SOCIETY OF
NUCLEAR MEDICINE
AND MOLECULAR IMAGING

July 19, 2016

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, Maryland 20993

Re: Comments to FDA re Guidance Document on Data Integrity and Compliance with CGMP

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) would like to provide the following recommendations with respect to the FDA's draft Guidance Document on Data Integrity and Compliance with CGMP. The Society, composed of 17,000 members, works to set standards for molecular imaging and nuclear medicine practice by creating guidelines, sharing information through journals, hosting meetings, and leading advocacy on key issues that affect molecular imaging and therapy research and practice.

SNMMI would like to provide the following comments on the Draft Guidance entitled "Data Integrity and Compliance with CGMP, Guidance for Industry" published in draft April 2016 and distributed to regulated entities for comment. Where possible, we reference the specific area of the document to which the comments apply.

1. SNMMI appreciates the Agency's recognition of the differences in CGMP requirements for the manufacture of PET drug products, in contrast to the requirements for conventional pharmaceutical manufacturing. However, we have concerns that mentioning PET drug manufacturing in parts of this Draft Guidance will result in the Agency imposing certain requirements on PET drug manufacturers that were not originally intended or previously required. Although we understand that guidance documents do not establish legally enforceable responsibilities, the mention of PET manufacturing in the same context as the interpretation of regulations required of conventional drug manufacturing (21 CFR 211) infers applicability beyond what is actually required by regulation in 21 CFR 212. While SNMMI appreciates several references to the agency's Guidance for Industry entitled "PET Drugs—Current Good Manufacturing Processes (CGMP)", we recommend that this document consistently delineate the difference between PET drug manufacturing and conventional drug manufacturing within this document.

2. SNMMI agrees with FDA that data integrity is an important component in the production of safe and effective PET radiopharmaceuticals. SNMMI agrees with Lines 24-28 of the Draft Guidance that CGMP regulations and guidance allow for flexible and risk-based strategies to prevent and detect data integrity issues. We assert that PET radiopharmaceutical firms should be allowed to implement meaningful and effective strategies that are appropriate to their operations. Effective management of data integrity can require different methodologies, in order to meet the needs of different types of drug manufacturing operations, including PET drug manufacturing. SNMMI recommends that this be emphasized in the Draft Guidance.

3. With respect to audit trails, we reference lines 109-111 and 224-245. We would like to point out that FDA has previously addressed the issue of electronic audit trail for PET drug manufacturing in the Federal Register published December 10, 2009. The following is a quote from this Federal Register reference:

   "(Comment 43) We received one comment on electronic audit trail capabilities. The comment stated that, as we estimated, there is very little if any software of this nature in use by PET drug producers. The comment stated that many items of production equipment are incapable of the necessary software upgrades due to age and existing operating systems. The comment maintained that requiring the use of electronic audit trail software would be unduly burdensome for the PET community, and it recommended that we not require an electronic audit trail as part of PET CGMP provisions.

   (Response) We agree that the additional level of quality assurance that might be provided through the use of electronic audit trail capability does not warrant the additional costs that would be imposed to implement this capability. Therefore, the CGMP requirements for PET drugs do not include electronic audit trail requirements." Federal Register / Vol. 74, No. 236 / Thursday, December 10, 2009 / Rules and Regulations, page 65428, comment 43

   In light of the above referenced Federal Register, SNMMI believes that the Agency has been clear in its determination that an electronic audit trail is not required as part of the documentation of the production of PET radiopharmaceuticals under 21 CFR 212. As mentioned in comment #43 above, many small business entity PET production sites do not employ Laboratory Information Management System- (LIMS) capable equipment or electronic batch records which have the capability of producing an audit trail. This is still the case in 2016. Requiring the use of audit-trail capable equipment and systems would be cost prohibitive for many PET drug manufacturing operations, particularly those which are considered small business entities.

   In the draft Guidance Document, lines 109-111, in the section on Audit Trails, the document references 21 CFR 212.110(b). This CFR reference is quoted below:

   21 CFR 212.110 (b) All records, including those not stored at the inspected establishment, must be legible, stored to prevent deterioration or loss, and readily available for review and copying by FDA employees.

   Thus, 21 CFR 212.110 (B) on recordkeeping for PET drug manufacturing does not require an electronic audit trail. Additionally, it is noted that FDA's Guidance for Industry documents entitled, "PET Drugs—Current Good Manufacturing Practice (CGMP)" published December 2009 and "PET Drugs—Current Good Manufacturing Practice (CGMP), Small Entity Compliance Guide" published August 2011 do not call out electronic audit trail requirements. We contend that by including PET drug manufacturers within the scope of the draft Guidance Document with respect to electronic audit trails, the document exceeds the intent of the current regulations for PET drug manufacturing which are currently in place. We recommend that the document state that the requirement for electronic audit trails does not apply to PET drug manufacturing.

