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

RE: Food and Drug Administration
Docket No. 2004N-0439
Docket No. 1998D-0266

To Whom It May Concern:

The Food and Drug Administration (FDA) has requested comments on the proposed rule for "Current Good Manufacturing Practice for Positron Emission Tomography Drugs" (Docket No. 2004N-0439) and the "Draft Guidance on Current Good Manufacturing Practice for Positron Emission Tomography Drug Products" (Docket No. 1998D-0266)- issued September 2005.

The Expert Committee on Radiopharmaceuticals and Medical Imaging Agents (RMI), as well as Expert Committee on Radiopharmaceutical Information (RI) of the United States Pharmacopeia (USP) wish to submit the following comments and recommendations regarding the new proposed rule and draft guidance on current good manufacturing practice (CGMP) for positron emission tomography (PET) drug products:

I. Definitions

Definition of "PET Drug"

Since a PET drug (e.g., I 124 sodium iodide) may also be used for tumor therapy, we suggest that the definition for "PET drug" be revised as follows:

A 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 or therapeutic procedures. The definition of PET drug 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.

12601 Twinbrook Parkway
Rockville, MD 20852

301-881-0666
www.usp.org

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Definition of “Active Pharmaceutical Ingredient”

In keeping with the above rationale, the definition for the term “active pharmaceutical ingredient” should be revised as follows:

Active pharmaceutical ingredient means a substance that is intended for incorporation into a finished PET drug product and is intended to furnish direct effect in the diagnosis, treatment, 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.

Definition of “Sub-Batch”

As the term “sub-batch” was repeatedly mentioned in the Proposed Rule, section § 212.1 titled “What are the meanings of the technical terms used in these regulations?” should include a definition for the term “sub-batch”. We suggest the use of the definition as per General Chapter <823>, “Radiopharmaceuticals for Positron Emission Tomography—Compounding,” in the 28th edition of the United States Pharmacopeia (USP 2005; USP 28).

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.

“PET Production Facility”

As per the proposed definition, the term “PET production facility” means a facility that is engaged in the production of a PET drug product. However, the term “PET production facility” does not accurately depict the actual function of the facility. The term “PET production facility” may mistakenly be interpreted to be a facility for the production of PET scanners or a facility for the acquisition of PET images.

As such, we recommend that the term “PET production facility” be revised to “PET drug production facility” to more precisely reflect the aforementioned proposed definition.

II. Conditional Final Release of PET Drug Products

a. Sub-section 212.70, (f) *Conditional final release*:

Item (iii) under this heading specifies that the facility responsible for production of the PET drug product must “immediately notify the receiving facility of the incomplete testing” of a PET drug product. It is recommended that this requirement be deleted since it is unlikely that personnel at the receiving facility will have sufficient knowledge of the surrounding CGMP conditional final release requirements and/or have sufficient expertise to base a decision whether or not to proceed with product administration. Thus it is felt that such notification will accomplish little other than creating confusion or undue concern on the part of receiving facility personnel. 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.

b. Sub-section 212.70, (f) *Conditional final release*:

Item (v) under this subsection states currently, “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. Additionally, pending on when the analytical equipment is repaired, one may not be able to obtain meaningful data for testing (e.g., radionuclidic identity, radionuclidic purity) as the radioactivity of the radionuclide of interest may be decayed to background level. As such, we would like to propose that the above-mentioned condition (i.e., § 212.70(f)(v)) be revised as follows:

“You complete the omitted test, if possible, 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.”

III. Although Sec 121 (a) (ii) (B) of the Modernization Act recognizes that PET drugs can be “compounded” and that the compounding can occur “by or on the order of a practitioner who is licensed by a State to compound or order compounding for a [PET] drug...; and is compounded in accordance with that State’s law, for a patient...”, the new proposed rule focuses primarily on manufacturing and does not appear to recognize the role of professional practitioners in the practice of medicine and pharmacy.

