

December 16, 2005

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

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/Madam:

The Society of Nuclear Medicine (SNM) appreciates the opportunity to provide the attached comments on the proposed rule for current good manufacturing practice for positron emission tomography drugs (21 CFR Part 212) as published in the September 20<sup>th</sup> *Federal Register*.

The SNM on behalf of its membership acknowledges the significant effort that the FDA has put into the rule and guidance documents for PET Drug Product CGMPs. These documents represent the outcome of many years of interaction between the FDA and the PET community. Many of the written responses and comments from the public meetings have been incorporated into the proposed rule and draft guidance documentation. As documented in this response we have identified a few sections of the document that require clarification or revision.

We look forward to continuing the open dialog with the FDA with regards to the regulation of PET Drug Products. Please feel free to contact Hugh Cannon at the SNM (703.708.9000) or any of the members of the working group if you have any questions regarding our response.

Sincerely,

SNM PET CGMP Working Group

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**Titles of the Proposed Rule and Draft Guidance:**

We direct the Agency’s attention to inconsistencies in the titles of the proposed rule and the draft guidance.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that the title of the draft 21 CFR Part 212 refers to “Positron Emission Tomography *Drugs*,” while the title of the draft guidance refers to “PET *Drug Products*.”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

**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.”

PET drug products, by design, should not elicit a pharmacological effect or response.

***Recommendation:***

We recommend the following definition for active pharmaceutical ingredient - ”*Active pharmaceutical ingredient* means a substance that is intended for incorporation into a finished PET drug product and is intended to furnish a 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.”

**Master production and control record:**

The proposed definition inadequately describes the relationship of the master formula instructions and batch sheet as they are used in PET. The batch record is the documented activity recorded as a result of following the master formula instructions.

***Recommendation:***

We recommend the following definition - *Master production and control procedure* means a compilation of records containing the procedures and specifications for the production of a PET drug product.

## **PET drug product versus PET drug**

The proposed definition states: a “*PET drug product* means a finished dosage form that contains a PET drug (*emphasis added*), whether or not in association with one or more other ingredients.” It is noted that this section also defines a “*PET drug*” as including the “nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of a PET drug”. A *PET drug product* (i.e., finished dosage form) does not, however, include these components of a *PET drug* thus necessitating a change in the definition of either the *PET drug product* or *PET drug*.

According to the proposed definition, “*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 the following definition - “*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.”

In addition to providing a better definition, this change should rectify the discrepancies observed between *PET drug product* and *PET drug*. We also believe that a generator system which produces a PET radionuclide from the decay of a longer half-lived parent radioisotope should be appropriately regulated under 21 CFR Part 211.

### **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 use the following definition – “*Quality control* means a system for ensuring the quality of active ingredients, PET drug products, intermediates, components that yield an active pharmaceutical ingredient, analytical supplies, and other components, including container-closure systems and in-process materials, through procedures, tests, analytical methods, and acceptance criteria.”

## **Definition of “Sub-Batch”**

The term “sub-batch” was repeatedly mentioned in the Proposed Rule, section § 212.1. However no definition is included for “sub-batch”. We suggest the use of the definition as per General Chapter <823>, “Radiopharmaceuticals for Positron Emission Tomography—Compounding,” in the current edition of the United States Pharmacopeia (USP).

### ***Recommendation:***

We recommend the use of the following definition - “*Sub-batch* means a quantity of PET drug product having uniform character and quality, within specified limits, that is produced during one succession of multiple irradiations, using a given synthesis and/or purification operation.”

### **Sub-section 212.5 (b) :**

This section refers to a specific edition of the United States Pharmacopeia (USP).

### ***Recommendation:***

Since the United States Pharmacopeia (USP) is updated frequently we suggest removing any reference to a specific edition of the USP here and elsewhere. This would always allow reference to the current edition of the USP. (e.g. ‘the current edition of the United States Pharmacopeia , which is incorporated by reference’)

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

Item 1 under this heading specifies that each laboratory performing tests related to the production of a PET drug product must keep complete records of all tests performed, including “a description of the sample received for testing, including its source, 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.” It is typically the case that testing to ensure that the PET drug product meets established specifications is performed contiguous with, and by the laboratory responsible for, production of the PET drug product; and the conduct of this quality control testing is addressed and documented as part of the batch record. While the level of documentation specified under this sub-section may be appropriate when testing components, in-process materials, or PET drug product by a laboratory external to the physical site where the PET drug product was manufactured, it is felt to be excessive when the testing is performed contiguous with PET drug production.

