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Electronic Comment to http://www.fda.gov/dockets/ecomments

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: **Docket No. 2004N-0439** – Proposed Rule on Current Good Manufacturing Practice for Positron Emission Tomography Drugs

Docket No. 1998D-0266 – Draft Guidance on Current Good Manufacturing Practice for Positron Emission Tomography Drug Products

Dear Sir or Madam:

The Council on Radionuclides and Radiopharmaceuticals, Inc. (CORAR) respectfully submits these comments on the above-referenced proposed rule and draft guidance, both of which were published by the Food and Drug Administration (FDA) in the September 20, 2005 issue of the Federal Register. 70 Fed. Reg. 55038 (Sept. 20, 2005) (proposed rule); 70 Fed. Reg. 55145 (Sept. 20, 2005) (draft guidance). CORAR is an industry association of manufacturers of radiopharmaceuticals, radionuclides, and radiochemicals, primarily used in medicine and life research. Radiopharmaceuticals manufactured by CORAR members are used in over 13 million medical procedures each year in the U.S., predominantly for diagnostic and monitoring applications, but also for therapeutic use.

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For the reasons set forth below, we request the following modifications and clarifications to the provisions of the rule and guidance:

I. COMMENTS ON THE PROPOSED RULE

1. Title. The title of the proposed rule refers to "Positron Emission Tomography Drugs," whereas the title of the draft guidance refers to "PET Drug Products." Given the focus of the rule on PET drug products, rather than on PET drugs, and to be consistent with the guidance, we recommend that the title of the rule be revised as "Current Good Manufacturing Practice for Positron Emission Tomography Drug Products."

2. Definitions.

Pet drug: The proposed definition of "PET drug" is:

> a radioactive drug that exhibits spontaneous disintegration of unstable nuclei by the emission of positrons and is used for providing dual photon positron emission tomographic diagnostic images. The definition includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of a PET drug.[1]

Although we recognize that the proposed definition tracks verbatim the statutory definition of "compounded positron emission tomography drug,"[2] it does not appear to serve any useful or practical purpose to include in the regulatory definition of "PET drug" items such as generators, accelerators, electronic synthesizers, and computer programs, since all of the requirements of the regulation apply to "PET drug products." The latter are by definition finished dosage forms containing a PET drug, and therefore will not include any generator, accelerator, target material, electronic synthesizer, or computer program. We therefore recommend deleting the entire second sentence from this definition.

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1 Proposed 21 C.F.R. § 212.1.

2 21 U.S.C. § 321(ii)(2).

Active pharmaceutical ingredient: An "active pharmaceutical ingredient" is currently defined as "a substance that is intended for incorporation into a finished PET drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis or monitoring of a disease or a manifestation of a disease in humans, but does not include intermediates used in the synthesis of such substance."[3] Because PET drug products are not intended to furnish pharmacological activity, the phrase "pharmacological activity or other" should be deleted from this definition.

Master production and control record: To more accurately reflect the fact that the batch records need not be exact copies of the master production and control document, the term "master production and control record" should be changed to "master production and control document," since the master will not be used as a "record." The definition of this term should be changed to the following: "a compilation of instructions containing the procedures for the production of a PET drug product and the specifications for the product."[4]

Quality control: We recommend that the word "maintaining" in the definition of "quality control" be replaced by the word "ensuring."

3. Laboratory Controls. The proposed rule and draft guidance set forth detailed requirements for the content of laboratory test records.[5] These requirements are excessive in light of the nature of most PET drug operations, in which QC functions are located in the same room as, or immediately adjacent to, the production room, and the laboratory analyst has a detailed understanding of the source of the sample. The rule requires, for instance, "[a] description of the sample received for testing, including its sources, the quantity, the batch or lot number, the date (and time, if appropriate) the sample was taken, and the date (and time, if appropriate) the sample was received for testing."[6] All of this information is already set forth in the master formula, which is referenced in the master production and control document, and in the individual batch records. We recommend that FDA clarify that existing documentation may satisfy the requirements for the test records in § 212.60(g).