4. It is noted that PET drug manufacturers generally follow the guidance published in Guidance for Industry "PET Drugs—Current Good Manufacturing Practice (CGMP)" and its companion guidance document for small entities. Though some PET drug manufacturers use an electronic batch record, most are currently using a paper method. The PET CGMP guidance document is quoted below:

Section 212.50(c) requires the use of a batch record to document the production and testing of each batch. The batch records provide complete traceability and accountability for production and control of each batch. We recommend that information in the batch record (paper or electronic copy) accurately reflect the information contained in the master production and control records. The control records may be cross-referenced and not be included as part of the batch record. The batch record must contain the information needed for a documented history of the batch produced, including:

- *Documentation of the execution of each critical production step (e.g., timed events occurred within specifications, heating steps occurred at the specified temperature, and ingredients were properly transferred into the reaction vessel) where feasible, taking radiation exposure concern into consideration. For an automated radiochemical synthesis unit, the printout or electronic record at the end of synthesis documenting the execution of the production steps and controls could be used for the chemical synthesis portion of the batch record.*

- *A compilation of tests and printouts that led to acceptance of the final product.*

Further into the PET CGMP Guidance Document, the following is quoted:

Batch records should include documentation that each significant step in the production was accomplished. When entries are made in batch records, an entry should be made directly after performing the activity (in the order performed) and would have to identify the person (signature or initials) making the entry. Corrections to paper entries would be dated and signed or initialed, leaving the original entry still readable. We recommend that each batch record be reviewed and approved for final release (signature/initials and date). For requirements and information on electronic records and signatures, interested persons should refer to part 11 (21 CFR part 11, Electronic Records; Electronic Signatures) and the Agency guidance on Part 11, Electronic Records; Electronic Signatures — Scope and Application.[7]

SNMMI asserts that PET drug manufacturers who follow this PET CGMP guidance from the Agency adequately demonstrate compliance with respect to Data Integrity. Again, the draft guidance on Data Integrity seems to require steps beyond those that were envisioned by the Agency during the development of PET drug manufacturing regulations and communicated in Guidance interpreting 21 CFR 212 for the regulated industry.

5. We would like to point out that many PET drug manufacturers generate and maintain batch records and other CGMP documentation that exist in paper only or a combination of paper and electronic portions of the record. The use of this hybrid system is provided for in the Agency's guidance on Part 11, Electronic Records; Electronic signatures – Scope and Application. Lines 164-171 of the Part 11 guidance state:

Under the narrow interpretation of the scope of Part 11, with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in

place of paper format, part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be "using electronic records in lieu of paper records" under §§ 11.2(a) and 11.2(b). In these instances, the use of computer systems in the generation of paper records would not trigger part 11.

Further, Part 11 guidance addresses the use of electronic records combined with paper records in Lines 185-199:

Records that are required to be maintained under predicate rules, that are maintained in electronic format in addition to paper format, and that are relied on to perform regulated activities. In some cases, actual business practices may dictate whether you are using electronic records instead of paper records under § 11.2(a). For example, if a record is required to be maintained under a predicate rule and you use a computer to generate a paper printout of the electronic records, but you nonetheless rely on the electronic record to perform regulated activities, the Agency may consider you to be using the electronic record instead of the paper record. That is, the Agency may take your business practices into account in determining whether part 11 applies. Accordingly, we recommend that, for each record required to be maintained under predicate rules, you determine in advance whether you plan to rely on the electronic record or paper record to perform regulated activities. We recommend that you document this decision (e.g., in a Standard Operating Procedure (SOP), or specification document).

SNMMI asserts that the Draft Guidance on Data Integrity seems to require steps beyond those envisioned in the development of PET drug regulations and associated guidance documents. Additionally, it seems to go beyond what was communicated in the Guidance Document on Part 11. As stated above, some computer software used to generate and process analytical data (or other data required under the predicate rule) may not have the electronic audit trail capability that would meet the expectations detailed in the Draft Guidance on Data Integrity. Changes to such dynamic data may be better accomplished with other controls, such as Change Control or Deviation.

