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APhA

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

[Submitted electronically to www.regulations.gov]

Re: Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities, Draft Guidance (Docket ID: FDA-2016-D-4318-0002)

Dear Sir/Madam:

APhA thanks FDA for the opportunity to submit these comments on the draft guidance entitled *Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities, Guidance for Industry* (hereinafter, the “Guidance”). Founded in 1852 as the American Pharmaceutical Association, APhA represents 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.

APhA appreciates FDA’s release of the Guidance in an effort to clarify the applicability of FDA’s Drug Quality and Security Act (DQSA) and related regulatory activity on the practice of nuclear pharmacy due to the fact that it is specifically exempted from 503A.¹ Adding to the need for clarity, is the fact that there is FDA guidance from 1984, which exempts nuclear pharmacy from cGMPs.² Our members are pleased the Guidance describes conditions under which FDA does not intend to take actions for violations of the Food Drug and Cosmetic Act (FD&C), in particular section 505 (concerning new drug 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).³

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>

² See FDA. Guidance for Industry. Nuclear Pharmacy Guideline. Criteria for Determining When to Register as a Drug Establishment. 1984. Available at: <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070293.pdf>

³ See Lines 24-28. 31-34.

As we have stated in our responses to previous DQSA regulatory activity, most of the work of nuclear pharmacies or of pharmacists handling radiopharmaceuticals is not actually 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 already FDA-approved—activity that falls outside of the FD&C’s definition of compounding.⁴ APhA appreciates FDA’s efforts to provide clarity to nuclear pharmacists and pharmacies when handling radiopharmaceuticals and recommends the following modifications to the Guidance to reflect this unique pharmacy setting.

I. Clarifying the Applicability of the Guidance to Nuclear Regulatory Commission (NRC) Licenses and PET Radionuclide Kits

Radioactive Materials (RAM) Licenses

The Guidance states that it applies to State-licensed nuclear pharmacies or Federal facilities.⁵ However, licensing for hospital-based nuclear pharmacies and nuclear medicine departments are issued by the NRC, or an Agreement State,⁶ and therefore, depending on the state, would not necessarily be a State-licensed nuclear pharmacy. Accordingly, APhA recommends that FDA modify the Guidance’s applicability to include the following—state-licensed nuclear pharmacies, Federal facilities or entities which hold RAM licenses for medical use from the NRC, or Agreement State agencies.

Additionally, the Guidance also states that “[a]n authorized nuclear pharmacist, as defined by the NRC, must be identified on a RAM license issued to a nuclear pharmacy where radiopharmaceuticals are prepared.”⁷ However, broad scope RAM licenses, which are typically issued to large academic institutions, do not specifically name personnel on the license. Therefore, APhA also recommends FDA modify the Guidance to allow the institutional radiation safety committee of a broad scope RAM license to name the authorized nuclear pharmacists, rather than restricting this requirement to the license itself.

PET Radionuclide Kits

The Guidance clearly states it does not address positron emission tomography (PET) drug production.⁸ Compounded PET drugs are also excluded under 503A.⁹ However, FDA recently approved a gallium-68 radiopharmaceutical, Ga-68 DOTATE, for PET diagnostic imaging of

⁴ See 21 U.S.C. §353a(f). Available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm376733.htm>

⁵ See Lines 45-46.

⁶ The NRC defines an Agreement State in part as one that has entered into an agreement with the NRC under section 274 of the Atomic Energy Act of 1954 (42 U.S.C. 2021). Available at:

<http://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title42-section2021b&num=0&edition=prelim>

⁷ See Lines 100-105.

⁸ See Line 40.

⁹ 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>

somatostatin receptor-positive neuroendocrine tumors.¹⁰ Unlike most PET radiopharmaceuticals, this new offering can be prepared from a kit utilizing a germanium-68/gallium-68 generator rather than a cyclotron. Accordingly, APhA recommends that PET drugs prepared from kits should be covered by the Guidance. Specifically, we recommend that the language in the Guidance makes clear that while the production of PET drugs are not addressed by the Guidance, PET isotopes used as an approved ingredient as part of an FDA-approved radionuclide kit are included.

II. Providing Additional Examples of “minor deviations”

While FDA generally views “compounding” as the combining, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug, the Guidance allows for “minor deviations” not contemplated in radiopharmaceutical preparations’ labeling. APhA and its members appreciate this flexibility 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. For example, adjusting the amount of radioactivity to accommodate for the time it takes to get a preparation to patients is a standard practice in nuclear pharmacy.

