

Cardinal Health's

Comments and Discussion on Proposed 21 CFR Part 212

211.1(a)

We commend the FDA for making this portion of the changes very clear. We believe the exclusion of PET drugs from part 211 is made clear with this revision. However, we also believe that FDA inspectors will need retraining to make this exclusion clear in practice as well. Our early experience indicates this will need to be a diligent effort as part 211 is well engrained in the inspection arm of the agency.

212.1 PET drug definition

The definition of "PET drug" seems clear in the first sentence of the definition. The remainder of the definition seems to greatly confuse the definition as well as how and where the definition applies. The terms "PET drug" and "PET drug product" are used somewhat interchangeably in proposed rule. Part 212.5 seems clear that these regulations apply only to "production, quality control, holding, and distribution of PET drug products". However, as an example, Part 212.40 is titled "How must I control the components I use to produce PET drugs and the containers and closures I package them in?" Liquid target material for PET production facilities would seem to fall into the definition of PET drug. We don't believe FDA intends the target producers to fall under Part 212 but the PET drug extended definition and subsequent use of the term seem to confuse the issue.

An alternative for this definition would be to develop consistency with 21 CFR Part 315 for diagnostic radiopharmaceuticals since PET drugs are radiopharmaceuticals. This consistency would help maintain clarity of language when discussing or describing all radiopharmaceuticals. Further it would help eliminate those things that confuse the definition of PET drug.

212.1 Active pharmaceutical ingredient definition

The "active pharmaceutical ingredient" (API) definition contains the phrase "...and is intended to furnish pharmacological activity or other direct effect in the diagnosis...". We believe the agency understands that PET radiopharmaceuticals do not provide any pharmacological activity or direct effect in the body. Yet this definition would lead future readers of this document and especially those schooled in part 211 to believe there is pharmacological effect of PET radiopharmaceuticals. To improve a good start at this definition we recommend the following definition.

“API for purposes of part 212 is a substance (excluding intermediates used in the synthesis of such substance) that is intended for incorporation into a finished PET drug product {possible change to PET radiopharmaceutical} and is intended to furnish the physiological pathway for the diagnosis or monitoring of a disease or a manifestation of a disease in humans.”

212.1 Quality Control definition

The CORAR comments have a recommendation to change “... maintaining the quality of...” to “....ensuring the quality of...”

212.20(d) Investigation of errors

212.20(d) states, “If errors have occurred, or a production batch or any component of the batch fails to meet any of its specification, you must determine the need for an investigation, conduct investigations when necessary, and take appropriate corrective actions.

The draft guidance at line 286 (p 7) states “Ensure that all errors are investigated and corrective action is taken”. The “all” is inconsistent with the determination for the need to conduct an investigation as necessary as stated in the proposed rule. We recommend that the language in the guidance be adjusted to conform to the proposed rule.

212.50(b)(6) Acceptance criteria on radiochemical yield

This section requires a statement of acceptance criteria on minimum radiochemical yield. Radiochemical yields can have significant variations in a well controlled PET manufacturing operation. Many factors during a normal manufacturing process can impact the yield. The radiochemical yield is not a significant predictor of product quality. Some products may have a low single digit radiochemical yield. Others could be much higher. Discarding useful product and having to produce another lot based on some arbitrary radiochemical yield increases radiation exposure to workers and doesn't predict product quality. We suggest radiochemical yield be deleted from the acceptance criteria.

212.50(c)(6) Recording of dates and times of production steps

This section requires the date and time to be recorded for each step of the production process. We concur that recording the time of critical production steps is appropriate but we believe the date and time on each step is not necessary. The manufacturing of PET drug products will take place over a few hours at most. Recording the date once on the batch record should be sufficient unless the production does, in fact, span two different dates. The recording of times should also be limited to critical steps. The manufacturing process is short and attempts to capture the times of the automated steps would lead to a de-emphasis on the critical steps.

