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FDA LISTENING SESSION:
Radiopharmaceutical Organizations
June 5, 2017
3:00PM-5:00PM

Statement of the American Pharmacists Association
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Director, Regulatory Affairs

Good afternoon, I am Michael Baxter, Director, Regulatory Affairs for the American Pharmacists Association (APhA). APhA, founded in 1852 as the American Pharmaceutical Association, represents more than 64,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, community health centers, physician offices, ambulatory clinics, managed care organizations, hospice settings, and the uniformed services.

I would like to thank the FDA for holding a listening session to gather stakeholder input on preparation of radiopharmaceuticals as part of FDA's efforts to ensure drug quality and security in the provision of safe, effective medications. As we have stated in our responses to previous Drug Quality and Security Act (DQSA) regulatory activity, most of the work of nuclear pharmacies or of pharmacists handling radiopharmaceuticals is not compounding. While compounding creates what are essentially new drug products designed to meet patient needs, most nuclear pharmacies are preparing radiopharmaceuticals from kits that are FDA-approved—activity that falls outside of the Food Drug and Cosmetic Act's (FD&C) definition of compounding. Special difficulties arise with radiopharmaceutical preparations because of the radiation hazards and the potential for biological contamination when using instruments to minimize the radiation hazard. Therefore, because of the uniqueness of the practice of nuclear pharmacy/ working with radiopharmaceuticals, FDA policies are needed to account for differences—a position validated by USP's decision to develop a new chapter, USP <825>, which will be specific for the preparation of radiopharmaceuticals.

APhA appreciates FDA's release of the December 2016 draft *Guidance for Industry Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies* (hereinafter, the "Guidance") to help clarify the applicability of DQSA and related FDA regulatory activity on the practice of nuclear pharmacy.[1] Better clarifying radiopharmaceutical regulatory requirements and guidance at the federal level will help states correctly craft their policies to allow for the practice of nuclear pharmacy and/ or preparation of radiopharmaceuticals. APhA's members appreciate the flexibility under this Guidance because it allows pharmacists to make needed adjustments to radioactivity, volume, and/ or the step-by-step procedures when preparing a patient-ready dose from an FDA-approved radiopharmaceutical product and dispense these unit doses based on patient time versus the name of the patient. APhA members are pleased FDA describes conditions under which it does not intend to take actions for violations of the FD&C, in particular section 505 (concerning new drug

[1] *See* 21 U.S.C. §353a(e). "``(e) Application.--This section shall not apply to-- ``(1) compounded positron emission tomography drugs as defined in section 201(ii); or ``(2) radiopharmaceuticals." Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm376733.htm

approval requirements), section 502(f)(1) (concerning labeling with adequate directions for use), and section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP) requirements).[2] However, there are provisions in the Guidance in which APhA requests clarification:

- **Applicability of the Guidance to Nuclear Regulatory Commission (NRC) licenses**. The Guidance very clearly states that it is not applicable to compounding or repackaging of radiopharmaceuticals that are not State-licensed nuclear pharmacies or federal facilities.[3] However, due to that particular wording, there are other valid licenses incorrectly excluded from the Guidance's purview. Licensing for hospital-based nuclear pharmacies and nuclear medicine departments are issued by the NRC, or an Agreement State, and therefore, depending on the state, would not necessarily be a State-licensed nuclear pharmacy. APhA believes it is not FDA's intention to exclude this type of licensure from the Guidance. In addition, the Guidance provides that an authorized nuclear pharmacist, as defined by the NRC, must be identified on a RAM license.[4] Broad scope radioactive material (RAM) licenses, which are typically issued to large academic institutions, do not specifically name personnel on the license. APhA asks FDA to clarify that the institutional radiation safety committee of a broad scope RAM license can name the authorized nuclear pharmacists, rather than restricting this requirement to the license itself.

- **Applicability to PET radionuclide kits**. Currently, the production of PET drugs are not addressed by the Guidance. Since the FDA approval of Gallium68 dotatate,[5] the position of the FDA has been to treat this product as if it will be prepared in the nuclear medicine department or nuclear pharmacies. PET isotopes used as an approved ingredient as part of an FDA—approved radionuclide kit should be treated similarly in regulations and guidances as radiopharmaceuticals.

- **Terminology in reference to radiopharmaceuticals.** To better delineate acceptable practices, APhA members are requesting additional examples of situations that would be considered "minor deviations," outside of FDA-approved labeling notated in the Guidance to better encompass the wide variety of products and practices. For example:
    - Diluting F-18 fludeoxyglucose (FDG), Tl-201 thallous chloride, or AdreView (Iobenguane I 123 Injection with normal saline (NS)) for the purposes of dispensing unit doses. This includes diluting multi-dose and single-dose vials taking into account factors such as buffers, bacteriostatic agents, and stabilizers that may already be present in the manufactured vial.
    - Substituting a generator brand from the brand mandated in the package insert as long as the two brands are essentially equivalent.
    - Substituting a validated quality control test such as media, solvents, and detectors for radiochemical or radionuclide purity testing.
    - Substituting a heating plate for a water bath where indicated in the package insert.