Accordingly, the FDA has determined that production of a PET drug product is exclusively an issue of regulatory adherence, apparently unintentionally removing the standard of professional responsibility traditionally established for the practice of medicine and pharmacy. All producers of PET drugs become manufacturers. As such, page 5 (lines 195-201) of the draft guidance for PET CGMP reads:

FDA has determined that the *production* of a PET drug product includes all operations to the point of final release of a finished dosage form, and these activities would be subject to CGMP. A PET drug product may be released to a hospital, institution, imaging facility, nuclear pharmacy (e.g., pharmacy bulk packages for use in accordance to USP <1> *Injections*), or other entity or part of an entity. After a finally released PET drug product is received by the receiving facility, FDA generally regards subsequent dispensing of a patient-specific dose and use of the drug product to be part of the practice of medicine and pharmacy.

Suggestion from USP's RMI and RI

The proposed rule and draft guidance should state that the requirements and guidelines contained in the above two documents only apply to non-compounded PET drugs. The compounding of PET drugs will continue to be subject to the requirements of the various state boards of medicine and pharmacy, as well as the PET compounding standards (<823>) and the official monographs of the USP.

- IV. The FDA has recognized many of the unique differences between traditional drug products and radiopharmaceuticals; many of these differences are related to potential for “in-house” preparation of radiopharmaceuticals and the radioactive nature, particularly short half-life.

Although directed in Section 121(c)(1)(B) of the Modernization Act to “take due account for the relevant differences between not-for-profit institutions that compound PET drugs and commercial manufacturers of such drugs.”, the FDA has concluded that the status of the facility—“either a not-for-profit or for-profit entity does not have a significant bearing on the quality of PET drugs that it produces and distributes to patients...” (Federal Register, Vol. 70, No. 181, page 55040, September 20, 2005).

The conclusion drawn therefore is that the only way to regulate the production of PET drugs, regardless of the nature of the facility is to require an NDA or ANDA.

The driving force behind decisions as how to enforce the FDA Modernization Act of 1997 appears to have been greatly influenced by the advent of the commercialization of PET drugs and the fact that many PET drugs and studies are currently reimbursed by the government and private insurance payors. As such, the language of the draft guidance (page 4, line 145-148) adopts the term “marketed” for agents that fall outside of the “investigational and research” categories:

PET drugs, other than investigational and research PET drugs, would have to meet the requirements of proposed part 212. PET drug products that would have to be marketed under an approved new drug application (NDA) or an approved abbreviated new drug application (ANDA) would have to be produced in accordance with proposed part 212.

The FDA, with the input and assistance of not-for-profit service institutions, has “simplified” the approval process for three PET Drugs, namely: Fludeoxyglucose F 18 Injection (FDG), Ammonia N 13 Injection, and Sodium Fluoride F 18 Injection, providing needed templates, guidelines, and instructions for institutions to follow in preparing NDAs and ANDAs. There are, however, numerous PET drugs currently in use. USP 25 contains monographs for twelve (12) PET drug products. We believe that maintaining the clinical availability of these agents alone will create an almost insurmountable hurdle for many facilities to provide NDAs for the PET drugs for which no template, guidance or instructions exist. One can envision significant delays by the FDA due to the need to provide assistance in creating the needed templates, guidelines, and instructions.

PET drug products approved by FDA may be protected from competition by patents issued by the U.S. Patent and Trademark Office or by periods of market exclusivity. Federal Register Vol. 65, No. 48, page 13005, 3/10/2000. As such, in the competitive climate of for-profit commercial manufacturers, it is unlikely that commercial PET facilities would want to share their NDA with others who may eventually provide competition to their operation.

- V. By design, NDAs control the manufacture and use of drug products and are typically only approved for specific indications. Labeling designates “approved” indications, dosages, etc. We believe that there is the potential that professionals, such as physicians, will be limited in their practice of medicine due to the nature of NDAs themselves as well as the language already quoted above. This is particularly relevant since some States and other organizations may limit use and reimbursement to approved indications only.

This may be further complicated in an institution where the physician may be considered the “manufacturer”.

The extent of whom and what constitutes the “manufacturer” needs to be clarified within the guidance document. This definition is especially critical for not-for-profit and academic institutions.

- VI.** Are NDAs and ANDAs needed or even realistic for very short-lived PET drugs that logistically require in-house preparation, such as those labeled with O-15 (half-life = 2 minutes)? In the traditional sense, the preparation of these drug products more closely falls under the definition of compounding than manufacturing due to their extremely short half-lives, which preclude marketing and distribution. Specifically, the criteria that differentiate compounding from manufacturing are the existence of a specific practitioner-patient-compounder relationship, the quantity of medication prepared (in this case, a single dose), and the conditions of sale, which are limited to a specific prescription order. The half-lives of these PET drugs mandate that these criteria will be met resulting in zero commercial potential and therefore, agents that are not distributed and marketed. Rather, these short-lived PET drug products are individually compounded onsite, one dose at a time, for specific individual patients.

