

# GE Healthcare

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Documents Management Branch (HFA-305)  
Food and Drug Administration  
5600 Fishers Lane  
Room 1061  
Rockville, MD 20852

**Re: Docket No. 1998D-0266  
Comments to Draft Guidance  
Current Good Manufacturing Practice for Positron Emission Tomography Drugs**

Dear Documents Management Staff:

Reference is made to the subject docket number published in the Federal Register Volume 70, Number 181, page 55145 which announced the availability of a draft guidance entitled "Current Good Manufacturing Practice for Positron Emission Tomography Drugs."

At this time, as requested by the Federal Register notice, GE Healthcare is providing its comments to the draft guidance on the following pages. Please note that in some cases our comments make cross-reference to the corresponding proposed rule for Current Good Manufacturing Practice for Positron Emission Tomography Drugs (Docket No. 2004N-0439 published in the Federal Register Volume 70, Number 181, page 55038).

Please call me at (609)-514-6573 if you have any questions or comments regarding this submission.

Sincerely,  
GE Healthcare



Fred Longenecker  
Director, Regulatory Development

**1998D-0266**

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**Draft Guidance – September 2005**

**Current Good Manufacturing Practices for Positron Tomography Drugs**

**(Docket No. 1998D-0266)**

**GE Healthcare Comments**

Note: In the comments below where we have recommended new or modified text, we have identified the added text using underlined and italicized text.

Global Comment

Throughout the Guidance the term “PET drug” has been used. We believe that in most cases the correct term should be “PET drug *product*”. We ask that this be changed as appropriate.

Specific Comments

Lines 160 through 162 – For larger scale PET drug production there likely will be more than one multiple-dose vial produced from a batch. To reflect this situation we recommend that this sentence be rephrased to read: “A sample from a vial that is representative of all doses to be administered....”

Lines 232 through 239 - This paragraph refers to production and QC activities but later in the document the releasing authority is said to be Quality Assurance, (line 1127) which is not mentioned in the roles above. This should be clarified.

We question the allowance for one person performing production, QC checks, and batch release. We agree that roles may be shared, however a second person to check at critical stages is not unreasonable given that a lone employee working in these establishments is not acceptable for safety considerations.

Lines 267 through 286 - This sub-section repeats parts of the requirements from the proposed regulation, but the text is incomplete on several important points. In the second bullet point (line 278) release of the finished dosage form is missing. In the third bullet point (line 282) the regulatory requirements are re-worded in a manner that makes the requirement unclear as compared to the proposed regulation. Whereas the proposed regulation requires QA to approve or reject specifications, methods and processes, the text in the draft guideline implies that only procedures affecting the above items should be examined. The approval or rejection of specifications, methods and processes is not mentioned in section A. It is acknowledged that requirements are reflected in sub-section B, but for clarity section A should simply refer to the regulation rather than repeating only parts of it.

Line 286 – The draft Guidance specifies that all errors must be investigated and corrective action taken. This appears contradictory to the proposed rule (section 212.20 (d)) which states that first a determination is to be made as to whether or not an investigation is necessary and if so the investigation is to be conducted and appropriate corrective action taken. The language in the guidance omits both the opportunity to determine the need for an investigation and reference to the appropriateness of corrective action. In the latter, the implication in the proposed rule is that in some cases “appropriate” might mean no action. Please clarify text in the Guidance so the two are consistent with each other.

Lines 290 through 316 – We recommend that the following additional responsibilities be added for the quality assurance function.

- Release production batches following successful batch record review and satisfactory QC testing.
- Ensure that all deviations from normal procedures are documented and justified.

Lines 319 through 334 - Reference to the proposed regulation's requirement to implement procedures and document activities has been omitted and should be included.

Lines 340 through 347 – This paragraph assumes aseptic production, however, it is technically possible to terminally sterilize some PET drug products and likely that future products will be so processed. To reflect this possibility we recommend that the following additional text be included at the end of this paragraph.

*“PET drug product sterile manufacture may be divided into two categories - those which are manufactured aseptically and those in which the product is terminally sterilized. The facility should maintain levels of environmental cleanliness appropriate for the type of operation being performed.”*

Lines 349 through 351 – Most “hot-cells” are not barrier isolators and many do not include laminar flow. When closed they tend to meet high grades of air cleanliness, dependent upon the degree of filtration of the feed air, however, when open they are exposed to the surrounding environment. For a satisfactory aseptic operation a sterile sealed fluid path consisting of tubing, sterilising filters and a sterile closed and sealed vial must be assembled under aseptic conditions and connected to the synthesiser / bulk solution to be filtered on the non-sterile side of the sterilizing filter. The microbial challenge on the “dirty” side of the filter should be minimized by controlling the environment to class 100,000 (in operation). To reflect this we recommend adding the following additional text at the end of the paragraph in lines 349-351.

