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

**Re: [Docket No. 99N-4063]
Current Good Manufacturing Practices for Positron Emission Tomography Drug
Product; Preliminary Draft Proposed Rule; Availability
21 CFR Part 212**

Dear Sirs/Madams:

I would like to provide the Food and Drug Administration (FDA) with the following comments and suggestions regarding the preliminary draft proposed rule concerning the current good manufacturing practices (CGMP's) for positron emission tomography (PET) drug products, which was published in the April 1, 2002 issue of the *Federal Register*. Please note that my comments as follows do not necessarily represent the viewpoints of the Mayo Clinic, the American Chinese Society of Nuclear Medicine (Secretary Treasurer, President-elect), the American Pharmaceutical Association (Chair, Section on Nuclear Pharmacy Practice), or the Society of Nuclear Medicine (Chair, Committee on Pharmacopeia, effective June 20, 2002). For your information, I have enclosed two hard copies of this letter, as per the instructions listed under the "Comments" section of the aforementioned issue of the *Federal Register*.

In General

After reviewing the preliminary draft proposed rule, I would like to take this opportunity to thank the members of the PET Steering Committee, FDA, for their sincere efforts in confronting many of the complex and/or unique issues related to PET drug production with a great deal of common sense, as well as a significant level of flexibility. The preliminary draft proposed rule not only streamlines some of the "traditional" CGMP requirements (e.g., personnel/organization, aseptic processing, quality control, etc.), but also serves to eliminate or simplify several items (e.g., deletion of "reserve sample" requirement, acceptance of retrospective validation, reduction of record retention time, etc.), which were previously stipulated in the *Preliminary Draft PET Drug CGMP Regulation*. As such, I feel that this new rule, once finalized, should help the PET community in meeting the CGMP requirements for PET drug products.

In order to obtain a better understanding of various issues as stated in the preliminary draft proposed rule, as well as to call attention to certain shortcomings concerning the aforementioned document, I would like to take this opportunity to raise some inquiries and comments/suggestions on the following pages.

99N-4063

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With regard to the issues related to the possible inclusion of a provision in the PET CGMP rule concerning "conditional release", please refer to pages 5-7 of this letter for my response to the six questions as listed in page 38 of the preliminary draft proposed rule.

Page 30, line 8

Please provide a definition for the term “laboratory”, which describes its functions, as well as its relations to the PET center.

Page 30, §212.60(a)

According to 21 CFR Part 210.3(9), the term “in-process material” seems to include any chemical entity that is derived from a chemical reaction(s) which occurs during the automatic synthesis process, and this “in-process material” may not appear in the final PET drug product. Consequently, it may not be possible to test this “in-process material” as it may be eliminated during either the production or purification process.

Since preliminary draft proposed §212.40 includes the control of containers and closures used to package the finished PET drug products, the laboratory testing procedures as listed in §212.60(a) should also apply to containers and closures.

The written procedures for the control of “components, containers, and closures”, as well as “finished PET drug products”, has been properly addressed under §212.40(a) under Subpart E “Control of Components, Containers, and Closures”, and §212.70(b) under Subpart H “Finished Drug Product Controls and Acceptance Criteria”, respectively. As such, it would seem to be unnecessary to reiterate those requirements in §212.60(a) under Subpart G “Laboratory Controls”.

Pages 30-31, §212.60(b)

Please refer to the comments regarding the term “in-process material” as stated under the subtitle “Page 30, §212.60(a)” on page 3 of this letter.

The standards for the testing methods used in the control of “components, containers, and closures”, as well as “finished PET drug products”, have been properly addressed under §212.60(b) under Subpart E “Control of Components, Containers, and Closures”, and §212.70(a) under Subpart H “Finished Drug Product Controls and Acceptance Criteria”, respectively. As such, it would seem to be unnecessary to reiterate those requirements in §212.60(b) under Subpart G “Laboratory Control”.