VII. Other comments on the “Draft Guidance on Current Good Manufacturing Practice for Positron Emission Tomography Drug Products”

a. Line 861

Since the format of a batch record can be either a paper or an electronic copy (as per line 851), with regard to the term “printout” as stated in line 861, which seems to refer only to the paper version of the documentation, we would like to suggest that the statement in line 861 be changed as follows:

861 unit, the paper printout or electronic display or record at the end of synthesis documenting the execution of the production

b. Line 864

Please refer to the above noted rationale with regard to the proposed revision of line 864 as listed below:

864 A compilation of tests and paper printouts or electronic display or record that led to acceptance of the final product.

c. Line 1187

Please refer to the text appears in red as stated below for the suggested revision of line 1187:

1187 recommend using approved NDA or RDRC specifications, or the IND accepted specifications. Under ...

d. Line 555

Section VI. FACILITIES AND EQUIPMENT, C.1.e. High performance liquid chromatograph (HPLC): On line 555, the sentence should end after properly, removing “and there is no bleeding of unintended materials (e.g., column material) into the mobile phase”.

This qualifying statement does not verify resolution or reproducibility of the HPLC system. Guidance for prep HPLC should be similar to the analytic guidance in VI.2.b. (line 584). A marker that would elute with a retention time different than the PET drug should be used to assure integrity of the HPLC system prior to use of the system.

e. Line 672

Production of Components, Containers, and Closures; B. Control of Components, Containers, and Closures. 3. Acceptance, release, and storage of materials: Insert (line 672), after the last sentence, “One exception to the requirement for a COA for a component material, is if a component is labeled U.S.P, the specifications do not require a COA, due to manufacturing compliance with USP standards and specifications.”

This exemption is taken from the Drug Master File (DMF) 9057, held by the Institute for Clinical PET in Fairfax, Virginia, and is modeled after the NDA #20-306 for Fludeoxyglucose F-18 Injection held by the Methodist Medical Center, Peoria, Illinois.

f. Lines 997-1000

Production and Process Controls; C. Microbiological Control on Aseptic Processing and Sterilizing Filtration. 8. Environmental and personnel monitoring: In this section (lines 997-1000) it is “recommended that microbiological testing of aseptic workstations be performed during sterility and critical aseptic manipulations.” We suggest that this testing should not be required for the following reasons:

- a. The recommendation in VII. C. 6. (lines 971-980) is that an operator complete 3 successful media fill runs to qualify as a new operator, then requalified annually.
- b. When new processes are validated, each process typically requires 3 batches with complete sets of quality control performed consecutively, which would include 3 sets of BET

and sterility testing for the radiopharmaceutical. All results must pass specifications.

- c. Generally, sterile laminar flow hoods are certified every 6 months, including environmental monitoring.
- d. Each PET drug is tested for BET and sterility, and historical data is maintained.
- e. If all of these criteria are met (a-d above), there should be no additional need to require that environmental monitoring daily during sterility testing and aseptic manipulation. If a PET drug is determined to be non-sterile, then an operator should be retrained rather than requiring constant environmental monitoring.

g. Lines 1198-1199

Finished Drug Product Controls and Acceptance Criteria C. Microbiological Tests for Sterile PET Drugs, (lines 1198-1199) requires that “Sterility testing would have to be started within 30 hours after the completion of PET drug production. If the same PET drug sample is held longer—over the weekend...Verification of equivalent results can be accomplished by inoculation of USP indicator organism(s) and demonstrate that there is little, if any, loss in viability of the inoculated microorganism.”

We feel that the verification of equivalent results required for storage of the sample over the weekend, prior to inoculation, is not necessary. The storage of E. coli, which is used in BET testing, in the refrigerator at 2-8 °C does not reduce the potency of the E. coli. Minimally, if a verification test must be performed, the PET facility should be allowed to use the E. coli as the bacteria as an acceptable organism (or other USP indicator organism) since E. coli is used for BET testing.

h. General Comments

- 1. Section VI. Facilities and Equipment, C. Equipment: It is felt that this section of the document is not evenly consistent regarding the amount of specific guidance that is being provided. For example, under item c. (Electronic or analytical weight balance) and item d. (Dry-heat ovens), very specific guidance is provided on how to check the performance of these equipment. However, item e. (High performance liquid chromatograph) provides only the general statement that the operator should “ensure that the system is working properly and there is no bleeding of unintended materials into the mobile phase.”