*“Where sterilizing filtration is performed using a sterile enclosed system it is permissible to perform this operation under class 100,000 conditions, however, aseptic manipulations to assemble the fluid path for the enclosed system must be performed under aseptic conditions in a separate LAF or barrier isolator facility.”*

Line 375 – We recommend deleting the parenthetical phrase “(production of multiple PET drug products)” as this would not necessarily increase complexity and there may well be other aspects of PET drug production that would increase complexity.

Line 381 (new text) - Many institutions share facilities with researchers experimenting in the synthesis of new PET compounds for analytical investigation and animal studies. The management of the unit must ensure that these activities will not compromise the production of PET products for administration to humans. We recommend adding the following text.

“As many PET facilities are situated in research institutions research staff may synthesise new PET compounds for nonclinical and early clinical studies. The QA function of the PET facilities must review and approve these research activities to ensure they do not pose a hazard to marketed PET drug products. The research staff must be adequately trained in the operation of the facility and cGMP rules that they must follow.”

Lines 401 through 402 – We recommend that the Agency specify that garb worn within aseptic work stations be non-shedding and cover the hair.

Lines 418 and 419 – Reference to USP <797> may be appropriate in that this sentence as it implies the need to set standards for monitoring environmental quality.

Lines 544 through 550 - The requirement in these lines is causing confusion in many PET centers as they are unsure if they must have the same degree of validation for endotoxin removal on QC glassware as they do for production glassware (despite the fact that this comes under the title of “production equipment” in the document. We recommend that the first sentence in this paragraph be revised to read: “If glassware and heat-stable materials used in the production of the PET drug product are depyrogenated and sterilized on-site....”

Lines 554 through 556 – As HPLC columns are potential sources of contamination we recommend that the Agency provide a statement on cleaning and storage conditions when the equipment is idle. We suggest adding the following text: “If the column is to be left idle or stored, we recommend that it is rinsed through and stored in a suitable solvent that is compatible with the column and will inhibit bacterial growth.”

Lines 592 through 597 - We do not think that instructions from dose calibrator manufacturers can be considered a nationally recognized standard. It is generally not possible for a PET center to be able to calibrate his instrument with a PET isotope national standard due to the short half life of most the PET products. The dose calibrator manufacturer should be able to produce a certificate for a derived response factor and provide guidance on how to perform routine performance checks using appropriate longer lived isotopes. To reflect this we recommend that the second sentence in this paragraph be revised to read: “The instrument should be calibrated in accordance with nationally recognized standards or with a certified dose response factor provided for the instrument at commissioning and during routine maintenance.”

Line 686 (new paragraph) - As PET products grow within the commercial field it is likely that producers with more than one PET centre will want to purchase components / raw materials and then store and perform QC testing at a centralized facility. When these materials are approved they would then be distributed to the “satellite” PET centers for use. On receipt at the “satellite” PET center the identity would be established from the labeling and the approval status would be checked. This has the advantage of economy of scale from a commercial point of view, but also allows for a more comprehensive QA system and QC testing regime thus bringing PET more into line with “traditional pharmaceutical manufacture”. To reflect this situation we recommend addition of the following paragraph.

“Organizations with more than one PET Center may store and perform Quality Control testing and approval of raw materials and components at a centralized facility. On receipt of the material, the “satellite” PET centers will check the labelling, condition of the deliver, and the approval status assigned by the central facility.”

Lines 745 through 748 – We recommend that a reference to USP <1211> Sterilization and Sterility Assurance of Compendial Articles be included in this paragraph.

Lines 708 through 715 – Please provide clarification regarding what finished product testing and other documentation about synthesis the Agency would consider appropriate to support a decision that components can be accepted on the basis of examination of a certificate of analysis. Some information was provided in the description of the proposed rule (FR Vol. 70, No. 181, page 55040) but has not been included in the draft Guidance where it would be more useful.

Lines 769 through 771 – We recommend that this sentence be revised to read: “...a PET drug product that meets applicable standards of identity, strength, quality, purity, and sterility.”

Lines 920 through 931 – Please clarify that there is not an absolute requirement to use Water for Injection (WFI) and that other categories of sterile water, such as USP Sterile Purified Water could be used in production.

Lines 973 through 982 – We recommend inclusion of a reference to USP <1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments for incubation conditions.

Lines 992 through 995 – We recommend clarification that filter integrity testing should be performed before the filtered product is administered to patients. In addition, we believe that other validated filter integrity tests may be employed. We propose the following wording for this paragraph.

*“Integrity testing of membrane filters should always be performed post-filtration and before the filtered PET drug product is administered to a patient. This is to ensure that the filter has performed according to specifications. Testing can be accomplished by performing a validated filter integrity test to show that the integrity of the filter was not compromised during or before use.”*

Line 1003 (new section) - There is a licensed terminally sterilized FDG drug product currently being marketed in Europe and where possible, the next generation of PET drug products likely will be terminally sterilized. Where terminal sterilization has been performed, using a validated cycle, it should be permissible to release the product using parametric release procedures. We recommend addition of the following new section VIII – D.

