

1. For day of use calibration, why does the chapter recommend only 2 injections of the known standard versus current standard of 3?

Response: The current Chapter <823> does not specify a number of standard injections which are required. Instead, the current chapter refers to General Chapter <621> Chromatography, which requires five injections for reproducibility if the relative standard deviation is 2.0% or less and six injections if the relative standard deviation is more than 2.0%. The revised Chapter <823> (*PF37(1)* [*Jan-Feb 2011*]), under *System Suitability of Quality Control Equipment* suggests that one standard injection may be performed if there is a standard curve, or “Create a single-point calibration at the beginning of each testing cycle from two injections of a known standard.” Additionally the new 21 CFR Part 212 Guidance, C.2.b. HPLC: states “At least one injection of the standard preparation should be done before the injection of test samples.

2. How is the new endotoxin testing different?

Response: The revised Chapter <823> refers to any USP recognized procedure in Chapter <85>, rather than the previously specified methods. Additionally the revision includes the statement “After a record of successful bacterial endotoxin tests is established for a particular PET drug, it is only necessary to test the first batch prepared each day for that PET drug” which was stated previously only for sterility testing.

3. Why was the requirement of endotoxin testing prior to release eliminated?

Response: It was not eliminated. The revised Chapter <823> states “Regardless of which test is utilized (for BET), it should be initiated before release of each batch for human administration.”

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4. What is the thought process to reduce sterility testing to one batch, and is there a reason that the first batch was chosen for the test?

Response: The current Chapter <823> in *USP 32* states, “After a record of successful sterility tests is established for a particular PET drug, only the first lot prepared each day shall be subject to a sterility test using cultivation methods. However, when a different PET drug is made at the facility or a new lot of sterile components is substituted, then the first daily lot of that PET drug is tested for sterility.” There is no difference in the revised Chapter <823> in this regard.

5. Our QC EQ system suitability acceptance criteria in an approved IND, slightly differ from the revised USP, but have been validated. Is it possible to continue to use those criteria?

Response: Yes, if you are operational under an IND, it has been reviewed and approved by the FDA, you may continue to use those approved criteria.

6. My understanding is that the USP revisions should be complimentary with USP 61/62/71. What is the rationale for requiring only a single Bug for Growth Promotion rather than the various bugs required for TSB/FTM?

Response: The single organism in the proposed revision reflects the methodology described in the 21CFR Part 212 Guidance, PET Drugs—Current Good Manufacturing Practice (CGMP) published December 2009 by the FDA. It appears in section XI. Finished Drug Product Controls and Acceptance Criteria, Part C. Microbiological Tests for Sterile PEET Drug Products.

7. Why is the Laminar Flow Hood only required for recalibration every year when the Aseptic Processing Guidelines require this every six months?

Response: The proposed revision states that “Certification should be performed at the inception of operation and **at least annually** thereafter,

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or after repair or replacement of the HEPA filter.” This was allowed for institutions that may not be operational under the Guidelines mentioned.

8. Concerning the language regarding validation runs, was it the committee intent to remove the requirement of 3 consecutive runs which met all specs?

Response: The removal of the requirement for the validation runs to be consecutive was done to allow for a process which might fail due to a technical problem that was not critical to the process.

9. Is use of Bactec system appropriate for sterility testing of PET products. This system provides results in shorter amount of time.

Response: Both the current version and the proposed revision of Chapter <823> rely on Chapter <71> as the fundamental methodology for sterility tests. Sterility test methods that are not described in Chapter <71> should be performed by an FDA-approved system or be described in an approved IND, NDA or ANDA.

10. Under 21 CFR 312 the production documentation for clinical batches is commonly kept until 2 years post approval. Under proposed Chapter <823> the documentation is retained for 1 year only. Does this deviate from 312?

Response: The record retention recommendation in the proposed revision of Chapter <823> reflects the requirements in the new 21 CFR Part 212, Current Good Manufacturing Practice for Positron Emission Tomography Drugs. Part 212.110 describes record retention. Clinical batches used for investigational purposes to support a marketing application should be maintained in a manner consistent with the requirements for the application. Since the proposed revision of Chapter <823> will apply to PET drugs used for investigational purposes, the USP will evaluate the recommendations for document retention.

11. Why can sterility testing with Hungate tubes be permitted to be sterility tested external to a Laminar Flow Hood?

Response: This provision was added to address radiation shielding requirements when inoculating radioactive samples for the sterility test. The committee felt the flexibility was necessary since many hot cells used for this purpose do not have laminar air flow and the use of a septum-sealed sterility test tube (e.g., Hungate style) provides adequate protection from accidental contamination during the inoculation process.

12. Will the sterility media recommendations be reviewed by the Expert committee on Sterile compounding

Response: This chapter has been reviewed by the Chapter <797> Compounding Sterile Preparations Expert Committee prior to the publication of the revision proposal in PF 37(1) [Jan-Feb 2011].

13. The FR Notice of Dec 10, 2009 (p. 65411 Col. B) states: Thus, after the later of the two specified times, the CGMP requirements that FDA will have established for PET drugs will apply to compounded PET drugs. The fact that some production or “compounding” of PET drugs is performed by physicians, including some academicians and researchers at facilities located in universities and other not-for-profit institutions, does not remove such production from the scope of the PET CGMP regulations. Consistent with the Modernization Act, the final rule ensures that the production of compounded PET drugs is subject to the CGMP regulations while permitting the dispensing and administration of PET drug products in accordance with State regulation of the practice of medicine and pharmacy. How does USP reconcile the revised chapter definition of compounding and the apparent sanctioning of compounding under medicine and pharmacy?

