UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

August 22, 2019

MEMORANDUM TO: Christopher J. Palestro, M.D., Chairman
Advisory Committee on the Medical Uses of Isotopes

FROM: Christian E. Einberg, Branch Chief ***/RA/***
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SUBJECT: RESPONSES TO THE ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES' NOVEMBER 2018 RECOMENDATIONS ON THE DRAFT GERMANIUM-68/GALLIUM-68 PHARMACEUTICAL GRADE GENERATORS LICENSING GUIDANCE

Below are the U.S. Nuclear Regulatory Commission's (NRC) staff responses from the November 2018 Advisory Committee on the Medical Uses of Isotopes (ACMUI) Report (ML19091A256) on the draft "Germanium-68 (Ge-68)/Gallium-68 (Ga-68) Pharmaceutical Grade Generators Licensing Guidance" (hereafter, the guidance). The NRC staff accepted all ACMUI recommendations and suggested changes.

The Licensing Guidance was issued in July 2019 (Agencywide Documents Access and Management System Accession No. ML19106A367).

1. **ACMUI Recommendation:** Page 1, 1st paragraph: Delete the sentence "Future Ge-68/Ga-68 radionuclide generators will be addressed in revisions to the licensing guidance."

   Staff Response: Accepted. The NRC staff implemented the change.

2. **ACMUI Recommendation:** Page 2, Section 4.1, 2nd paragraph: Replace the words "FDA approved" with "if utilizing an Food and Drug Administration (FDA)- approved kit for radiolabeling."

   Staff Response: Accepted. The NRC staff implemented the change.

3. **ACMUI Recommendation:** Page 3, Authorized Use for commercial nuclear pharmacies: Add "(Form 313 Item 5)" under "Radionuclides," "Chemical/Physical Form," and "Maximum Possession Limit."

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Staff Response: Accepted. The NRC staff implemented the change.

4. **ACMUI Recommendation:** Page 4 Section 4.4, 1st paragraph: Replace "to develop/create Ga-68" with "to elute Ga-68."

   Staff Response: Accepted. The NRC staff implemented the change.

5. **ACMUI Recommendation:** Page 4, Section 4.4: The training for authorized individuals has omitted an "alternate pathway" option for Authorized Nuclear Pharmacists (ANPs), similar to 10 CFR 35.55(b), and written attestation signed by a preceptor ANP.

   Staff Response: Accepted. The NRC staff implemented the change and added the alternate pathway as an option to the guidance.

6. **ACMUI Recommendation:** Page 5, Written attestation requirement: Replace "35.1000 Ge-68 generator use" with "35.1000 Ge-68/Ga-68 generator use."

   Staff Response: Accepted. The NRC staff implemented the change.

7. **ACMUI Recommendation:** Page 5, Section 4.4, last sentence: Replace "Physicians or nuclear pharmacists" with "other individuals."

   Staff Response: Accepted. The NRC staff implemented the change.

8. **ACMUI Recommendation:** Page 6, 1st bullet: Delete the word "to."

   Staff Response: Accepted. The NRC staff implemented the change.

9. **ACMUI Recommendation:** Page 6, 3rd bullet: Begin the sentence with "Eluting…"

   Staff Response: Accepted. The NRC staff implemented the change.

10. **ACMUI Recommendation:** Page 6, 7th bullet: Remove the value of 0.001 percent, as this is specific to a particular manufacturer. Replace with a generic reference to "the manufacturer's recommended breakthrough limit."

    Staff Response: Accepted. The NRC staff implemented the change.

11. **ACMUI Recommendation:** Page 6, 7th bullet: Delete the sentence "Not knowingly distributing or administering to a patient or human research subject any material containing Ga-68 which is determined to exceed the manufacturer's 0.001 percent breakthrough limit." This topic is covered by the revised 8th bullet, below.

    Staff Response: Accepted. The NRC staff implemented the change.

12. **ACMUI Recommendation:** Page 6, 8th bullet: Revise to read "During the course of breakthrough testing, if the eluate exceeds the manufacturer's breakthrough limits, the eluate will not be distributed or administered to a patient or human research subject;"

    Staff Response: Accepted. The NRC staff implemented the change.

13. **ACMUI Recommendation:** Page 6, 10th bullet: Move this bullet to be the last bullet in the series.

    Staff Response: Accepted. The NRC staff implemented the change.

14. **ACMUI Recommendation:** Page 6, 11th bullet: The criteria for "multiple" and "unusable" are vague. Delete "on multiple occasions rendering the generator unusable in human patients and research subjects." Adopt the language from the new 10 CFR 35.3204 for telephone reports to the NRC Operations Center within 7 days.

    Staff Response: Accepted. The NRC staff implemented the change.

15. **ACMUI Recommendation:** Page 6, 12th bullet: "Center" should be capitalized.

    Staff Response: Accepted. The NRC staff implemented the change.

16. **ACMUI Recommendation:** Page 7, general: Due to the extended time necessary for completing a breakthrough test, the guidance should specify when a generator failure is "effective." The Subcommittee recommends specifying that a generator has "failed" on the date when the breakthrough calculation is performed. This should be no more than 7 days from the date of the previous breakthrough calculation.

    Staff Response: Accepted. The NRC staff implemented the change.

17. **ACMUI Recommendation:** Page 7, 1st bullet: Remove this bullet. There is no reasonable scenario where a breakthrough failure could cause a reportable medical event due to Ge-68, based on 5 rem effective dose to the whole body or 50 rem dose to an organ.

    Staff Response: Accepted. The NRC staff implemented the change.

18. **ACMUI Recommendation:** Page 7, 2nd bullet: In the first sentence, replace "manufacture's" with "manufacturer's."

    Staff Response: Accepted. The NRC staff implemented the change.

19. **ACMUI Recommendation:** Page 7, 3rd bullet: Revise the sentence to read "Conduct surveys of all areas of licensed material use, including the generator storage and kit preparation areas, for contamination each day of use; and"

    Staff Response: Accepted. The NRC staff implemented the change.

20. **ACMUI Recommendation:** Page 7, 4th bullet: Remove the bullet. This bullet appears to be less stringent than the guidance in NUREG-1556, Vol. 13, Appendix R, which says that areas where licensed material is stored must be surveyed for contamination weekly. What additional survey should be performed every three months that would not be captured in the required weekly surveys?

    Staff Response: Accepted. The NRC staff implemented the change.

21. **ACMUI Recommendation:** Page 8, Section 7.3.2: Distributor (in 2 cases) should be spelled with an "o."

    Staff Response: Accepted. The NRC staff implemented the change.

22. **ACMUI Recommendation:** Page 9, Section 7.4.1, 2nd paragraph: In the last sentence, delete the first "for" to read "…must provide financial assurance for decommissioning…"

    Staff Response: Accepted. The NRC staff implemented the change.

23. **ACMUI Recommendation:** Page 10, Section 8, 1st paragraph: Add "Medical" at the beginning of the first sentence.

    Staff Response: Accepted. The NRC staff implemented the change.

24. **ACMUI Recommendation:** Page 10, Section 8, 2nd paragraph: Delete "also."

    Staff Response: Accepted. The NRC staff implemented the change.

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