February 23, 2017

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852


Dear Sir or Madam:

The Council on Radionuclides and Radiopharmaceuticals (“CORAR”) submits these comments on FDA’s Draft Guidance for Industry on Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies and Federal Facilities (hereinafter, the “Draft Guidance”).

CORAR is an association of companies in the United States and Canada that manufacture radiopharmaceuticals, sealed sources, and radionuclides primarily used in nuclear medicine procedures, as well as nuclear pharmacies that dispense these drugs to health care providers for administration to patients in such procedures.

FDA has recognized that legitimate radiopharmaceutical compounding, like the compounding of conventional drugs, is essential in order to fill treatment gaps where available approved products are not suitable for individual patients. On the other hand, nuclear pharmacies, like their conventional pharmacy counterparts, must be prevented from engaging in practices that may compromise the quality, sterility, or potency of compounded products, or from using compounding as a pretext for unlawfully marketing unapproved drugs. We commend FDA for successfully balancing these competing interests by presenting well-reasoned, workable, and enforceable conditions under which nuclear pharmacies may engage in legitimate compounding and repackaging without fear

of prosecution under sections 505, 502(f)(1), or 501(a)(2)(B) of the Federal Food, Drug,
and Cosmetic Act (“FDC Act”). Moreover, in doing so, FDA has succeeded in taking
into account the unique characteristics of radiopharmaceuticals – such as their extremely
short shelf-lives, their complex preparation methods, and their potential for causing
radiation exposure – which often require nuclear pharmacists to exercise greater
discretion than conventional pharmacists in preparing compounded drugs.

In short, CORAR is strongly supportive of the Draft Guidance. Nevertheless, we
believe that there are particular areas where it could be improved. To that end, we
provide our comments below.

1. Definition of Essential Copy

A compounded radiopharmaceutical is not eligible for the enforcement relief
described in the Draft Guidance if it is “essentially a copy of a marketed FDA-approved
radiopharmaceutical.”2 The Draft Guidance sets forth conditions under which a
compounded radiopharmaceutical will be considered essentially a copy of a marketed
FDA-approved radiopharmaceutical, among which is the condition that the active
ingredient(s) in the former have the same or similar dosage strength (i.e., radioactive
dose) as the active ingredient(s) in the latter.3 A footnote explains that “similar strength”
means that the “strength of the compounded radiopharmaceutical is within 10% of the
strength of the approved radiopharmaceutical.”4

CORAR opposes the use of a fixed maximum percentage to determine whether a
compounded radiopharmaceutical is a copy of an approved product. Any fixed
percentage will permit unscrupulous nuclear pharmacies to avoid the prohibition on
essential copies merely by increasing or decreasing the radioactivity by slightly more
than the established percentage. For example, if the 10% rule is finalized, a nuclear
pharmacy will be permitted to compound a copy with radioactivity that differs by 11%
but is otherwise the same as an approved product, without any premarket approval or any
determination that the compounded product makes a clinical difference for an individual
patient. This would create an unacceptably large loophole in the prohibition against
essential copies.

Moreover, a standard that compares the radioactive strength of a compounded
product to that of an approved product would be confusing and difficult to comply with
or enforce. Many radiopharmaceuticals are prepared from cold kits by lot, after which
individual patient doses are drawn from the lot into syringes. The manufacturer’s
instructions for such a radiopharmaceutical typically provide two different radioactivity

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2 P. 7, lines 241-42. Page numbers refer to the Draft Guidance, unless otherwise noted.
3 P. 7, lines 249-51.
4 P. 7, footnote 16.
recommendations: one for the strength of the lot, and another for the individual adult dose. A variance percentage test for equivalence in radioactive dose would first raise the question whether the permitted variance percentage applies to the radioactive strength of the lot or the recommended adult dose, or both.

If the recommended adult dose is the relevant strength, additional questions would arise. For radiopharmaceuticals more than conventional drugs, the manufacturer’s recommendation for the radioactive dose for an adult is very often disregarded by prescribing physicians, who may order a different strength depending on the type of nuclear medicine study, the type of imaging equipment, the weight of the patient, or other factors. It would be illogical to base the essential copy determination on a fixed percentage variance from a parameter (individual radioactive dose) that itself varies widely from patient to patient. We urge FDA to delete the radioactive dose criterion from Section III(A)(9). It is sufficient to rely on the other factors identified in the Draft Guidance in order to determine whether a compounded product is an essential copy.

