the burden on small facilities with limited staff.*

Change to:
For microbiological evaluation of ISO classified areas, and ISO class 5 aseptic processing areas, viable air samples must be tested annually as part of the PEC certification or more frequently in response to documented evidence of recoverable ISO-5 CFU alert levels detected as part of established production process environmental monitoring trending.

6.3.3 Data Evaluation and Action Levels for Monitoring Surfaces

“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).”

- *Premise = This requirement is misleading it must be rewritten to acknowledge the scope of risk. Genus level identification requirement should be limited to environmental monitoring of the PEC ISO Class 5 PEC aseptic work area. Genus level identification requirement should be limited to environmental monitoring of the PEC ISO Class 5 PEC aseptic work area.*

Requested Change:
If recoverable CFU levels measured during surface sampling in the PEC ISO-5 aseptic processing area exceed the recoverable CFU 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).

7.2 Disinfecting Supplies for 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.”

- *Premise:*
  Use of must in the statement “they must be wiped” is overly prescriptive. Qualified

sanitization techniques exist that utilize disinfection solutions, sprays, and vapors, without physical wiping are available and effective in sanitizing items to be introduced into an ISO-5 aseptic processing environment.

Request change:
Before items are introduced into an ISO classified area, they must be adequately sanitized with a sporicidal agent, EPA-registered (or equivalent) one-step disinfectant cleaner, sterile 70% IPA or any other qualified sanitization process shown to be effective in removing objectionable organisms or contaminants.

9.1 Process Controls

"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."

- *Premise:*
  *Annual review is redundant considering that processes and steps described in the master formula should be reviewed any time a change is made to the production process to ensure that the changes are captured in all processes/steps. No sense reviewing something annually to make sure it is current if you haven't mad*e any changes.

Request Change:
The processes and steps described in the master formula must be reviewed any time a change is made to the production process to ensure any changes are captured in all process steps. Prior to the implementation of updates, appropriate validation and/or verification must be approved and performed."

9.3.3 Sterility Test Inoculations

"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."

- *Premise: Septum cap media container sampling time is misworded*

Change to Read:
"Media containers with a septum cap can be inoculated in a shielded area that does Incorporate ISO-5 quality air but must be sampled within 30 hours of final aseptic membrane filter sterilization. The 30- hour requirement may be exceeded due to a weekend or holiday, but if the sample for sterility testing is held longer than 30 hours, it must be validated that the longer period does not adversely affect the sample and the test results.

11.1 Quality Control Tests

"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."

- *Premise: QC sub-batch half-life justification is not adequately described. Add definition to be consistent with 11.3.1.*

Request Change:
Add definition of very short-lived radionuclide as being defined as having a Half-life less than 10 minutes in all sections and in Glossary.

11.1 Quality Control Tests

"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."

- *Premise: Specify requirement to be completed before patient dose release.*

Change to read:
The QC tests described in the previous paragraph should be considered for the QC sub-batch and completed before release of subsequent sub-batches for human administration.

11.3 Microbiological Tests for Sterile PET Drug Products

"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."

- *Premise: Add QC sub-batch testing requirement:*

Request Change to:

In the case of PET drug products with $T_{1/2}$ < 10 min, complete the filter integrity test on the initial QC Sub-batch thus allowing for release of subsequent sub-batches of the PET drug product for human administration before completion of any subsequent sub-batch filter integrity test which must be completed as soon as possible after release.

Glossary:

- *Premise: Unclear definition of very short-lived radionuclide as justification for Qc sub-batch process authorization.*

Suggested change:

In all sections and Glossary add definition of very short-lived radionuclide as being defined as:

PET drug products with radioactive half-lives of less than 10 minutes.

Thank you for your consideration. Please contact me if I can provide additional information or if you have questions.

Sincerely,

Helen Nadel, MD, FRCPC (Diag Rad), (Nuc Med), ABR (Ped Rad), ABNM, FACNM, FSNMMI
President, SNMMI