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3 Proposed 21 C.F.R. § 212.1.

4 Id.

5 Proposed 21 C.F.R. § 212.60(g); Draft Guidance at 25.

6 Proposed 21 C.F.R. § 212.60(g)(1).

4. Finished Drug Product Controls and Acceptance Criteria. With respect to sterility testing, FDA is proposing to require that all receiving facilities of products that are determined to fail the sterility testing be notified of the results "immediately."[7] However, FDA's expectation of the timing and content of such notification is unclear. The detection of a growth in an inoculated media does not necessarily equate to the sterility failure of a lot. Rather, such growth will trigger an out-of-specification investigation, the results of which might not be known for two to four weeks. We recommend that FDA revise the rule as follows: "Receiving facilities must be notified immediately if an investigation into a nonconforming sterility test concludes that the PET drug product was non-sterile."

With respect to sterile PET drugs, the draft guidance permits the distribution of such drugs after the initiation of a pharmacopeial bacterial endotoxin test, but prior to obtaining the test results, provided that the results are determined to meet acceptance criteria before the drug is administered to humans.[8] Currently, this provision on bacterial endotoxin testing is only mentioned in the guidance, not the rule. We request that this provision of the draft guidance be incorporated into the rule.

II. COMMENTS ON THE DRAFT GUIDANCE

1. Quality Assurance. The draft guidance interpreting the QA functions states that all errors must be investigated and corrective action taken.[9] This appears to contradict the language of proposed § 212.20(d), which provides that, with respect to errors in production records, the manufacturer "must determine the need for an investigation, conduct investigations when necessary, and take appropriate corrective actions."[10] FDA should address this inconsistency by revising the language of the guidance to conform to that of the rule.

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7 Proposed 21 C.F.R. § 212.70(e).

8 Draft Guidance at 28.

9 Draft Guidance at 7, line 286 (emphasis added).

10 Proposed 21 C.F.R. § 212.20(d) (emphasis added).

2. Control of Components, Containers, and Closures. The draft guidance recommends that facilities accept reagents, solvents, gases, purification columns and other auxiliary materials provided they meet applicable specifications from approved reliable sources.[11] Given the reliance of PET drug producers on commercially prepared growth media for purposes of sterility testing, we recommend the addition of "commercially prepared growth media" to the list of components in Line 694-95 of the draft guidance.

3. Production and Process Controls. There is some ambiguity in the language of the draft guidance concerning the relationship between the master production and control record and a batch record. The draft guidance makes the following statements about master production and control records and batch records:

- "Proposed § 212.50(c) would require that a batch production record be generated from the master production record template for each new batch of a PET drug product."[12]

- "The master production record serves as a template for all batch records, documenting how each batch will be produced."[13]

- "The batch record is therefore a simplified version of the master production and control records that should contain the information needed for a documented history of the batch produced...."[14]

We believe that the third point appropriately describes the batch record and its relationship to the master production and control record – i.e., that the batch record need not be a replica of the master production and control record, but rather, should be input/output oriented. This concept should be clarified and reiterated throughout this section of the guidance. The first two statements, which suggest that the master production record is a "template" from which batch records are replicated, are inconsistent with this

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11 Draft Guidance at 16, lines 692-700.

12 Draft Guidance at 18 (emphasis added).

13 Id. (emphasis added).

14 Id. at 20.

notion. In addition, consistent with our earlier comment in the definitional section, the term "master production and control record" should be changed uniformly throughout to "master production and control document."

4. Terminology. Finally, consistent with our earlier comments, there are number of references in the draft guidance to "PET drug" where we believe the term "PET drug product" is more appropriate – e.g., Lines 1192 and 1211. We request that the agency revise the terms "sterile PET drugs" in these lines to "sterile PET drug products."

Respectfully submitted,

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AMK/eam