2. Interstate Distribution

FDC Act Section 503A, which applies to pharmacy compounding of non-radiopharmaceutical drugs, contains a restriction on the interstate distribution of inordinate amounts of compounded drug products. This is consistent with long-standing FDA policy that large-scale interstate distribution of compounded drugs is an indication that a pharmacy is acting as a manufacturer marketing unapproved drugs rather than compounding drugs for individual patients within the practice of pharmacy. CORAR has heretofore recommended to FDA that any radiopharmaceutical compounding guidance should, similar to section 503A, prohibit the interstate distribution of inordinate amounts of compounded radiopharmaceuticals (excluding minor deviations). CORAR proposed to FDA that the distribution of compounded radiopharmaceuticals should be considered inordinate if the number of compounded radiopharmaceutical prescriptions (excluding minor deviations) that are distributed annually to locations that are not within the state in which the nuclear pharmacy is located, or in immediately contiguous states, is greater than 20% of the total number of prescriptions dispensed or distributed (including both intrastate and interstate) by the nuclear pharmacy, excepting inter-company transfers. However, FDA did not include any restriction on inordinate interstate distribution of compounded radiopharmaceuticals in the Draft Guidance.

The inordinate interstate distribution prohibition in section 503A, due to an unrelated constitutional defect, was without effect in June 2012 when the New England Compounding Center began distributing 6,500 vials of contaminated methylprednisolone injection to customers in 23 states, causing over 65 deaths and many more illnesses from fungal meningitis. Had section 503A’s inordinate interstate distribution prohibition been in effect, this tragedy might have been avoided. The large majority of
radiopharmaceuticals are also sterile injectables. We strongly urge FDA to add such a prohibition to the section of the Draft Guidance on “Radiopharmaceutical Compounding That Involves Manipulation Other Than Minor Deviations,” in order to prevent unscrupulous nuclear pharmacies from using compounding as a pretext to manufacture and solicit orders for large volumes of unapproved sterile injectable drugs and ship them nationwide. The 20% test described above would strike a balance between discouraging abusive compounding, while permitting nuclear pharmacies to service their regional area with legitimately compounded radiopharmaceuticals. Accordingly, we recommend that the following paragraph be added on page 9 after line 300:

14. The radiopharmaceutical is distributed by a nuclear pharmacy that does not distribute inordinate amounts of compounded radiopharmaceuticals interstate. FDA considers interstate distribution of compounded radiopharmaceuticals to be inordinate if the number of compounded radiopharmaceutical prescriptions that involve manipulations other than minor deviations distributed during the previous 12 calendar months to locations that are not within the state in which the nuclear pharmacy is located, or an immediately contiguous state, is greater than 20% of the total number of prescriptions dispensed or distributed (including both intrastate and interstate) by the nuclear pharmacy. This limitation on interstate distribution does not apply to inter-company transfers.

3. Requirements for Notation of Clinical Difference

The Draft Guidance provides that a compounded radiopharmaceutical will not be considered to be essentially a copy of an approved marketed product if there is “a change that produces for an identified individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded radiopharmaceutical and the comparable FDA-approved radiopharmaceutical . . . .”\(^5\) The Draft Guidance requires that the prescriber’s determination must be documented in writing on the prescription or order by either the prescribing practitioner or by the compounder, reflecting a conversation with the prescriber. The Draft Guidance does not prescribe the format for the notation, but it must “make clear that the prescriber identified the relevant change and the clinical difference produced for the patient.”\(^6\) The Draft Guidance provides the example of “No Dye X, patient allergy.”\(^7\)

This dual requirement to identify both the change and the clinical difference (i.e., the reason) is important. Identifying the change but not the reason for the change would

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\(^5\) Pp. 7-8, lines 258-60.
\(^6\) P. 8, lines 266-68 (emphasis added).
\(^7\) P. 8, line 271.
make it easy for a pharmacy to sidestep the copy prohibition by soliciting orders that specify a change – for example, a preservative-free formulation or a liquid dosage form – that makes no clinical difference for any patient.

The Draft Guidance contains useful illustrations of inadequate notations that identify only the patient name and the formulation, or that identify a lower price as a reason. We urge FDA to add to these negative examples an additional one that illustrates the inadequacy of a notation containing merely the change, but not the reason. The Draft Guidance should make clear that a mere generalized notation that a clinical difference determination has been made (e.g., “compound clinically necessary”) would be insufficient, as would a notation that merely notes the change from the approved product – e.g., “No Dye X,” “liquid form,” or “alcohol-free” – but not the nature of the clinical difference for the patient.

4. Beyond Use Date (“BUD”)

One of the requirements both for manipulations that involve repackaging or minor deviations and for manipulations that involve compounding other than minor deviations is that the radiopharmaceutical must comply with USP Chapter <797> if it is a sterile radiopharmaceutical or USP Chapter <795> if it is non-sterile, “except for the BUD.”

The reason for the BUD exceptions in the Draft Guidance is unclear. The BUD sections of Chapters <795> and <797> set forth generally applicable principles for beyond use dating. Among other things, they identify potential sources of relevant information for establishing a BUD (e.g., consultation with the manufacturer, reliance on literature), describe factors to consider, explain the preference for product-specific experimental studies over theoretical predictions, and recommend written SOPs for beyond use dating. We believe the principles and recommendations in these USP chapters apply equally to radiopharmaceuticals and non-radioactive drugs. We recommend that FDA delete the BUD exceptions from the Draft Guidance.

Respectfully submitted,

Michael Guastella

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8 P. 7, lines 230-34 and p. 9, lines 322-27.