*“D. Terminally Sterilized PET Drug Products*

*Where the PET drug product has been terminally sterilized in its final container, using a validated procedure, it is permissible to parametrically release the product for sterility providing the pre-determined criteria established during validation have been met. Guidance for parametric release requirements can be obtained in the USP <1222> Terminally Sterilized Pharmaceutical Products – Parametric Release.”*

Lines 1017 and 1018 – The final sentence in this paragraph states that “The determination not to conduct process verification should be supported by scientific rationale and data.” This is an additional requirement to that in the proposed rule (section 212.50(f)(1)) which states that: “For a PET drug product for which each entire batch undergoes full finished-product testing to ensure that the product meets all specifications, process verification, as described in paragraph (f)(2) of this section, is not required.” The sentence in lines 1017 and 1018 of the guidance should be deleted.

Line 1037 – The introductory phrase, “Because PET drugs have short half-lives,” is inaccurate. The impetus for wanting to conduct concurrent evaluation is more the expense of components that would be used in a “one-off” study. We recommend deletion of the introductory phrase.

Lines 1037 through 1044 – The last sentence of this paragraph should be clarified as it implies that under other circumstances strict adherence to procedures would not be required.

Lines 1048 through 1055 – Would the requirement for software validation of an automated synthesis apparatus require production of “validation” batches? Please clarify.

Lines 1090 through 1108 - The requirement for validation of analytical methods is unclear. Paragraph 1 requires limited validation (sensitivity, specificity and accuracy) whereas paragraph 2 refers to ICH and thereby indicates that there would be a requirement for full validation. Paragraph 3 recommends USP methods be verified as suitable, but it is not clear what parameters would be included in such verification. There seems to be inconsistency between the requirement given in the draft guideline and the requirement for validation of specification methods in part 212.70 (b) of the proposed regulation which specifies accuracy, sensitivity, specificity and reproducibility. Please clarify.

Lines 1120 through 1125 - Please clarify that once a given piece of analytical equipment has been validated it is acceptable on a daily basis to run a single system suitability standard to ensure that the response for that piece of equipment lies on the standard curve.

Lines 1196 through 1203 - This paragraph makes no reference to terminally sterilized products which some of the next generation of PET products are likely to be (refer to our comment on line 1003, above). We recommend that this paragraph be revised to read as follows.

*“When the product has been terminally sterilized in its container using a fully validated cycle and in accordance with the requirements of USP <1222> Terminally Sterilized Pharmaceutical Products – Parametric Release, it is not necessary to perform a sterility test.*

*For all other sterile PET drugs products, sterility testing would have to be started within 30 hours after the completion of PET drug production. If the sample for sterility testing is held longer than indicated (e.g., over the weekend), PET producers should demonstrate that the longer period does not adversely affect the sample and the test results obtained will be equivalent. The samples should be stored appropriately (e.g., under refrigeration). 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. The USP General Chapter <71> Sterility Tests provides information about media and incubation conditions.”*

Lines 1216 through 1218 - This section of the draft guidance allow distribution of the finished drug product under controlled conditions after endotoxin testing has been initiated but before the results are available, providing the drug is not administered by the receiving facility until a satisfactory test result has been received. This allowance is not part of the corresponding section (Subpart H) of the proposed rule. We request that this allowance be added to the proposed rule.

Lines 1233 through 1244 – This sentence implies that that sterility tests are the only long duration tests that would not be completed before the PET drug product would be administered. There are tests other than sterility, such as those for long lived radionuclidic impurities, which may have to be conducted and would not be completed until after the radioactive drug substance has decayed. We recommend the following alternative paragraph text.

“In many cases, modifications to this standard procedure for product release may be appropriate. For example, transportation deadlines may justify a pre-release for distribution before all elements of testing and review are finalized. Under proposed § 212.70, before the product can be used, certain pre-determined critical tests must be completed, and the drug product approved for use by the PET production facility's QA function. The PET production facility should provide a notice of final release to the receiving facility so that the dose may be given to the patient. We recommend the establishment of effective procedures for immediate notification of the receiving facility if there is evidence of an out-of-specification result. Notification of the receiving facility due to product failure should be documented.”

Lines 1260 and 1261 – The draft guidance expects the site to determine if testing that is missing (as part of a situation of conditional release) would affect safety and effectiveness of the drug. It is not clear how the Agency expects this to be determined. Please clarify.

Lines 1311 through 1316 - For aseptic operations, if labels are attached before filling, the process should be designed to ensure that sterility is not compromised. As labels cannot be sanitized and tend to shed particles this will present a considerable stress to any aseptic operation. We recommend the text in this paragraph be revised to read:

“Because of radiation exposure concern, it is a common practice to prepare much of the labelling in advance, however due to particle shedding and the difficulty of sanitizing paper labels the process should be designed so that sterility is not compromised. For example, a closed empty product vial can be prelabeled with partial information (e.g., product name, batch number, date) prior to filtration of the radioactive product, and upon completion of QC test, the outer shielded container can be labelled with the required information (e.g., radioactivity). Alternatively, a string label can be used to label the immediate container provided that there is a way to associate the label with the vial if the label were to come off.”