### ***Recommendation:***

Because of the volume of input we received from our members on this issue, we recommend the separation of the definition for components and in-process materials test records versus finished PET drug products. . It would also be appropriate to address the reduced requirement for such documentation in the Guidance document We suggest the following wording –

(g) *Test records for components, in-process materials or PET drug products tested in a facility physically external to the manufacturing facility. etc ...*

Subparagraphs (1) – (5) as written

-and-

(h) *Test records for PET drug products (internal testing) – etc ...*

(1) Test records for PET drug products tested internally shall be inclusive to the batch record for that PET drug product.

Subparagraphs (2) – (5) as written

**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. Growth observed in a media tube during the incubation period, does not immediately constitute a lot failure of the sterility test. Rather, such a result would initiate a sterility Out of Specification investigation that would lead to an informed determination of potential non-sterility. This investigation would include speciation of the growing organism(s), interviews 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. Should an investigation conclude 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 justified. Immediate notification of a receiving facility of positive microorganism growth in a media tube prior to the completion of such investigation and without information about the identity or infectious nature of the organism would be alarming and unproductive.

***Recommendation:***

We recommend sentence in subpart b be changed to the following: “Receiving facilities must be notified immediately if an Out of Specification 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.

**Sub-section §212.70(f)(iii), Conditional final release: Notification –**

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.

***Recommendation:***

Strongly recommend that Sub-section 212.70 (f) *Conditional final release. (iii)* be removed. Notifying the receiving facility of the incomplete testing, may result in confusion and will raise unnecessary concern. The additional provisions under this sub-section provide adequate protections to patients, and item (vi) provides for immediate notification of the receiving facility if subsequent testing reveals an out-of-specification result.

**Sub-section §212.70 (f)(v) Conditional final release:**

This subsection currently states, “You complete the omitted test using the reserve sample after the analytical equipment is repaired and you document that reasonable efforts have been made to ensure that the problem does not recur.” It will never be possible to “ensure” that the problem will not recur.

***Recommendation:***

We recommend that the sub-section read - “You complete the omitted test using the reserve sample after the analytical equipment is repaired and you document that reasonable efforts have been made to prevent recurrence of the problem.”

**Subsection §212.100(a) Written Complaint Procedures:**

It is felt that the wording of this subsection is overly broad and may be construed to include inappropriate complaints such as those involving pricing issues, shipping delays, etc.

***Recommendation:***

We recommend revision of this description to state: “You must develop and follow written procedures for the receipt and handling of all complaints concerning the quality or purity of, or possible adverse reactions to, a PET drug product.” It would also be appropriate to address this requirement in the Draft Guidance document.

**Section III Analysis of Economic Impacts E. Regulatory Flexibility Analysis – Item 5 - Description of Alternatives:**

The FDA is soliciting comment regarding ‘Electronic Audit Trail Capabilities’. As the FDA noted, there is very little if any software of this nature in use in the PET industry. Many items of production equipment are incapable of the software upgrades that would be necessary due to age and existing operating systems. To require the use of electronic audit trail software would be unduly burdensome and crippling for the industry.

***Recommendation:*** We recommend that the FDA stand by its decision not to require an electronic audit trail as part of the CGMPs for PET drug products.

**Section V. The Paperwork Reduction Act of 1995, I. Out-of -Specification**

**Investigations** The number of Out-of -Specification Investigations (OOS) are grossly underestimated. Whereas a true product failure may only occur once per year, OOS investigations are necessary each time a single item in the final product testing process results in an OOS. Because quality control on each batch is executed quickly most OOS conditions are directly due to operator or equipment failure and rectified by retesting. However, in most cases the frequency of occurrence for an OOS investigation is 2 to 3 times per month.

***Recommendation:*** The wording should be changed from ‘one’ OOS to ‘36’. Making the total time required 36 hours.

**Pediatric Requirements –**

Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients – Numerous federal regulation under 21 CFR require that manufacturers collect pediatric data with their submissions for new drug applications. PET drug products by definition are for metabolic, and/or diagnostic studies and do not elicit pharmacologic effect. Therefore, if the metabolic pathway being studied is functional in pediatric patients, it stands to reason, that the drug will appropriately provide the diagnostic data needed. If these regulations are allowed to impact 21 CFR 212, many normal children will be unnecessarily be exposed to radiation and inappropriately delay NDA (New Drug Application) submissions for the sole purpose of meeting these regulations without scientific benefit.

***Recommendation:***

We recommend that the proposed rule titled ‘Current Good Manufacturing Practice for Positron Emission Tomography Drugs (21 Part 212) be exempted from any and all regulation (e.g. 21 CFR 201, 312, 314, 602, etc) that require pediatric data collection or submission to the Agency for primary or continued approval.

***Final Recommendation:***

It is recommended that when the above proposed changes are adopted, they be made consistent with the Draft Guidance document.