November 26, 2014

BY EMAIL

Jane Axelrad
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Food and Drug Administration
White Oak Office Building 51
10903 New Hampshire Avenue
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Re: Definitions of Radiopharmaceutical Preparation and Compounding

Dear Ms. Axelrad:

The undersigned organizations, all of which participated in the September 24, 2014 Listening Session on Radiopharmaceutical Compounding, are pleased to submit this consensus statement regarding the distinction between radiopharmaceutical compounding and preparation. We have attached recommended definitions of these terms that FDA can consider for incorporation into a guidance on radiopharmaceutical compounding by nuclear pharmacies. As discussed during the Listening Session, clear definitions of radiopharmaceutical compounding and preparation will have obvious importance in determining whether or not a nuclear pharmacy activity constitutes compounding and is thus subject to FDA's radiopharmaceutical compounding guidance.

Nuclear pharmacies are an important link in patient care, as they provide patient-specific unit-dose radiopharmaceutical products to hospitals and clinics throughout the United States. The practice of nuclear pharmacy, and the minor deviations that are made in radiopharmaceutical preparation, ensure patient access to vital diagnostic and therapeutic radiopharmaceutical drugs in a safe and cost-effective manner to health care providers.

You will see that we have defined "radiopharmaceutical preparation" to mean either activities performed in accordance with the instructions in the FDA-approved labeling, or minor deviations from those instructions. It is important to note that minor deviations apply to very short-lived radiopharmaceutical drugs that are generally prepared and administered within 24 hours. We have added a definition of

"minor deviations" in order to more clearly distinguish these from compounding. We are proposing that "minor deviations" be limited to changes in (i) radioactivity; (ii) volume; or (iii) the step-by-step procedures for preparing the radiopharmaceutical in a patient-ready dose. The addition of components not specified in the FDA-approved labeling goes beyond a minor deviation and should be considered compounding.

At the Listening Session, we discussed examples of minor deviations in radioactivity and volume that are made to account for radioactive decay in relation to geographical distance from the patient and time of administration to the patient. We have included these examples in the attached proposed definitions. Note, however, that a nuclear pharmacy that adds additional radioactivity and volume under these circumstances must perform quality, identity, and purity quality control testing as an assurance that the deviation does not compromise the safety and effectiveness of the radiopharmaceutical for its intended use.

The notion of minor deviations in step-by-step procedures requires some explanation. Minor deviations in the step-by-step procedures contained in the FDA-approved labeling may be warranted in order to incorporate new technologies; enhance quality control procedures; or substitute procedures that have been found to reduce potential radiation exposure without compromising the finished preparation for the patient. Following are several examples of such minor deviations. We have not included these examples in our proposed definitions because they are too specific and detailed to include in a guidance document, but we provide them here for your background.

- *The use of a solid crystal sodium iodide well chamber and/or multi-channel analyzer in place of an ion chamber to determine the final radiochemical purity in the preparation of Technescan MAG3™ Kit for the Preparation of Technetium 99m Mertiatide.* The package insert states that the activity of the sample elutions should be assayed using an ion chamber. However, it has become standard nuclear pharmacy practice to instead use a solid crystal well chamber, based on its greater accuracy for gamma emission detection and spectral analysis.[1] Also, because of the greater sensitivity of the solid crystal well chamber, a sample size of less than 10µL is used instead of the 0.1mL recommended for the ion chamber in the manufacturer's package insert. The smaller sample size provides better resolution of complexes and reduces potential radiation exposure to pharmacy personnel.

[1] T. B. Saleh, Radiopharmaceutical Quality Control, Basic Sciences of Nuclear Medicine, 56-58 (Magoly M. Kahil, ed., 2011).

- *The use of a smaller sterile evacuated vial than those supplied by the manufacturer for the preparation of Sodium Pertechnetate Tc 99m injection using an Ultra-TechneKow DTE (Technetium Tc 99m Generator).* The package insert for the generator provides instructions for elution with 10mL and 20mL sterile evacuated vials supplied with the generator. However, it has become the preferred practice to substitute a smaller sterile evacuated vial (e.g., 5mL), which obtains the same result but reduces radiation exposure to pharmacy personnel.