212.60(g)(1) Laboratory Controls-Test Records and guidance at lines 1072-1074):

We believe a reference to the batch or lot number on samples is more than adequate since it would contain all the necessary information. It appears this section stems from a misperception of typical PET manufacturing operations. Samples stay in the same general area and testing personnel have full access to the batch record. Thus the proposed requirements seem to stem from an inaccurate understanding of the relationship between QC and production in the PET environment, where the analyst has a detailed understanding of the source of the sample.

212.70(e) Sterility Testing

Growth in an inoculated media (which observation may be up to 14 days post inoculation), does not necessarily constitute a lot failing the sterility test. Rather, this would generate an OOS sterility test investigation, which may or may not lead to a conclusion that the batch was not sterile. Regardless, two to four weeks may elapse for an original observation and the conclusions of an investigation. At this juncture post production and product use, it is questionable what benefit would be served by notifying the receiving facility, and what advice would be appropriate or meaningful to provide the receiving facility. We suggest FDA reconsider this requirement or at the least, make some recommendations in the guidance regarding what the receiving facility should be told.

212.70(f) Conditional final release

This section provides for the conditional release of PET drug products when some analytical equipment is inoperable. We commend the FDA for recognizing the need for such a conditional release. We are concerned about how the frequency of conditional releases gets defined or somehow a defacto standard gets set in the document. Supplementary Information section II(L), p. 36 contains the statement:

“...so conditional final release should not be necessary except in very rare circumstances. Repeated conditional final releases based on unavailability of equipment that is difficult to envision failing or that is easily replaced could be considered to be a failure to take ‘reasonable efforts*** to ensure that the problem does not recur’ and could lead to FDA taking enforcement action.”

Section V(H) of the supplementary information in discussing PRA, this “very rare circumstance” is estimated at one conditional release per year for each PET production facility. There appears to be no consideration for size or production volume of the facility. We believe such a number is

arbitrary and the use of conditional release should be tracked by PET drug product producers to look for trends in equipment failures that need corrective actions. This is another quality element requiring investigation and corrective actions. In our opinion, the diligence applied in these corrective actions should be the measure for taking “reasonable efforts to ensure that the problem does not recur” not some arbitrary or ill-defined defacto standard.

212.70(f)(iii) Notification of receiving facility of conditional release

Should conditional release occur, this section requires that you immediately notify the receiving facility of the incomplete testing. It may be unlikely that personnel at the receiving facility will have sufficient knowledge of the surrounding cGMP conditional 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 would accomplish little other than creating confusion or undue concern on the part of the receiving facility personnel and potentially the patient. 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 a product failure.

We recommend the section §212.70(f)(iii), requirements to notify receiving facility about conditional release, be removed.

212.70(f)(v) Completion of omitted test

This section requires that the omitted test is completed using the reserve sample after the analytical equipment is repaired and that you document that reasonable efforts have been made to ensure that the problem does not recur. We acknowledge the use of reasonable efforts in the language although it would be subject to interpretation as to what reasonable efforts are. Clearly it will never be possible to ensure that equipment will not break down in the future or as mentioned previously give some guarantee as to the length of time before such breakdown. We recommend the statement be changed to read as follows:

“You complete the omitted test using the reserve sample after the analytical equipment is repaired and you document the repair and corrective and preventive actions.”

Draft Guidance Document

VII.B.4.a Control of components.....acceptance testing (lines 694-695)

The draft guidance allows acceptance of reagents, solvents, gases, purification columns and other auxiliary materials provided they meet internal written specifications and that a COA is obtained and examined.

USP chapter <71> Sterility Tests requires that prepared media be tested for growth promotion every 90 days. Commercially prepared media carry a manufacturer's expiration date. Retesting of commercially prepared growth media for growth promotion should not be required. Commercial growth media has been proven to be robust and reliable. In order to comply with the USP requirement for growth promotion, each PET producer would be required to have a microbiology laboratory. Such testing cannot be performed in a parenterals production facility without a separate microbiology lab. Producers of PET radiopharmaceuticals have not planned for this type of requirement.

Recommendation: Line 694 should be changed to read: "Reagents, solvents, gases, purification columns, commercial prepared growth media, and other auxiliary materials.