Page 31, §212.60(c)

Appropriateness of the analytical methods used in the control of “components, containers, and closures”, as well as “finished PET drug products” has been properly addressed under §212.40(a) under Subpart E “Control of Components, Containers, and Closures”, and §212.70(b) under Subpart H “Finished Drug Product Controls and Acceptance Criteria”, respectively. As such,

it would seem to be unnecessary to reiterate those requirements in §212.60(c) under Subpart G “Laboratory Controls”.

Pages 31-32, §212.60(e)(f)

The suitability and maintenance issues concerning all equipment used in the control of components, containers and closures, as well as finished PET drug products have been properly addressed under §212.30(b) of Subpart D “Facilities and Equipment”. As such, it would seem to be unnecessary to reiterate those requirements in §212.60(e)(f) under Subpart G “Laboratory Controls”.

Pages 32-33, §212.60(g)

The record keeping requirements with regard to the testing relating to control of (1) components, containers, and closures, (2) finished PET drug products, and (3) equipment have been properly addressed in (1) §212.60(e) under Subpart E “Control of Components, Containers, and Closures”, (2) §212.70(d)(2) under Subpart H “Finished Drug Product Controls and Acceptance Criteria”/ §212.50(c)(6) of Subpart F “Production and Process Controls”, and (3) §212.30(b) of Subpart D “Facilities and Equipment”, respectively. As such, it would seem to be unnecessary to reiterate those requirements in §212.60(g) under Subpart G “Laboratory Control”.

Page 35, last line

The commonly employed “gel-clot technique” for the determination of bacterial endotoxins concentration requires a 60-min incubation period (please refer to *United States Pharmacopeia* (USP) General Chapter <85> *Bacterial Endotoxin Test*). Since the remainder of the required quality assurance testing for fludeoxyglucose F 18 (¹⁸F-FDG) injection, with the exception of the sterility test, can be completed in approximately 20-30 min, it is not practical and is, in fact, quite wasteful to delay release of the short-lived ¹⁸F-FDG injection for an additional 30-40 min.

As indicated in USP General Chapter <823> *Radiopharmaceuticals for Positron Emission Tomography – Compounding*, the completion of an in-process 20-min endotoxin “limit test” is accepted as one of the release criteria for a PET drug product radiolabeled with a radionuclide having a $T_{1/2} \geq 20$ min. Therefore, I would like to suggest that the standard 60-min bacterial endotoxin test (BET) be waived as a required test prior to the release of ¹⁸F-FDG injection. Instead, a 20-min BET could be used as a pre-release standard for ¹⁸F-FDG injection, whereas passing the standard 60-min BET could be the “green light” for final acceptance of ¹⁸F-FDG injection as a drug product suitable for use in a human subject (i.e., patient or volunteer).

Page 36, lines 7-8

The stipulated 24-hour window for the initiation of sterility testing may not be appropriate for the following reason(s);

- When the production of the PET drug products is completed on a Friday afternoon, laboratory personnel may be required to return to the PET center to start the required sterility test either Friday evening or Saturday.
- When the sterility test is to be conducted by an outside laboratory that does not accept any test sample which is radioactive, as it may take more than 24 hours for the radioactivity of a sample to decay to background or non-detectable level.

In view of the aforementioned reasons, I would like to suggest that the sterility testing must be initiated within a reasonable time frame (e.g., 24-72 hours) after sterile filtration is completed (end of production).

Page 38, question 1

How frequently do breakdowns of analytical testing equipment occur?

If the equipment is properly calibrated, operated, and/or maintained, the breakdown frequency should be very minimal. In addition, most of the failures of analytical testing equipment can be easily fixed if the broken part(s) is/are readily available. However, "Murphy's Law" may apply with regard to the possibility for unforeseen situations, even when the aforementioned conditions are met.

Page 38, question 2

What is the likelihood that an alternative testing method would be available?

Even though an alternative testing method may be available, most PET centers likely do not have the required analytical equipment to conduct the test.

