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

August 23, 2024

MEMORANDUM TO: Hossein Jadvar, MD, PhD, Chair
Advisory Committee on the Medical Uses of Isotopes

FROM: Christian E. Einberg, Branch Chief
Medical Safety and Events Assessment Branch
Division of Materials Safety, Security, State,
and Tribal Programs
Office of Nuclear Material Safety
and Safeguards

Signed by Einberg, Christian
on 08/23/24

SUBJECT: U.S. NUCLEAR REGULATORY COMMISSION RESPONSES TO THE ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPE'S RECOMMENDATIONS ON THE DRAFT PROPOSED RULE AND ASSOCIATED DRAFT IMPLEMENTATION GUIDANCE FOR REPORTING NUCLEAR MEDICINE INJECTION EXTRAVASATIONS AS MEDICAL EVENTS

On June 17, 2024, the Advisory Committee on the Medical Uses of Isotopes (ACMUI) held a public teleconference to discuss their subcommittee report on the NRC staff's proposed changes to the U.S. Nuclear Regulatory Commission's (NRC) requirements for medical use of byproduct material to address reporting of nuclear medicine injection extravasations as medical events. To provide their recommendations, the ACMUI subcommittee was provided the NRC Staff's preliminary proposed rule to report nuclear medicine extravasations, associated implementation guidance, and model procedures. During this meeting, the full ACMUI voted to approve the subcommittee report, which can be found at Agencywide Documents Access and Management System Accession Number ML24170A316.

As stated in the ACMUI report, the ACMUI supported the staff's draft proposed rule and associated draft implementation guidance which they found to be well-written and containing useful information for licensees. In addition, the ACMUI provided specific comments on the NRC staff's preliminary documents which they reviewed. Below are the NRC's staff responses to these specific comments.

Recommendations

1. **ACMUI Recommendation:** "As proposed in this rule, the NRC defines extravasation to mean the unintentional presence of a radiopharmaceutical in the tissue surrounding the blood vessel following an injection." The subcommittee believes that this is overly specific and excludes other possible injection errors that may occur such as during intraarterial injections, intrathecal injections as well as injections intended to be into a specific body cavity or space (i.e., pleural, peritoneal, etc.)

Staff Response: Partially Accepted. The staff revised “intravenous” injections to be “intravascular” injections, to reflect that extravasations could also occur during intraarterial injections. The staff did not accept the ACMUI’s recommendation to revise the definition of an extravasation to include injections into a specific body cavity or space, because the staff felt this would expand and change the scope of the rulemaking. In addition, incidents associated with injecting a radiopharmaceutical into the wrong body cavity or space may already be reportable as wrong route of administration under 10 CFR 35.3045(a)(1)(ii)(B) as described in the draft guidance section 1.1.2.2. The draft guidance was updated to include reference to intrapleural and intraperitoneal.

CONTACT: Daniel DiMarco, NMSS/MSST
(301) 415-3303

2. **ACMUI Recommendation:** Replace the term “potential” with either “likely” or “expected” in the proposed rule language for 10 CFR 35.3045(a)(3), “The administration of byproduct material that results or has the *potential* to result in a radiation injury from an extravasation, as determined by a physician.”

   Staff Response: Not Accepted. As stated in the FRN, focusing on the "potential” for harm ensures that licensees have adequate procedures to detect and assess extravasations while the patient is still in care of the licensee. However, the term “potential” does not require licensees to determine the probability that an extravasation will result in a radiation injury or add a subjective weight like the terms “expected” or “likely”.

3. **ACMUI Recommendation:** Change text on page 1 to “This proposed rule would affect medical licensees that administer radiopharmaceuticals for diagnostic and therapeutic purposes.”

   Staff Response: Partially Accepted. In line with the staff’s revision in response to the ACMUI’s first recommendation, the staff replaced all instances of “intravenous” throughout the rulemaking package with “intravascular.” The staff chose to replace “intravenous” with “intravascular” because the staff is choosing to keep the rulemaking focused on intravascular injections, rather than also including injections into body cavities and spaces, because the staff felt this would expand and change the scope of the rulemaking. The passage now reads, “This proposed rule would affect medical licensees that administer intravascular radiopharmaceuticals for diagnostic and therapeutic purposes.”

4. **ACMUI Recommendation:** Change text on page 11 to “This proposed rule would affect all NRC and Agreement State medical licensee who administer radiopharmaceuticals for diagnostic therapeutic purposes.”

   Staff Response: Partially Accepted. See response to comment #3. The text now reads “This proposed rule would affect all NRC and Agreement State medical licensee who administer intravascular radiopharmaceuticals for diagnostic therapeutic purposes.”

5. **ACMUI Recommendation:** Add “potential” to the following passage on page 13 of the FRN: “Moreover, since an extravasation can occur during almost any radiopharmaceutical IV injection, imposing a dose-based criterion would require monitoring millions of administrations per year, which would result in significant regulatory burden for medical licensees for only a marginal increase in radiation safety. In light of the above information on the *potential* risks posed by extravasations of radiopharmaceuticals, the NRC believes such a dose-based requirement would be inappropriate.”

