



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Rockville MD 20857

AUG 12 1998

Jorge R. Barrio, Ph.D.  
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Box 956948  
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Dear Dr. Barrio:

This is to confirm that the Food and Drug Administration (FDA) will meet with you and other representatives of the Institute for Clinical PET on Thursday, August 27, 1998, to discuss issues relating to the chemistry, manufacturing, and controls (CMC) for positron emission tomography (PET) drug products. The meeting will be held from 9 a.m. to 5 p.m. at the Parklawn Building, 5600 Fishers Lane, Conference Room C, in Rockville, Maryland.

As we discussed, the meeting will be placed on FDA's upcoming meetings calendar, which can be accessed at FDA's Web site at [www.fda.gov/po/upcoming.html](http://www.fda.gov/po/upcoming.html). Interested members of the public may attend the meeting. After our discussions are concluded, interested persons will be provided an opportunity to express their views.

We have developed a list of CMC issues (see attachment) that we would like to discuss at the meeting. The list includes issues that relate to all PET drugs as well as drug-specific issues (e.g., [<sup>18</sup>F] fludeoxyglucose, [<sup>13</sup>N] ammonia). The list represents some of the CMC issues identified to date that relate to developing PET drug approval procedures.

Please contact me if you have any questions about the meeting.

Sincerely,

Jane A. Axelrad  
Associate Director for Policy  
Center for Drug Evaluation and Research

Attachment

cc: Jennifer Keppler

98D-0266

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## LIST OF PET DRUG CMC ISSUES FOR DISCUSSION

### I. GENERAL TOPICS

- A. Clarification and Harmonization of Terminology
  - 1. What constitutes a "batch" of a PET drug product?
  - 2. What constitutes a "lot" of a PET drug product?
  - 3. What does "yield" mean for a PET drug product?
  - 4. What does the PET community consider "validation" for a PET drug product?
- B. Controls for and Classification of Cyclotrons
  - 1. What operating controls are necessary to reproducibly ensure the desired particle of requisite energy and beam current at the irradiation site?
  - 2. Should cyclotrons be classified based on energy levels or some other criterion?
- C. PET Drug Manufacturing for Different Dosage Forms
  - 1. Could a dosage form other than a solution (e.g., a gas) be manufactured for use?
  - 2. How would the manufacture, purification, and packaging of such a dosage form differ from that for a solution?
- D. Simultaneous Manufacture of Multiple PET Drugs
  - 1. Does the PET community expect to seek approval to manufacture (for distribution and use) multiple drug products, drug substances, or intermediates during a single irradiation cycle using a multicompart ment target body?
  - 2. What additional controls may be needed in this scenario?
- E. Inactive Ingredients in Drug Products
  - 1. For different manufacturing methods or at different PET centers, what inactive ingredients are being used for each of the following drug products: (1) fludeoxyglucose F-18 injection; (2) ammonia N-13 injection; (3) water O-15 injection; (4) sodium fluoride F-18 injection; and (5) fluorodopa F-18 injection?
- F. Quality Controls
  - 1. What quality control procedures should be performed on each batch of the drug product on a regular schedule?
  - 2. What QC procedures should be performed on a scientifically valid periodic schedule?
- G. USP Specifications and Tests Methods
  - 1. For generally used methods or USP methods, what data support the adequacy of specifications and methods for the following: (1) ammonia N-13 injection; (2) water O-15 injection; (3) sodium fluoride F-18 injection; and (4) fluorodopa F-18 injection?

#### H. Microbiological Issues

1. What validation is needed to ensure that manufacturing procedures and/or equipment does not contaminate the product with endotoxins?
2. What validation is necessary to ensure that the drug product manufacturing procedures are capable of eliminating microbes from the final product, if present during the course of manufacturing?
3. Under what circumstances can a filter integrity test be considered suitable as a critical parameter for indicating sterility of a batch?
4. Can a filter integrity test be conducted aseptically prior to product filtration in a PET drug facility?
5. What bioburden testing is necessary for equipment and components?

### II. DRUG-SPECIFIC ISSUES

#### A. Fludeoxyglucose F-18 Injection

1. What are the identifiable differences in a drug product prepared by the nucleophilic process vs. one prepared by the electrophilic process?
2. The USP monograph for fludeoxyglucose F-18 injection indicates that additional tests and specifications may be necessary because this product may be prepared by different methods. What additional specifications and test methods (including information on kryptofix and organic volatile solvents) may be necessary to control the identity, strength, quality, and purity of the drug product?

#### B. Ammonia N-13 Injection

1. Which salt forms are currently being used?
2. For both in-target production and chemical synthesis, which particular methods of manufacturing are being used to produce clinical material?

#### C. Water O-15 Injection

1. For both in-target production and chemical synthesis, which particular methods of manufacturing are being used to produce clinical material?
2. For a continuous manufacturing process, how would QC be performed?

#### D. Sodium Fluoride F-18 Injection

1. What additional issues should be considered when the drug product or its active ingredient is manufactured by in-target production methods?

#### E. Fluorodopa F-18 Injection

1. What are identifiable differences (including specific activity) between a drug product prepared by the nucleophilic process vs. one prepared by the electrophilic process?
2. What controls are necessary to ensure the stereoisomeric character (purity) of a chiral drug product (considering both the C-11 and F-18 molecules)?