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[2] *See* FDA. Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies. Draft Guidance for Industry. Lines 24-28. 31-34. December 28, 2016. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534811.pdf
[3] *See* Lines 45-46. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534811.pdf
[4] *See* Lines 100-105. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534811.pdf
[5] FDA. FDA approves new diagnostic imaging agent to detect rare neuroendocrine tumors. Press Release. June 1, 2016. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm504524.htm

- **Beyond Use Date (BUD) for radiopharmaceuticals**. As stated in our previous comments, APhA requests that FDA further clarify the effect of "(except for the BUD)."[6] By excepting the BUD requirements of USP Chapters <795> and <797>, one would infer that there is no BUD requirement under the Guidance and therefore, pharmacists would rely on other state or federal requirements, if any, with regard to BUD. A BUD for radiopharmaceutical preparations should comply with USP standards for radiochemical purity, radionuclidic purity, chemical purity, sterility and stability, per the applicable USP monographs.

- **Reference to USP <795>.** According to the Guidance, an allowable "minor deviation" includes when a radiopharmaceutical is non-sterile and "compounded or repackaged in accordance with USP Chapter <795> (except for the BUD)."[7] At present, USP Chapter <795> specifically exempts radiopharmaceuticals because of the "special training" involved that is "beyond the scope of this chapter."[8] Accordingly, FDA should remove this provision. As previously noted, USP is currently working on a stand-alone radiopharmaceutical (sterile and non-sterile) chapter.

APhA also urges FDA to reference, or otherwise include in its radiopharmaceuticals' regulations and guidances, the current USP <797> language, which permits "the use of technologies, techniques, materials, and procedures" "so long as they have been proven to be equivalent or superior with statistical significance to those described herein."[9] Due to changing products, equipment, and evolving evidence, the use of techniques and procedures beyond those listed in the current USP Chapter <797>, is important to nuclear pharmacists and the practice of nuclear pharmacy and should not be prohibited if based on evidenced and do not negatively impact patients. These evidenced-based alternatives may actually be superior, such as those used to minimize the radiation exposure of personnel, and, in some cases, patients.

Finally, APhA continues to urge FDA to clarify certain provisions/ language in FDA's draft *Guidance for Industry on Insanitary Conditions at Compounding Facilities* that will be problematic to this important area of practice.[10] This guidance discusses appropriate procedures in unidirectional air hoods.[11] FDA should allow an accommodation for the temporary blocking of unidirectional air when necessary for the safe handling of radiopharmaceuticals in a vertical hood if patient safety is not affected to align with the practice of preparing radiopharmaceuticals. This guidance also contains language warning against "quick movement of personnel [that] disrupts the airflow and increases the risk of bringing lesser quality air into the ISO 5 area." An exemption should be provided for the handling of radiopharmaceuticals as this language conflicts with existing requirements under 10 CFR 835 "Occupational Radiation Protection" to comply with ALARA (as low as reasonably achievable)[12]

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[6] *See* Lines 230-234. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534811.pdf
[7] *See* Lines 230-234. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534811.pdf
[8] USP. General Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations. Revision Bulletin. January 1, 2014. Available at: http://www.usp.org/sites/default/files/usp_pdf/EN/gc795.pdf
[9] *See* USP. General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. Pg. 2. September 25, 2015. Available at: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/usp-gc-797-proposed-revisions-sep-2015.pdf
[10] *See* FDA. Guidance on Insanitary Conditions at Compounding Facilities. Draft Guidance. August 3, 2016. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf
[11] Ibid. *See* Lines 150-155. "Conducting aseptic manipulations or placing equipment/supplies in an area that blocks the movement of first pass air around an open container, whether before or after it is filled with sterile product. If unidirectional air over the critical surface is blocked, the area is no longer protected. If it is blocked by personnel conducting aseptic manipulations, contamination on personnel, particularly on exposed skin, could be introduced to the critical area."
[12] *See* 10 CFR 20.1003. Available at: https://www.nrc.gov/reading-rm/doc-collections/cfr/part020/part020-1003.html "ALARA means making every reasonable effort to maintain exposures to radiation as far below the dose limits in this part as is practical consistent with the purpose for which the licensed activity is undertaken, taking into account the state of technology, the economics of improvements in relation to state of technology, the economics of improvements in relation to benefits to the public health and safety, and other societal and socioeconomic considerations, and in relation to utilization of nuclear energy and licensed materials in the public interest." Also, *See* 10.CFR.835 "Occupational Radiation Protection." Available at: https://www.gpo.gov/fdsys/pkg/CFR-2015-title10-vol4/pdf/CFR-2015-title10-vol4-part835.pdf

for shielding, distance and time requirements in regards to directional air in an ISO 5 environment for radiopharmaceuticals.

I would like to close by thanking FDA for continuing to work with APhA and other pharmacy stakeholders to provide regulatory clarity to pharmacists and pharmacies handling, preparing and repackaging radiopharmaceuticals. We would like to reiterate our willingness to be a resource for FDA, especially with regard to the practice of nuclear pharmacy. Thank you again for the opportunity to provide comments on this important issue.