Page 38, question 3

If a PET drug product could not be released for administration to patients because laboratory testing could not be completed due to equipment failure, what is the likelihood that a different PET center could provide the appropriate PET drug product for these patients?

This will depend on the following factors:

- (1) **Distance** – If the PET center is situated in a remote location, it may be difficult for that PET center to obtain the required PET drug product(s).
- (2) **Time** – If the PET center has a full schedule or needs to perform the PET imaging studies within a specific time frame, some of the studies may have to be rescheduled or cancelled. For patients who may have traveled a long distance to undergo the PET imaging procedure, this would certainly result in causing more anxiety, as well as additional cost (e.g., lodging, meals, as well as other miscellaneous expenses), for the patients.
- (3) **Availability** – Even when the aforementioned two factors do not present as obstacles for the PET centers, the required PET drug product(s) may not be available from another source due to possible supply issues related to the production capacity of the other PET centers and/or contractual restrictions which exist between the receiving PET center and other PET center(s) having excess quantity of the required PET drug products.

Page 38, question 4

Should there be a specific regulation permitting final release of a PET drug product even though testing cannot be completed due to a failure of equipment?

Yes.

Page 38, question 5

If so, what conditions for release should be established to limit potential risk to patients and ensure that such release does not become standard practice?

In addition to the three conditions for release (i.e., as appearing in italics in the section below) as stated on page 37, lines 13-19, I would like to recommend the addition of one more of the following conditions for release as follows:

- (1) *Possess documentation of the previous successful use of the test that cannot be completed, as well as evidence to demonstrate consistent performance with multiple batches meeting the specifications.*

- (2) Possess documentation of proper calibration, operation, as well as maintenance of analytical testing equipment in accordance with the established written procedures.
- (3) *Complete the omitted test, if applicable, using the reserve sample after the analytical equipment is repaired.*
- (4) *Notify the receiving facility in the case of any out-of-specification result.*

The added phrase “if applicable” in condition (3) is necessary in the event that the omitted test involves the measurement of radioactivity (e.g., half-life determination, radiochemical purity, and radionuclidic purity, etc.), of the reserve sample which has either decayed to background or is below measurable limit at the time that the analytical equipment is repaired.

Page 38, question 6

Should the receiving facility be notified of the information that is unavailable because of the equipment failure?

Yes.

Page 48, lines 14-16

Please refer to pages 3-4 of this letter for the comments concerning the deletion of §212.60(a)(b)(c)(e)(f)(g).

Page 50, lines 6-12

Please refer to the comments and suggestions for the term “active pharmaceutical ingredient” as stated under the subtitle “Page 15, lines 6-16” on page 2 of this letter.

Page 50

Please add a definition for the term “batch production and control record”.

Page 51

Please add a definition for the term “laboratory”, and describe its functions, as well as its relationship to the PET center.

Page 52, line 16

Please define the term “active ingredient” if the term “active pharmaceutical ingredient” is retained in 21 CFR Part 212.

Page 53, lines 3-5

Please refer to the comments and suggestions with regard to the term “receiving facility” as stated under the subtitle “Page 16, paragraph 2” on page 2 of this letter.

Page 55, line 5
Page 56, line 2

Since “quality control” is defined as a system (please refer to page 52, line 15), it is redundant to include the word “systems” in the term “quality control systems”. Accordingly, the term “quality

control systems” as it appears on page 55, line 5, as well as on page 56, line 2, should be replaced with the term “quality control”. Additionally, the word ‘system” as it appears within the context of the term “quality control systems” (page 19, line 10) should be deleted.

Page 55, lines 7-8

The title (iv) (i.e., Control of components, in-process materials, and finished products) should be revised to read “Control of components, containers, and closures” in order to match the title of Subpart E (page 58).

