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

RE: Docket No. 2004N-0439

Dear Sir or Dear Madam:

I appreciate the opportunity to comment on a proposed rule to create specific CGMP regulations for PET drugs in 21 CFR 212, as published in September of 2002. I consult on a regular basis with a major commercial PET drug firm, and to a lesser extent, with several other firms. I have had an opportunity to participate in the management of their quality systems, and thus, to observe intimately their progress in complying with the proposed rule. I commend the Agency's revision of the rule in response to public comments in 2002. I offer the following comments:

**Proposed 212.60(g)(1) Laboratory Controls; Test Records**

The required documentation needs streamlining because of the limited time and human resources during production and QC activities. The level of proposed documentation is excessive in the presence of comprehensive and verified procedures. The requirements should be revised to state that the sample received for testing must be suitably identified.

**Proposed 212.70(a) Finished Drug Product Controls; Specifications**

It seems more appropriate to set specifications for apyrogenicity rather than pyrogenicity.

**Proposed 212.70(e) Finished Drug Product Controls; Sterility Testing**

The requirement regarding notification of a failed sterility test is totally inappropriate. Such notification would occur several days after administration and critical data, such as species identification, would not be available. Immediate, unqualified notification would be alarming and unproductive. I suggest the following revision:

"Receiving facilities must be notified if an investigation into a non-conforming sterility test concludes that the corresponding drug product was non-sterile."

**Proposed 212.70 (f) Finished Drug Product Controls; Conditional Final Release**

The prescriptive criteria for conditional release in the proposed rule are outrageous and must be completely discarded. Further, the tone of the conditional-release statement implies inaccurately that every Pharmacopeial test is required and must be conducted on a product before release in order to assure its quality; such a notion is in contradiction to the USP General Notice, Test and Assays. I urge a revision of proposed 212.70(f) to read as follows:

*2004N-0439*

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"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 an invalid condition, 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 must implement written procedures that 1) determine which finished-product tests are applicable for conditional release, 2) specify steps that are required to correct the cause of the invalid condition or equipment failure in a timely fashion, and 3) document all conditional release activities."

The veracity of process validations and the immensity of reliable historical data more than authenticate the adoption of 'conditional release' for PET drug products under the criteria stated above. The Agency should continue to promote the principle of building quality into a production system rather than relying on a strategy of testing PET drug products into compliance. The current section for conditional release just simply sends the wrong message.

It is also necessary to remove the requirement for notifying a receiving facility of conditional release action. Personnel at a receiving facility will not have sufficient understanding of such regulatory action or sufficient expertise to decide whether or not to administer the drug. Therefore, such notification would accomplish little other than to create confusion and undue concern on the part of healthcare personnel at the receiving facility.

#### **Proposed 212.70(g) Finished Drug Product Controls; Test Frequency**

This new part (g) would accommodate testing on less than a 100% basis. Many tests are amenable to daily or skip testing. For example, bacterial endotoxin tests (BET) for FDG F 18 always generate a non-detectable BET result because the alumina cartridge in the FDG production process quantitatively removes all endotoxin. With regard to a need for sterility testing, I have reviewed radiation dosimetry calculations for FDG F 18 processes and discovered that the radiation levels for a bombarded target render the target and its contents sterilized by ionizing radiation. Further, the repeated passage of commercial-level quantities of FDG F 18 ( $\geq 4$  Ci) through a production system renders the fluid pathway sterilized by ionizing radiation because the radiation dose is cumulative. The Sterility Assurance Level achieved by exposure to ionizing radiation and passage of the API through a sterilizing membrane filter (integrity tested) into sterile containers renders the retrospective sterility test a moot point. Therefore, I propose the following addition to 212.70:

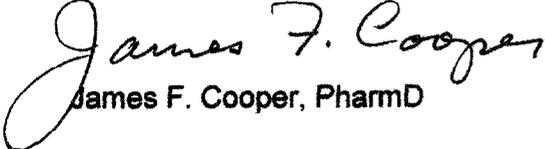
"You must conduct process verification and establish procedures for finished product testing on a daily basis rather than every batch of finished product."

#### **Proposed 212.100(a) Complaint Handling; Written Complaint Procedures**

This section should be clarified to require documentation of complaints that are related to the quality or efficacy of a PET drug product or adverse reactions.

I may be reached for [jimandfran@att.net](mailto:jimandfran@att.net) for further interaction.

Sincerely,

  
James F. Cooper, PharmD