Response: FDA is establishing regulations for all PET drugs within the scope of its authority under federal law, which in the Agency’s view (as discussed on p. 65411 referenced above) includes both compounded and

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noncompounded PET drugs. USP is not addressing the extent of FDA's regulatory authority, either in these Qs and As or in the course of revising Chapter <823>. However, by its terms, Chapter <823> applies to the "compounding of PET radiopharmaceuticals for human use," whether such compounding is or is not subject to federal regulation. What FDA has stated is that for investigational and research PET drugs, even though the Agency deems them to be subject to FDA jurisdiction, including the Part 212 Final rule establishing GMP requirements, "the requirement under the act to follow current good manufacturing practice is met by complying with the regulations in this part [212] or by producing PET drugs in accordance with Chapter <823> [USP-32]." 21 CFR 212.5(b). Accordingly, from the perspective of the USP compendium whatever version of Chapter <823> is currently official applies to all PET compounding, and from the perspective of FDA any requirement to comply with federal GMPs can be met, in the case of investigational and research PET drugs, by complying with the version of Chapter <823> specified in federal regulations, currently that in *USP 32*.

14. How would you describe the feedback received so far on the proposed changes?

Response: So far, the feedback to the proposed changes has been supportive and helpful. As with any process that involves the setting of a public standard, feedback is a critical component. The USP strongly encourages feedback throughout the public comment period, which ends on March 31, 2011. All feedback will be evaluated by the USP.

15. Some monographs products (e.g. acetate) have specificity requirements that are not related to safety. When will there be an opportunity to revise these monographs?

Response: The USP Small Molecules 4 Expert Committee and PET Expert Panel will be addressing the revision of all existing PET monographs. This will begin this year. USP encourages the PET community, both academia and industry, to submit new or revised monographs for PET drugs.

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Interested parties should contact Ravi Ravichandran for information prior to the submission of monographs.

16. Point of clarification, if multiple synthesis units are used for the same product, sterility testing must be done on each initial batch produced per synthesis unit for the day, right?

Response: That is correct. Sterility testing must be performed on each initial batch produced per synthesis unit for the day.

17. If the manufacturer of the growth media provides COA that contains growth promotion testing, do we still need to do this in our lab?

Response: Yes, even if the manufacturer provides a COA, you should assure the viability of media by growth promotion testing of the media. A simplified growth promotion test that employs a single organism is adequate to demonstrate the suitability of media for use in sterility tests. Alternatively, a positive control can be performed during the execution of each sterility test inoculation.

18. Process Validation proper is not a requirement under 212 if full testing is done. Why is it for Chapter <823>?

Response: Section 212.50(f) of the PET GMP's states that "when the results of the production of an entire batch of a PET drug are not fully verified through finished-product testing or when only the initial sub-batch in a series is tested, the PET drug producer must demonstrate that the process for producing the PET drug is reproducible and is capable of producing a drug product that meets the predetermined acceptance criteria."

In addition, in the Paperwork Reduction Act section of the Federal Register Notice (Federal Register vol. 74, no. 236, 65409-65436) states "Because process verification is only required when results of the production of an entire batch are not fully verified through finished-

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product testing, we believe that process verification will be a very rare occurrence..."

Based on these statements, USP will evaluate similar requirements in the proposed revision of Chapter <823>.

19. My understanding is the FDA 21 CFR 212 will "trump" Chapter < 823>. Is this a concern where testing in this proposed document is minimized?

Response: FDA 21 CFR 212 states that research drugs, IND and RDRC regulated, can be produced under Part 212 or Chapter <823> as published in *USP 32*. If the FDA accepts this chapter, they will need to amend the existing Part 212 rule to list the appropriate new edition.

20. When is the anticipated time for the finalization of the revised USP 823?

Response: The public comment period for the proposed revisions to Chapter <823> will end on March 31, 2011. Based on the feedback received, USP will work with the Expert Panel and Expert Committee to determine whether additional review will be necessary or if the chapter is ready to advance to the balloting step for official adoption. If the proposal advances as originally planned, the revised Chapter <823>, with appropriate changes as needed, will be submitted to the USP General Chapters Physical Analysis Expert Committee for balloting in May 2011. If the Expert Committee approves the revision, the revised chapter will be included in *USP 35-NF 30*, which will be published in November 2011 and official as of May 01, 2012. In terms of legal recognition and with regard to the CGMP implications, upon publication USP intends to petition FDA to update the reference in its regulation. Until that is accomplished, investigational and research PET drug manufacturers will have to comply with the Chapter <823> as published in *USP 32-NF 27* or the Code of Federal Regulations Title 21 Part 212 to meet CGMP requirements. All other PET drugs (not for investigational or research uses) are expected to meet CGMP stipulations of Part 212.

21. Can you describe the documentation that would be required to verify/validate the use of a sterile assembly in a Less than ISO-Class 5 environment.

Response: The proposed revision of Chapter<823> describes the preparation of the final product vial assembly should be performed aseptically in an ISO Class 5 environment. Once the assembly is prepared, it is a self-contained, closed system that may be filled in a non-controlled environment.

22. Are the class 3 residual solvent tests (given PQIT testing time) the same as VOC test that we now complete on every batch?

Response: Examples of noncritical attributes might include radionuclidic purity, as well as certain low-level nontoxic impurities and class 3 residual solvents. For a particular noncritical attribute, a PET drug producer might conduct a periodic quality indicator test (PQIT), which can be performed at a predetermined interval rather than on a batch-to-batch basis. Any residual solvent other than Class 3 would need to be tested on every batch.

23. Why does the API definition under Chapter<823> include "therapeutic use", which is explicitly excluded from 212?

Response: It is correct that therapeutic PET drugs are excluded from 212. However, the Expert Panel believes that the standards as stated in the revised Chapter <823> should be the same for any PET drug whether it is for diagnostic or therapeutic use.