



April 29, 2002

9547 02 00 00 01 00
Mayo Clinic
200 First Street SW
Rochester, Minnesota 55905
507-284-2511

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Draft Guidance on Current Good Manufacturing Practices for Positron
Emission Tomography Drug Products; Availability
[Docket No. 98D-0266]**

Dear Sirs/Madams:

We would like to provide the members on the PET Steering Committee, Food and Drug Administration (FDA), with the following comments and suggestions regarding the draft guidance on current good manufacturing practices (CGMP's) for positron emission tomography (PET) drug products, which was published in the April 1, 2002 issue of the *Federal Register*. For your information, two hard copies of this letter are enclosed as per the instruction listed under the "Comments" section of the aforementioned *Federal Register*.

In General

After reviewing the latest draft guidance, we would like to take this opportunity to congratulate the members on the PET Steering Committee, FDA, for the nice job that they have done. We believe that the document confronts many of the difficult issues related to PET drug production with a great deal of common sense, as well as a significant level of flexibility. As such, we feel that this new guidance should enable the PET community in meeting the CGMP requirements. We very much hope that the response received from the PET community proves to be an encouragement for the FDA in the future regulation of all PET drug products.

While we realize that the proposed guidance may not be possible to satisfy everyone in every possible circumstance, we would like to take this opportunity to raise the following inquiries in order for us to have a better understanding of certain issues as stated in the draft guidance.

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The Quality Control Unit

Page 7, lines 291-297 Since the staffing and responsibility of the quality control unit is determined by the size of the PET centers, we believe that the guidance should offer amore precise definition of a "small" PET center, as well as a "large" PET center.

Page 7, lines 292-297 It seems that the draft guidance suggests that the performance of quality control functions should be audited by an independent unit (i.e., an outside consultant or an independent expert for a small PET center, or in the case of a large PET center, a quality control unit that is independent from the production unit). While the notion of having a third-party verification is a good intention, we believe that this approach may prove to be "overkill", as well as very costly for the PET centers due to the following two reasons:

1. Under "Personnel Resources" (page 5, lines 218-219 and page 6, lines 220-224), it is recommended that a second-person check or self-checks (especially with regard to a PET center which is operated by one person) be instigated at various stages of production and test verification. We feel that this repetitive confirmation system is sufficient in assuring the compliance of each critical step in production and quality control.
2. PET centers are currently facing unprecedented cost constraints, as well as a significant shortage of qualified persons in the PET field. We believe that this distressing situation will be further worsened if each PET center is required to set up an independent quality control unit.

Aseptic Processing Facility

Page 9, lines 374-376

With regard to air quality (i.e., limits of microorganisms and particulate matter) in the aseptic processing area, we would like to suggest inclusion of the following two references in order to provide the end users with more detailed information, as well as to ensure consistency of the guidance format (e.g., automated radiochemical synthesis apparatus – page 11, lines 473-477; multichannel analyzer – page 14, lines 608-610; laboratory controls – page 26, lines 1123-1124, etc.):

- For air quality of the aseptic processing area that houses an LAFW, please refer to *United States Pharmacopeia* (USP) General Chapter <1206> *Sterile Drug Products for Home Use*.
- For air quality of the aseptic processing area that houses a barrier isolator, please refer to USP General Chapter <1208> *Sterility Testing – Validation of Isolator Systems*

Page 10, lines 403-406

Page 10, lines 415-416

With the reasons as stated above, we would like to recommend that the same references (i.e., USP General Chapters <1206> and <1208>) should be provided with regard to the method, frequency, equipment, and materials used to clean and sanitize the aseptic processing area used to hold the LAFW and barrier isolator, respectively.

Aseptic Workstation

Page 12, lines 497-498

Although the level of cleanliness of the air within an aseptic workstation is stipulated to be Class 100 in the section titled “Aseptic Processing Facility” (page 9, line 379), it is necessary to re-state the aforementioned class limit in this section (i.e.,

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"Aseptic Workstation"), which is specifically designed to lay out the criteria for an acceptable aseptic workstation.