Pages 59-60, §212.40(c)(2)

The control requirements as stated in the first sentence of §212.40(c)(2) should apply only either to a component that yields an active (pharmaceutical) ingredient or an inactive ingredient. As per the definition for the term “component” (page 50, lines 17-20), any ingredients such as precursors, reagents, and solvents is also considered as a component. According to the draft guidance on CGMP for PET drug products (page 16, lines 693-708), it is not required to perform identity testing of the aforementioned materials since they are unlikely to appear in the final PET drug product. The amount of solvents or reagents in the finished PET drug product is typically reduced or eliminated during production or purification. Consequently, the first sentence of §212.40(c)(2) should be rewritten as follows:

- (2) In addition to identity testing, one must ensure that a component which yields an active (pharmaceutical) ingredient, as well as inactive ingredient, meets the written specifications by examining the certificate of analysis.

With regard to the establishment of reliability of the supplier’s test results, please refer to my comments under the subtitle “Page 16, line 722; Page 17, lines 723-726, on pages 5-6 of my letter concerning the draft guidance on CGMP for PET drug products.

Page 61, §212.50(b)(2)

The name and weight or measurement of each inactive ingredient (e.g., diluent, stabilizer, or preservative) per batch or per unit of weight or measurement of the drug product should be included.

Page 61, §212.50(b)

A description of the labeling and packaging requirements for the finished PET drug product should be included as one of the required items in the master production and control record.

Page 62, line 9

The term “action limits” should be replaced with “acceptance criteria” to be consistent with the term used in the International

Conference on Harmonization guidance, as well as in the preliminary draft proposed rule (page 49, last line and page 50, lines 1-3).

Pages 62-63, §212.50(c)

According to the draft guidance on CGMP for PET drug products (page 19, lines 820-822), a master production and control record should serve as the template for the batch production and control record.

Hence, in addition to the information as listed on pages 62-63, I would like to suggest that the following information should also be included in the batch production and control record:

- Name and strength of the PET drug product
- If applicable, the name and weight or measurement of each active (pharmaceutical) ingredient, as well as any inactive ingredient (e.g., diluent, stabilizer, or preservative) per batch or per unit of weight or measurement of the drug product
- Names of all components
- Packaging requirements

Page 63, line 5

Due to the very short half-life of some PET radionuclides, it is necessary to document the times, as well as the dates of the production steps with regard to item (4) of the batch production and control record.

Pages 64-66, §212.60

Please refer to pages 3-4 of this letter with regard to the comments and suggestions concerning the following issues:

- Definition and testing of “in-process material”
- Inclusion of “containers and closures for packaging the final PET drug product” in §212.60(a)
- Deletion of §212.60(a)(b)(c)(e)(f)(g)

Page 67, line 20

Please refer to the comments and suggestions as stated under the subtitle “Page 35, last line” on page 4 of this letter, with regard to the inclusion of a 20-min BET test as one of the pre-release criteria for a PET drug product radiolabeled with a radionuclide having a $T_{1/2} \geq 20$ min.

Page 68, lines 14-15

Please refer to the comments and suggestions as stated under the subtitle “Page 36, lines 7-8” on page 5 of this letter, concerning the time frame for initiating sterility testing after sterile filtration of a PET drug product is completed (i.e., end of production).

Dockets Management Branch, FDA
Docket No. 99N-4063
Page 10
June 5, 2002

Page 73, §212.110(b)

Should any system validation record be kept as long as the system is still in use, as per the recommendation stated in the draft guidance on CGMP for PET drug products (page 31, lines 1382-1383)?

Many thanks for the opportunity that the Agency has provided to the PET community in allowing us to express our concerns and comments with regard to the preliminary draft proposed rule on CGMP for PET drug products. If you have any questions or need additional information regarding my comments and suggestions, please do not hesitate to contact me by phone: (507) 284-4399, fax: (507) 266-4461, or e-mail: jhung@mayo.edu. Thank you very much for your kind attention and consideration.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Joseph C. Hung". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Joseph C. Hung, Ph.D., BCNP
Director of Nuclear Pharmacy Laboratories and PET Radiochemistry Facility
Professor of Pharmacy
Professor of Radiology

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