



# American Pharmacists Association

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December 16, 2005

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

RE: Docket No. 1998D-0266

Dear Sir/Madam:

Thank you for the opportunity to comment on the draft guidance on current good manufacturing practice for position emission tomography drug products as published in the September 20<sup>th</sup> *Federal Register*. The American Pharmacists Association (APhA), founded in 1852 as the American Pharmaceutical Association, represents more than 53,000 practicing pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in advancing the profession. Within APhA, the Section on Nuclear Pharmacy Practice is comprised of nearly 300 pharmacists involved in nuclear pharmacy, many of whom work wholly or in part in positron emission tomography (PET) drug production.

APhA appreciates the Food and Drug Administration's (FDA) efforts to develop meaningful regulations and guidance for the production of PET drugs, which enable unique, critically important imaging studies. We recognize that the Agency has been deliberate in the development of the draft guidance on current good manufacturing practice (CGMP) for PET drug products, and the related proposed CGMP regulations, because of the regulatory challenges presented by this unique form of drug production. The draft guidance and proposed regulations address many of the concerns raised in public meetings and individual communications regarding earlier drafts of both documents. However, a few areas of the draft guidance must be revised and clarified to account for the complex and varied nature of PET drug production.

APhA offers the following comments on a few of the specific areas outlined in the draft guidance:

***Title of the Draft Guidance:***

The title of the draft guidance refers to "PET *Drug Products*", while the proposed rule refers to "Positron Emission Tomography *Drugs*". The titles should be revised in order to be consistent with the definitions presented in the proposed rule. We recommend that the Agency keep the title of the draft guidance as proposed and revise the title of the proposed rule to match. Both documents should refer to "Current Good Manufacturing Practice for Positron Emission Tomography Drug Products".

***V. A. Quality Assurance; Regulatory Requirements:***

Line 286 of the draft guidance states that PET production facilities must, “Ensure that all errors are investigated and corrective action is taken.” The statement that all errors be investigated is inconsistent with the requirements included in the proposed rule. Section 212.20(d) of the proposed rule would require that facilities “determine the need for an investigation [and] conduct investigations when necessary”. The proposed rule makes clear that an investigation of *all* errors is not required; rather an investigation should be conducted only when it is determined to be necessary. We recommend that the language in the guidance be revised to conform to the proposed rule.

***VII. B. 4. a. Control of Components, Containers and Closures; Acceptance Testing:***

Lines 694 – 700 of the draft guidance allow the acceptance of reagents, solvents, gases, purification columns, and other auxiliary materials provided that they meet internal written specifications and that a COA is obtained and examined. We note that microbial growth media is excluded from this list. Although USP Chapter <71> on Sterility Tests requires a growth promotion test (GPT) every 90 days, commercially prepared media carries a conservative manufacturer’s expiration date. Retesting of commercially prepared growth media for GPT should not be required because it would pose an enormous burden upon PET sites without benefit. PET sites would have to hire a microbiologist and dedicate a site for such microbiological testing. A requirement for GPT of a commercially prepared microbial growth media is inconsistent with the spirit of the other provisions of the CGMPs for PET drug products. We strongly urge a change in this section to include “commercially prepared growth media” to the list of materials accepted by COA review and compliance with assigned commercial product expiration dating.

***VIII. A. Production and Process Controls; Regulatory Requirements:***

The draft guidance contains inconsistent descriptors for the requirements of a batch record. At line 778, the draft guidance states, “Proposed §212.50(c) would require that a batch production record be generated from the master production record template for each new batch....” And at line 799 the guidance states, “The master production record serves as a template for all batch records.....” However, at line 853 the guidance states, “The batch record is therefore a simplified version of the master production and control records that should contain the information needed for a documented history of the batch produced.” The statements at lines 778 and 799 are inconsistent with proposed Section 212.50(c) which would require the creation of a unique batch production and control record each time a batch is produced. We believe the statement at line 853 of the guidance is more consistent with the requirements in the proposed rule, and we request that the FDA revise lines 778 and 799 to make them consistent with Section 212.50(c).

***XI. B. Finished Drug Product Controls and Acceptance Criteria; Finished Product Testing:***

We recommend that the Agency insert the following text at line 1190:

“Pursuant to and consistent with the current revision of the USP **General Notice, Test and Assays**, data derived from manufacturing *process validation* [verification studies] and from *in-process controls* may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of samples drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards. An applicant who wishes to eliminate specific end product testing should provide adequate supporting data in a drug application.”

***XI. C. Finished Drug Product Controls and Acceptance Criteria; Microbiological Tests for Sterile PET Drugs:***

APhA recommends that the title of the section which begins on line 1192 be changed from “Microbiological Tests for Sterile *PET Drugs*” to “Microbiological Tests for Sterile *PET Drug Products*.” This recommendation would help create consistency among the references to PET drug products throughout the draft guidance document and the proposed regulation for CGMP.

We request that the Agency make a similar modification at line 1211 of the draft guidance. The current statement, “...sterile PET drug that is intended for injection” should be revised to read, “...sterile PET drug *product* that is intended for injection.”

In conclusion, APhA supports the direction the FDA has taken in regard to the development of CGMP standards for PET drug products. The draft guidance provides PET drug product producers with substantial information to guide their compliance with CGMP regulations and is a helpful accompaniment to the related proposed rule. APhA encourages the Agency to include the guidance document with the release of the final rule.

As the Agency reviews comments and begins development of the final guidance document and final rule, APhA recommends that the dialogue between the Agency, the PET community, and professional organizations that represent health care professionals that produce or utilize PET drug products continue. APhA and its nuclear pharmacy members are interested in working with the Agency to ensure that CGMP regulations for PET drug products provide for the production and administration of safe and effective PET drug products.

Thank you for your consideration of the views of the nation’s pharmacists. Please contact Marcie A. Bough, APhA’s Senior Manager of Practice Development and Research at 202-429-7540 or mbough@aphanet.org, or Susan K. Bishop, APhA’s Associate Director of Regulatory Affairs at 202-429-7538 or sbishop@aphanet.org with any questions.

Sincerely,



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