Page 12, lines 495-520 With regard to the certification, monitoring, as well as maintenance requirements for the aseptic workstations (i.e., LAFW and barrier isolator), please list the aforementioned references (i.e., USP General Chapters <1206> and <1208>) within this section. In addition to checking the number of particulates, it is also critical to measure the airborne and surface microbial organisms. Please refer to USP General Chapters <1206> and <1208> for further information.

Dose Calibrator

Page 13, lines 579-586

Page 14, lines 587-589

According to the new *Code of Federal Regulations (CFR)*, Title 10, Part 35.60, it no longer lists the procedure and acceptability criteria for the calibrations of accuracy, linearity, geometry, and precision. The current requirement for calibration of a dose calibrator is to adhere either to "*nationally recognized standards or the manufacturer's instructions*".

Page 14, line 588

Due to the changes in 10 CFR, Part 35, the section titled "§ 35.50 *Possession, Use, Calibration, and Check of Dose Calibrators*" has been replaced by a new section titled "§ 35.60 *Possession, Use, and Calibration of Instruments Used to Measure the Activity of Unsealed Byproduct Material*".

Components that Yield an Active Pharmaceutical Ingredient (API) and Inactive Ingredients

Page 17, lines 738-741

Since F 18 fluoride is not considered as a component that yields an API of fludeoxyglucose F 18 injection (page 17, lines 730-731), it is not clear as to why F 18 fluoride is listed in the second example of testing(s) of component that yields an API.

For a component that yields an API, the proposed guidance requires the performance of verification of the certificate of analysis (COA), as well as identity testing. If F 18 fluoride is recognized as a component that yields an API, then the examples provided with regard to the testing should include a description of the method(s) that can be utilized for the identity testing, rather than an examination of the COA.

Page 17, lines 748-751

The syntax of this sentence is poor and needs to be revised as follows:

Under proposed § 212.40(c)(1), if a product that is marketed as a finished drug product, and intended for intravenous administration, this product would not be required to be tested using a specific identity test, provided the product is used as an inactive ingredient.

Master Production and Control Record/Batch Production and Control Record

Page 21, lines 915-917

With regard to the proper procedure for making corrections to electronic records, the proposed guidance stipulates that one should follow to 21 CFR Part 11. According to 21 CFR Part 11.10(e), if closed computer systems are used to store electronic records, there should be "*secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information.*"

We would like to request that you provide us with the names of the recommended software/hardware systems that are capable of performing the aforementioned functions (i.e., time-stamped audit tails). We are not certain as to whether these certified "audit trail" systems (if they are commercially available) are compatible with various electronic record-keeping systems that are currently used in PET centers.

Bubble-Point Test

Page 23, lines 1018-1020 To help the end user who may not be familiar with the bubble-point test, as well as to be consistent with the format of the draft guidance, it would be useful to cite USP General Chapter <823> *Radiopharmaceuticals for Positron Emission Tomography – Compounding*.

Recommendations on Labeling and Packaging

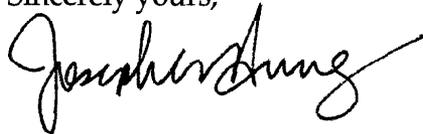
Page 29, lines 1287-1304 With regard to the labeling requirement, it would be helpful to include a statement such as “(see the labeling requirement as stated in the USP monograph for the specific PET drug)”.

References

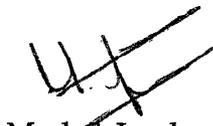
Page 32, lines 1403-1418 The current versions of the USP and the National Formulary (NF) are USP 25 and NF 20, respectively. The official date upon which both the USP 25 and NF 20 go into effect is January 1, 2002.

If any member of the FDA PET Steering Committee, FDA, has any questions or would like to request additional information regarding our comments and suggestions, please do not hesitate to contact us by phone: (507) 284-4399, fax: (507) 266-4461, or e-mail: jhung@mayo.edu or jacobson.mark17@mayo.edu. Many thanks for your kind attention.

Sincerely yours,



Joseph C. Hung, Ph.D., BCNP
Professor of Pharmacy
Professor of Radiology
Director of Nuclear Pharmacy and PET Radiochemistry Facility



Mark S. Jacobson, B.Sc.
Manager of PET Radiochemistry Facility

JCH:vsk