   Staff Response: Not Accepted. While the majority of extravasations do not cause radiation injury, past cases of radiation injury due to extravasation described in literature do show extravasations can pose a risk of radiation injury.

6. **ACMUI Recommendation:** On page 14 of the FRN, add “may”: “...written directive and intended by an authorized user (AU) is administered to a patient. While there may be some delay time, normal biological processes *may* transport the dose to the intended target.”

   Staff Response: Accepted. This change was made to the FRN

7. **ACMUI Recommendation:** Delete the following sentence on page 17 of the FRN: “For example, extravasations from I-131-iodocholesterol resulting in an erythematous plaque and Thallium-201”. Both radiopharmaceuticals mentioned are not currently commercially available in the US. The subcommittee suggests this sentence be removed.

   Staff Response: Not Accepted. The staff’s reference of these extravasation examples from scientific literature is intended to illustrate that diagnostic extravasations have caused patient harm. The current commercial availability of these radiopharmaceuticals is not relevant to the idea being conveyed.

8. **ACMUI Recommendation:** Change text on page 26 to “The conclusion from the analysis is that this proposed rule and associated guidance would result in a cost to the industry (NRC and Agreement State medical licensees that administer radiopharmaceuticals for diagnostic and therapeutic purposes),”

   Staff Response: Partially Accepted. See response to comment #3. The text now reads “The conclusion from the analysis is that this proposed rule and associated guidance would result in a cost to the industry (NRC and Agreement State medical licensees that administer intravascular radiopharmaceuticals for diagnostic and therapeutic purposes),”

9. **ACMUI Recommendation:** Change text on page 30 of the proposed rule to “Who will be required or asked to respond: NRC and Agreement State licensees who administer radiopharmaceuticals for diagnostic and therapeutic purposes.”

   Staff Response: Partially Accepted. See response to comment #3. The text now reads “Who will be required or asked to respond: NRC and Agreement State licensees who administer intravascular radiopharmaceuticals for diagnostic and therapeutic purposes.”

10. **ACMUI Recommendation:** Comment on the Draft Regulatory Guide: Section 1.1.1: Add a statement about whether it is reportable if an unintended dosage was administered and the licensee didn't fill out a written directive when they should have (i.e., there was no "prescribed" dosage). This would address situations where the administered dose was >20% different from the intended dose but the physician failed to complete a written directive.

    Staff Response: Accepted. This change was made to the Draft Regulatory Guide.

11. **ACMUI Recommendation:** Comment on the Draft Regulatory Guide: Section 4: Instead of referencing the best practices via ML number, the Subcommittee recommends listing the best practices explicitly in the regulatory guide as there are only five short best practices.

    Staff Response: Accepted. This change was made to the Draft Regulatory Guide.

12. **ACMUI Recommendation:** Comment on the Draft Regulatory Guide: Appendix B: Add example of microsphere medical event.

    Staff Response: Accepted. This change was made to the Draft Regulatory Guide.

13. **ACMUI Recommendation:** Comment on the Draft Regulatory Guide: Appendix B: Two of the examples use Lutathera. The subcommittee recommends limiting to one example per radiopharmaceutical, or describing the radiopharmaceuticals generically (i.e., a beta-emitting radiopharmaceutical).

Staff Response: Accepted. The change was made to the Draft Regulatory Guide, the radiopharmaceutical is described generally.

14. **ACMUI Recommendation:** Comment on the Draft Model Procedures: Informed consent should not be required by the NRC for either diagnostic or therapeutic nuclear medicine procedures. Patient education whether done verbally and/or in printed format is the appropriate method of communication between patient and physician.

    Staff Response: Accepted. Changes were made to the Draft Model Procedures to clarify that they address patient education but do not include informed consent.

15. **ACMUI Recommendation:** Comment on the Draft Model Procedures: Guidelines for observation of unexpected sensations by the patient or other developments observed by the medical staff or the patient should be developed by each facility in accordance with recommendations from the professional medical societies such as the Society for Nuclear Medicine and Molecular Imaging (SNNMI), the American College of Radiology (ACR), the American Society for Radiation Oncology (ASTRO), and the American Association of Physicists in Medicine (AAPM).

    Staff Response: Accepted. The staff agrees that guidelines should be developed by each facility in accordance with recommendations from professional medical societies.

NRC Response to Extravasation Subcommittee DATE August 26, 2024

DISTRIBUTION:
HJadvar, NMSS/MSST

ADAMS Accession No.: Memo ML24190A072

OFFICE	NMSS/MSST/MSEB	NMSS/MSST/MSEB	NMSS/MSST/MSEB	
NAME	DDimarco *DD*	KTapp *KT*	CEinberg *CE*	
DATE	Aug 2, 2024	Aug 5, 2024	Aug 23, 2024	

OFFICIAL RECORD COPY