- *The use of two syringes instead of one for the dilution of Technescan MAG3 Kit for the Preparation of Technetium 99m Mertiatide.* The FDA-approved package insert indicates that normal saline should be used to dilute sodium pertechnetate Tc 99m solution to the desired concentration prior to addition to the vial. However, studies have shown that the radiation dose to the pharmacist's hands is reduced, with no detrimental effect on the quality or stability of the final radiopharmaceutical, if one syringe is used for drawing up Tc 99m solution and another is used for drawing up normal saline, and their respective contents are then added separately to a vial to obtain the desired concentration.[2]

- *The use of a heating block in place of a rolling boil water bath for heating the reaction vial.* The instructions for certain Tc 99m-based radiopharmaceuticals state that a boiling water bath should be used for heating the contents of the reaction vial. *See*, *e.g.*, package inserts for Kit for the Preparation of Technetium Tc 99m Sulfur Colloid Injection; Technescan MAG3 Kit for the Preparation of Technetium 99m Mertiatide. However, a heating block has largely replaced the boiling water bath as the preferred method of heating a reaction vial, because the water bath, being non-sterile and therefore having to be located outside the aseptic preparation area, introduces opportunities for contamination when the reaction vial is transported to or placed in the bath.

[2] A. Mackenzie, Reduction of Extremity Dose in the Radiopharmacy, 18 Nucl. Med. Comm. 578-81 (l997); T.V. Bogsrud et al., Effects of Alternative Reconstitution Procedures on the Labeling Efficiency and In Vitro Stability of 99TcM-labeled Radiopharmaceuticals, 20 Nucl. Med. Comm. 61-65 (1999).

We thank you and your colleagues for soliciting stakeholder input on this question and other issues relating to radiopharmaceutical compounding. We would be happy to answer any questions you may have about the attached definitions.

Sincerely,

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PROPOSED DEFINITIONS FOR
FDA RADIOPHARMACEUTICAL COMPOUNDING GUIDANCE

"**Radiopharmaceutical Preparation**" means:

(1) Combining, admixing, mixing, diluting, reconstituting, or other similar activities performed in accordance with directions contained in the FDA-approved labeling of a radiopharmaceutical; or

(2) Making a minor deviation from the directions in the FDA-approved labeling of a radiopharmaceutical, by or under the supervision of a licensed nuclear pharmacist or a physician, when warranted in order to accommodate improvements in nuclear pharmacy technique or technology; to account for radioactive decay in relation to geographical distance from the patient and time of administration to the patient; or to account for other circumstances not contemplated in the manufacturer's directions. A nuclear pharmacist or physician making a minor deviation must perform quality control testing to ensure the quality, identity, and purity of the prepared radiopharmaceutical, as an assurance that the safety and effectiveness of the radiopharmaceutical are not compromised.

"Minor deviation" means a deviation in (i) radioactivity; (ii) volume; or (iii) the step-by-step procedures for preparing the radiopharmaceutical in a patient-ready dose. The addition of components not specified in the FDA-approved labeling is not a minor deviation and constitutes radiopharmaceutical compounding rather than radiopharmaceutical preparation.

An example of a minor deviation in radioactivity is the addition of a supplemental amount of Tc-99m sodium pertechnetate to an FDA-approved kit to ensure access of the radiopharmaceutical to a geographically distant patient with a later use time that does not compromise the safety and effectiveness of the drug.

An example of a minor deviation in volume is the use of an additional quantity of normal saline to reduce the concentration of the prepared radiopharmaceutical in cases where a supplemental amount of Tc-99m sodium pertechnetate has been added, as described above. The additional radioactivity may necessitate a corresponding increase in volume so that the quantity of the radiopharmaceutical to be drawn up into a unit-dose syringe can be more precisely measured.

Minor deviations in the step-by-step procedures for preparation are process changes that result in the same finished radiopharmaceutical, but that are made in order to incorporate improvements in technology, enhance quality control procedures, and/or decrease radiation exposure to pharmacy personnel.

"Radiopharmaceutical Compounding" means combining, admixing, mixing, diluting, reconstituting, or otherwise altering an FDA-approved radiopharmaceutical, or formulating a radiopharmaceutical from bulk drug or radionuclide substances. Radiopharmaceutical

compounding does not include radiopharmaceutical preparation as defined above (i.e., activities performed in accordance with (or with minor deviations from) directions contained in the FDA-approved labeling).