PET drug manufacturing firms that employ paper only or a hybrid documentation system should not be required to implement LIMS or Electronic Batch Record (EBR) systems to comply with Data Integrity expectations. This would require an unnecessary resource burden without concomitant benefit, especially for small entity firms. Larger firms that may decide to implement an electronic data management system that is Part 11 compliant should be able to generate appropriate audit trail data. However, SNMMI requests that the Agency edit the Draft Guidance to recognize the need to apply a risk-based approach to the assessment of paper-based, hybrid, or electronic data management systems. SNMMI asserts that PET manufacturers who follow the PET CGMP guidance would adequately demonstrate compliance with Data Integrity.

6. Referencing the Draft Guidance Document section on restricting access to CGMP computer systems (beginning with line 176), SNMMI agrees with the paragraph appearing in lines 189-195. We would emphasize that many PET drug manufacturers are staffed with only a few personnel, particularly at sites which could be considered as “small entity”. In this case, the person who

would have the appropriate knowledge and experience to produce the PET drugs and generate data for the batch record content would generally also have the expertise to serve as the system administrator, and may be the individual on staff with the expertise necessary to change settings or data when warranted. This is in contrast to a large drug manufacturer where these data security and production roles are separated. The small staff situation for PET drug manufacturers appears to be acknowledged in the Guidance Document by the paragraph appearing in lines 189-195. We would suggest that documenting the description of the changes made in this situation be carried out with a change control procedure. This type of document could be reviewed by FDA inspectors and would be an appropriate risk-based control. This approach is consistent with lines 282-284 of the Draft Guidance on Data Integrity.

7. Lines 210-219 of the Draft Guidance on Data Integrity address the need to control blank forms and describe the issuance of blank forms followed by reconciliation of all forms as an example of document control. While this may be appropriate in the case of a large pharmaceutical firm, the forms used in PET drug manufacturing do not require this level of control. In most cases, the form for documenting manufacture of a PET drug is issued on the day of manufacture, and a single form is issued. SNMMI recommends removing this example from the Draft Guidance, or at least describing this as an optional procedure.

   Additionally, lines 221-222 refer to issuance of bound paginated notebooks that have been issued by the document control group. There are few notebooks used in most PET drug manufacturing operations, and such requirement adds an unnecessary burden. SNMMI recommends removal of this example, or at least describing this as an optional procedure.

8. SNMMI would like to point out that according to 21 CFR 212.5(b). PET drug manufacturers who produce drugs used in investigational or research studies (administered under an IND or RDRC oversight) are allowed to follow the CGMP requirements spelled out in USP General Chapter <823> entitled “Radiopharmaceuticals for Positron Emission Tomography—Compounding.” It is noted that within this USP chapter, the requirements of system suitability are detailed. The Draft Guidance on Data Integrity also describes system suitability (See lines 332 to 360). The USP chapter provides specific guidance related to system suitability requirements for analytical HPLC systems. This guidance is important to PET drug manufacturers who produce investigational or research PET drugs. Therefore, SNMMI recommends that USP <823> also be referenced in this section of the guidance document.

9. The Draft Guidance on Data Integrity addresses the requirements for remediation of data integrity problems identified during inspections, in warning letters, or in other regulatory actions. See line 403-416. SNMMI views the corrective actions detailed in this section as too specific and prescriptive. Depending upon the situation, these corrective actions may not be meaningful and effective strategies for remediation. For example, if the data integrity issue identified during an inspection was not found to be a deliberate misstatement of data, the corrective action of removing individuals from CGMP positions would be ineffective. Rather, we

SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

suggest the firm may engage other methods to more effectively remediate the situation. In light of this, SNMMI recommends following edits to this section, with edits indicated in bold:

> "FDA encourages you to demonstrate that you have effectively remedied your problems by **implementing appropriate and effective corrective actions which may include one or more of the following**: hiring a third party auditor, determining the scope of the problem, **designing and** implementing a corrective action plan (globally) **appropriate to the scope of the problem**, ~~and~~ **(delete this "and") addressing personnel issues up to and including** removing at all levels individuals responsible for problems from CGMP positions, **or other appropriate corrective actions commensurate with the situation.** FDA may conduct an inspection to decide whether CGMP violations involving data integrity have been remedied**."**

SNMMI appreciates the opportunity to comment on the Draft Guidance entitled "Data Integrity and Compliance with CGMP." SNMMI is ready to discuss any of its comments or meet with the FDA regarding the above issues. In this regard, please contact Caitlin Kubler, Manger, Regulatory Affairs, by email at ckubler@snmmi.org or by phone at 703-326-1190.

Sincerely,

Sally Schwarz, MS, RPh, BCNP
SNMMI President