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. While we understand that there is no way to provide an all-inclusive or exhaustive list of acceptable scenarios, we believe there should be additional examples to provide better clarity regarding the varied scenarios involving radiopharmaceutical preparation. For example:

- Diluting F-18 fludeoxyglucose (FDG) or Tl-201 thallous chloride with normal saline (NS) for the purposes of dispensing unit doses.
- Substituting a generator brand from the brand mandated in the package insert as long as the two brands are essentially equivalent.
- Diluting AdreView (Iobenguane I 123 Injection) in NS.
- 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.

III. Clarifying BUD for Radiopharmaceuticals

According to the Guidance, an allowable “minor deviation” includes when a radiopharmaceutical is prepared or repackaged:

- *“If it is a non-sterile radiopharmaceutical, it is compounded or repackaged in accordance with USP Chapter <795> (except for the BUD); or*
- *If it is sterile radiopharmaceutical, it is compounded or repackaged in accordance with USP <797> (except for the BUD).”¹¹*

¹⁰ 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>

¹¹ See Lines 230-234.

APhA requests that FDA further clarify the effect of “(except for the BUD).” 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. Making this provision more confusing is the fact that at present, USP Chapter <795> specifically exempts radiopharmaceuticals because of the “special training” involved that is “beyond the scope of this chapter.”¹² Accordingly, FDA should remove the provision referencing USP Chapter <795>.

With regard to BUDs for radiopharmaceuticals, APhA believes that when supported by data, the pharmacist or compounder should be able to assign BUDs based on the assigned USP’s risk levels. A BUD for radiopharmaceutical preparations needs to include compliance with USP standards for radiochemical purity, radionuclidic purity, chemical purity, sterility and stability, per the applicable USP monographs and apply to all radiopharmaceutical preparations. The lack of clarity by FDA and USP regarding radiopharmaceuticals and the practice of nuclear pharmacy is why APhA’s Nuclear Special Interest Group (SIG) recently requested USP define parameters for the nuclear pharmacy industry in a stand-alone radiopharmaceutical chapter.

IV. Requesting Changes to Draft Guidance for Industry on Insanitary Conditions at Compounding Facilities to Accommodate Radiopharmaceuticals

While we appreciate FDA’s issuance of this Guidance, we are concerned that some of FDA’s previously released guidance related to compounding do not accurately account for radiopharmaceuticals and the practice of nuclear pharmacy. As mentioned in previous APhA comments, and recognized in this radiopharmaceutical Guidance, in most cases, the activities by nuclear pharmacists and others handling radiopharmaceuticals involves preparing FDA approved products for patients, rather than compounding. Furthermore, while APhA and its members working with radiopharmaceuticals are committed to the highest quality standards to ensure patient safety, we believe the unique nature of nuclear pharmacy and radiopharmaceuticals (e.g., due to the decay (self-limiting time) of these preparations, nearly all are given a BUD of less than 24 hours) warrants policies that allow for this critical practice area without affecting patient safety. Accordingly, APhA reiterates our call for clarity of the provisions/language in FDA’s *Guidance for Industry on Insanitary Conditions at Compounding Facilities* (hereinafter, the “Guidance”) that will be problematic to this important area of practice.¹³

That Guidance discusses appropriate procedures in unidirectional air hoods.¹⁴ While this language aligns with USP Chapter <797>, APhA would like FDA to provide allowances for the

¹² 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

¹³ 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>

¹⁴ 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.”

preparations of radiopharmaceuticals. Nuclear pharmacists must operate behind shielding, using lead or other material in a primary engineering device, and use shielding around syringes and vials. In addition, nuclear pharmacists must draw vertically, thus blocking the top-down unidirectional air in a laminar flow hood when handling radiopharmaceuticals. Therefore, APhA strongly urges FDA to 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. In addition, the Guidance contains language warning against “quick movement of personnel disrupts the airflow and increases the risk of bringing lesser quality air into the ISO 5 area.” This language conflicts with existing requirements under 10 CFR 835 “Occupational Radiation Protection” to comply with ALARA (as low as (is) reasonably achievable)¹⁵ for shielding, distance and time requirements in regards to directional air in an ISO 5 environment for radiopharmaceuticals.

Finally, APhA urges FDA to acknowledge the current USP Chapter <797> language which states that “the use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein.”¹⁶ The use of techniques and procedures beyond those listed in USP Chapter <797> is important to nuclear pharmacists and the practice of nuclear pharmacy and should not be prohibited if they are evidenced-based 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.

APhA appreciates FDA’s efforts 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. If you have any questions or require additional information, please contact Michael Baxter, Director of Regulatory Affairs, at mbaxter@aphanet.org or by phone at (202) 429-7538.

Sincerely,



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Executive Vice President and CEO

¹⁵ 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>

¹⁶ 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

APhA Comments to FDA on Draft Guidance: “Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities, Draft Guidance”

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cc: Stacie S. Maass, RPh, JD, Senior Vice President, Pharmacy Practice and Government Affairs