

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. 2004N-0439  
21 CFR Parts 210, 211, and 212  
Current Good Manufacturing Practice for Positron Emission Tomography Drugs,  
Proposed Rule, Availability [70 **Federal Register** 55038]

Dear Sir or Madam:

P.E.T.Net<sup>®</sup> 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 proposed rule, and wishes to comment on the proposed rule. 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was for the expert public to assist the Agency in their development of the proposed 21 CFR Part 212 and the associated draft guidance, and by commenting on the previous versions of these documents.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 proposed rule 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**Titles of the proposed rule and draft guidance:**

We direct the Agency's attention to inconsistencies in the titles of the proposed rule and the draft guidance.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that the title of the draft 21 CFR Part 212 refers to "Positron Emission Tomography *Drugs*," while the title of the draft guidance refers to "PET *Drug Products*."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*.”

**SUPPLEMENTARY INFORMATION:**

**II. Description of the Proposed Rule:**

**Section E, Adequate Personnel and Resources:**

This section states that “A PET production facility having a simple operation that produces only one or two *doses* each day (or week) of a single PET drug would need fewer personnel and other resources than a facility having a more complex operation that produces multiple PET drug products or a facility producing larger amounts of a PET drug product.”

There are not likely to be any operations either commercial or non-commercial that produce only one or two doses each day (or week). Therefore, this statement unrealistically portrays a “simple operation.” The draft guidance, (at lines 226-230), more accurately defines a small operation as one that produces only one or two *batches* of PET drug product daily. We suspect that this may be a typographical error.

***Recommendation:***

We recommend that the wording in the introduction to the final rule be changed to be consistent with the wording in the draft guidance.

**Proposed 21 CFR Part 212**

**Sub-section §212.1: Definitions**

This section of the proposed rule defines the meaning of the technical terms used in the document. We submit the following comments on the proposed definitions.

**Active Pharmaceutical Ingredient:**

The proposed definition states: “Active Pharmaceutical Ingredient means 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.”

Radiopharmaceutical diagnostic imaging agents, by design, should not elicit a pharmacological effect or response.

***Recommendation:***

We recommend that the definition of Active Pharmaceutical Ingredient does not include the descriptive term *pharmacological activity*.

**PET drug:**

The proposed definition states: “PET drug means 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 non-radioactive 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.”

The inclusion of the additional items in the second sentence of the definition is superfluous and inaccurate within the practical and technical meaning of a drug and specifically within the meaning of a PET drug.

***Recommendation:***

We recommend that the definition of a PET drug be limited to the first sentence of the proposed definition to exclude the other listed terms. We also believe that a generator system which produces a PET radionuclide from the decay of a longer half-lived parent isotope should be appropriately regulated under 21 CFR Part 211. The agency should consider inclusion of a statement to this effect in the final rule.

**Master Production and Control Record:**

The proposed definition states: “Master Production and control record means a compilation of records containing the procedures and specifications for the production of a PET drug product.”

The proposed rule at §212.50(c) lists the information that must be included in the batch record to include each major production step. In the draft guidance at line 853, it states, “The batch record is therefore a simplified version of the master production and control record that should contain the information needed for a documented history of the batch produced.” Therefore, the Master Production and Control Record should be a detailed step by step instruction set, while the input and output information from the production batch is recorded in the batch record. Thus the Master Production and Control Record is more accurately an instruction or procedure rather than an actual record of the batch production.

***Recommendation:***

We recommended that the Agency rename the Master Production and Control *Record* to Master Production and Control *Procedure*.

**Quality Control:**

The proposed definition states: “Quality control means a system for maintaining the quality of .....” Quality control activities are more commonly defined as those activities intended to *ensure* quality rather than to *maintain* quality as stated in the definition.

***Recommendation:***

We recommend that the Agency substitute the word *ensuring* for the word *maintaining* in the definition.

**Sub-section §212.60(g)(1), Test Records:**

This section describes how the QC sample is tracked from production to QC for testing and provides a list of requirements that must be used to identify the sample. In the case of PET production facilities, where the production activities are in close proximity to the testing activities, the testing activities are contiguous to the production activities, and where limited personnel are involved, we feel the list of the elements the Agency is requiring to record regarding test sample traceability are overly prescriptive.