It is recommended that this guidance document consistently incorporate specific guidance on how to check the performance of all equipment

routinely used in the production of PET drug products and/or reference a corresponding USP Chapter that addresses this information.

2. Section VIII. Production and Process Controls, C. Microbiological Control on Aseptic Processing and Sterilizing Filtration: Item 8, *Environmental and personnel monitoring* states the following: “We recommend that microbiological testing of aseptic workstations be performed during sterility testing and critical aseptic manipulation. Methods can include using swabs or contact plates for surfaces and settling plates or dynamic air samplers for air quality.” These statements imply that the suggested methods for microbiological testing of aseptic processing be performed during the sterility testing and critical aseptic manipulations of each batch of a PET drug product. Recommending such testing for each batch of a PET drug product is felt to be excessive, especially if prior batches of the PET drug product have been shown to be routinely negative for microorganism contamination.

It is recommended that this section of the guidance document address the acceptability of a reduced frequency of microbiological testing once routine sterility of the PET drug product (i.e., prepared in accordance with established procedures by appropriately trained individuals) has been established.

3. Section XIV. Complaint Handling, A. Regulatory Requirements: Sentence 1 of this section currently states “Proposed 21 CFR 212.100 would require that procedures be developed and implemented for receipt and handling of all complaints pertaining to a specific PET drug product, including review ---.” It is recommended that this sentence be changed to “Proposed 21 CFR 212.100 would require that procedures be developed and implemented for receipt and handling of all complaints pertaining to the quality or labeling of, or possible adverse reactions to, a specific PET drug product, including review ---.” It is not within the scope of cGMP to require the documentation of complaints related to, for example, ordering errors or delays in receiving the PET drug product, the pricing of the PET drug product, etc. (See corresponding recommended change to proposed 21 CFR 212.100.)

VIII. Other comments on –Proposed Rule on “Current Good Manufacturing Practice for Position Emission Topography Drugs”

a. Sub-section 212.1, *PET drug product*:

As per the current definition, 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*.

b. Sub-section 212.1, *Quality control*:

It is recommended that this definition be changed to “*Quality control* means a system for ensuring the quality ---.” (i.e., rather than “maintaining the quality” as currently written.)

c. Sub-section 212.60, (g) *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 of the PET drug product is performed by a laboratory external to the site where the PET drug product was manufactured; it is felt to be excessive when the testing is performed contiguous with PET drug production. A reduced requirement for such documentation in this latter situation should be addressed in the Guidance document.

d Subsection 212.100, (a) *Written complaint procedures*:

This subsection currently states “You must develop and follow written procedures for the receipt and handling of all complaints concerning a PET drug product.” It is recommended that this statement be changed to “You must develop and follow written procedures for the receipt and handling of all complaints concerning the quality or labeling of, or possible adverse reactions to, a PET drug product.” It is not within the scope of CGMP to require the documentation of complaints related to, for example, ordering errors or delays in receiving the PET drug product, the pricing of the PET drug product, etc.

Positron emission tomography has proven to be a valuable tool in the diagnostic armamentarium, however, as a clinical modality; it does not exist without PET drugs.

The purpose of the USP's RI and RMI is to provide standards and information to ensure the safe and appropriate use of radiopharmaceuticals. Our purpose is analogous to that of the proposed rule. The comments above are directed toward not only ensuring safe and effective PET drugs but also PET drugs that remain available to the American people.

For Radiopharmaceutical Collaborative Group

A handwritten signature in black ink, appearing to read "Andrzej Wilk". The signature is fluid and cursive, with the first name "Andrzej" written in a larger, more prominent script than the last name "Wilk".

/Andrzej Wilk

Liaison to the USP Radiopharmaceuticals and Medical Imaging Expert Committee, and
USP Radiopharmaceutical Information Expert Committee.

aw@usp.org

Tel. (301) 816 8305

Fax. (301) 816 8373