

December 5, 2005

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

VIA ELECTRONIC SUBMISSION

RE: Docket No. 1998D-0266
Draft Guidance on Current Good Manufacturing Practice for Positron Emission
Tomography Drug Products; Availability [70 **Federal Register** 55145]

Dear Sir or Madam:

P.E.T.Net[®] Pharmaceuticals, Inc., doing business as PETNET Solutions, (PETNET), is a wholly owned subsidiary of Siemens Medical Solutions USA, Malvern Pennsylvania. PETNET is an international health product company dedicated to positron emission tomography (PET) imaging agents and services. We operate 43 cyclotron-based PET nuclear pharmacies in twenty-eight states, and we are a leading producer of radiopharmaceuticals for PET imaging. Additionally, PETNET operates four international PET radiopharmaceutical production facilities in South Korea and the United Kingdom.

As such, PETNET is affected by the draft guidance, and wishes to comment on this draft document. PETNET has provided input on the development of PET cGMP's for several years through participation in previously held public meetings, which intent was for the expert public to assist the Agency in their development of the proposed 21 CFR Part 212 and the associated draft guidance, and by commenting on the previous versions of these documents. PETNET supports the draft guidance and is pleased to provide these comments in an effort to assist in its further development.

Titles of the proposed rule and draft guidance:

We direct the Agency's attention to inconsistencies in the titles of the proposed rule and the draft guidance. Specifically, we note that the title of the draft 21 CFR Part 212 refers to "Positron Emission Tomography *Drugs*," while the title of the draft guidance refers to "PET *Drug Products*." We suggest for sake of clarity and consistency that these titles be consistent with the definitions for "PET Drugs" and "PET Drug Products" as defined in the proposed rule.

Recommendation:

We recommend that the title of the final rule be changed to “Current Good Manufacturing Practice for Positron Emission Tomography Drug *Products*.”

Section V.A Regulatory Requirements:

This section describes the activities of the quality assurance function as set forth in the proposed rule at §212.20. In the draft guidance, at line 286 (p7), it states, “Ensure that *all* errors are investigated and corrective action is taken.” The requirement for *all* errors to be investigated is inconsistent with the proposed rule at §212.20(d) which states, “If errors have occurred, or a production batch or any component of the batch fails to meet any of its specifications, you must *determine the need for an investigation, conduct investigations when necessary*, and take appropriate corrective actions.” The statements in the draft guidance are inconsistent with the requirements in the proposed rule.

Recommendation:

We recommend that the language in the draft guidance be revised to conform to the wording in the proposed rule.

VII.B.4.a Control of components, containers and closures, acceptance testing:

This section provides examples of materials and components that may be accepted into use provided that they meet the applicable specifications, they are purchased from an approved and reliable source, and that a COA and container label are verified against a written specification. We note the absence of commercially prepared growth media from the list of examples.

Commercially prepared growth media is provided with a manufacturer’s Certificate of Growth Promotion and is labeled by the manufacturer with an expiration date. We further note the requirement in USP <71> Sterility Tests, which calls for a growth promotion test every ninety days. We believe that commercially prepared growth media has been demonstrated to be reliable and robust when stored according to the labeled requirements and when used within its labeled expiration date. The necessity for repeated performance of growth promotion testing every ninety days would cause several significant hardships. It would not be feasible to send material to an outside laboratory for repeated testing as this would make it impossible to control inventories, and resultant further exposure of the material to uncontrolled shipping conditions may further compound the interpretation and validity of the results to material retained for use. Additionally, and most importantly, to perform such testing internally, a PET drug product manufacturer, especially those situated outside of a medical institution setting, would have to employ a microbiologist and have a separate and dedicated site for microbiological testing, which would be economically unfeasible.

Recommendation:

We recommend that commercially prepared growth media be added to the example list of materials in this section.

VIII.A. Production and Process Controls, Regulatory requirements:

This section describes the requirements for a batch production and control record as such a record is required under §212.50(c) of the proposed rule. Statements in the draft guidance regarding the nature of the batch production and control record are inconsistent with the description and list of requirements for such a record as presented in the proposed rule at §212.50(c), as follows:

- At line 778 it states, “Proposed §212.50(c) would require that a batch production record be generated from the master production record template for each new batch....”
- At line 799 it states, “The master production record serves as a template for all batch records.....”
- However at line 853 it states, “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.”

The first and second bulleted statements above are inaccurate with regard to §212.50(c). The third bulleted statement is consistent with the itemized requirements in the proposed rule.

Recommendation:

We recommend statements in the draft guidance be aligned and consistent with section §212.50(c) in the proposed rule.

XI.B. Finished Drug Product Controls and Acceptance Criteria, Finished Product Testing:

This section expands on the requirements for finished product testing as stated in §212.70 of the proposed rule.

Recommendation:

We recommend that the following paragraph be added to this section:

“In accord with the current revision of the USP General Notice, Test and Assays, data derived from manufacturing process verification studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of samples drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards. An applicant who wishes to eliminate specific end product testing or wishes to reduce the frequency of a test should provide adequate supporting data in a drug application.”

XLC Finished Drug Product Controls and Acceptance Criteria, Microbiological Tests for Sterile PET Dugs:

This section expands on the requirements for finished product testing as stated in §212.70(e) of the proposed rule.

Recommendation:

At line 1192, the wording in the heading of paragraph “C” should be changed from “Microbiological Tests for *Sterile PET Drugs*: to “Microbiological Tests for *Sterile PET Drug Products*.” This would add consistency with the definition of “PET Drugs” and “PET Drug Products” as defined in the proposed rule.

The wording of the paragraph at line 1211 should be changed to read “*PET Drug Product*” rather than “*PET drug*.”

PETNET thanks the Agency for this opportunity to comment on the draft guidance on PET Drug Products-Current Good Manufacturing Practice (CGMP).

If the Agency has any questions, please contact Ken Breslow at (865) 218-2383.

Sincerely,



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