***Recommendation:***

We recommend that §212.60(g)(1) is changed to read: “Samples received for testing should be suitably identified to avoid mix-ups.” We further suggest that this recommendation be addressed in the draft guidance document as well.

**Sub-section §212.70(e), Sterility Testing:**

This paragraph states in part: “If the product fails the sterility test, all receiving facilities must be notified of the results immediately.”

Sterility testing using the direct inoculation method requires an incubation period of 14 days. Should growth be observed in a media tube during the incubation period, it is not immediately concluded that the product was not sterile, but rather a sterility Out of Specification investigation should be initiated. This investigation will include speciation of the growing organism(s) as well as other investigative avenues. The investigation should lead to an informed determination whether in fact the product batch was not sterile, or that a technical error occurred to cause a false positive result. If an investigation concludes that a batch was not sterile and the observed growth was not caused by an operator error or other explainable cause, then notification of the receiving facility is in order. Notification of the receiving facility immediately upon observing a positive growth and without first completing and investigation which leads to a conclusion that in fact the product was not sterile and identifying the nature of the organism and whether such organism is infectious to humans, would cause undue alarm and would be unproductive.

***Recommendation:***

We recommend that the statement concerning immediate notification of the receiving facility of a failed sterility test be changed to state the following:

“Receiving facilities must be notified immediately if an investigation into a non-conforming sterility test concludes that the drug product was not sterile.

**Sub-section §212.70(f), Conditional Final Release:**

This section in (1) states: “If you cannot complete one of the required finished product tests for a PET drug product because of a breakdown of analytical equipment, you may approve the conditional final release of the product if you meet the following conditions.” It goes on to list those conditions.

The agency’s allowance for conditional final release is only partially consistent with the Tests and Assays section of the General Notices of the United States Pharmacopeia (USP). This section provides that process validation and in-process controls may provide greater assurance that a drug product conforms to release specifications than conducting each test on every final product batch. We recognize that it is the obligation of an application holder to provide adequate evidence to allow routine reduction in the frequency of end product testing. Therefore, in the context of the USP allowances, we support the agency’s allowance for conditional release.

We take issue, however, with the proposed requirement to inform the receiving facility of a conditional release. The personnel at the receiving facility are not knowledgeable of the proposed GMP conditional release allowance and do not have the expertise to interpret the meaning of such a release in the context of patient safety and product efficacy. It would, therefore, place the individual in an untenable position whether to administer the product to patients and would cause uncertainty and undue apprehension which would not serve the best interest of the patient.

We also suggest that in addition to the statement in §212.70(f)(2), which would disallow a conditional release if radiochemical purity and identity cannot be performed, that the Agency add a similar requirement if the specific activity of a PET drug product with mass-dependent target localization and/or potential to elicit a physiological effect, and where the specific activity limit is quantitatively expressed.

***Recommendation:***

We recommend that the Agency revise this section to read as follows: “If you cannot complete one of the finished product release tests for a PET drug product on a timely basis because of a breakdown of analytical equipment, inconclusive result, or invalid condition, and where such test is stipulated in an approved application, you must maintain a reserve sample for completing the test at the earliest possible time. You may approve the conditional final release of the product if there is historical evidence to substantiate that the conditionally released product will likely meet the established specifications. You may not conditionally release a product if the breakdown in analytical equipment prevents the performance of a radiochemical identity/purity test, or prevents the determination of the specific activity of a PET drug product with mass-dependent

target localization and/or has the potential to elicit a physiological effect, and where the specific activity limit is quantitatively expressed.”

PETNET thanks the Agency for this opportunity to comment on the proposed 21 CFR Part 212 regulation.

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

Sincerely,



Ron Nolte  
Vice President  
Quality and Regulatory Affairs  
Siemens Medical Solutions USA  
Siemens Molecular Imaging

CC:

Danny Bingham, Senior Quality Assurance Specialist  
Ken Breslow, Senior Regulatory Affairs Specialist  
Michael Nazerias, Manager, Quality and Regulatory Affairs  
Tom Welch, Vice President, PETNET Solutions  
Marc Weichelt, Senior Director of Filed Production Support, PETNET Solutions  
Steve Zigler, Senior Director, Technical Affairs, PETNET Solutions