UPDATES TO INJECTION QUALITY MONITORING, CLASSIFICATION, AND REPORTING REQUIREMENTS FOR EXTRAVASATIONS

A Report for the
U.S. Senate Committee on Appropriations
U.S. House of Representatives Committee on Appropriations

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INTRODUCTION

The U.S. Nuclear Regulatory Commission (NRC) developed this report in response to requests in House of Representatives Report No. 116-83, "Energy and Water Development and Related Agencies Appropriations Bill, 2020" (Ref. 1), and Senate Report No. 116-102, "Energy and Water Development Appropriations Bill, 2020" (Ref. 2). Specifically, these reports called on the Commission to provide updates to injection quality monitoring, classification, and reporting requirements with regard to extravasations not later than 90 days after the enactment of Public Law 116-94, "Further Consolidated Appropriations Act, 2020" (Ref. 3).

Currently, the NRC does not classify radiopharmaceutical extravasations as medical events and thus does not require them to be reported to the agency. However, considering recent and anticipated advancements in nuclear medicine, the NRC staff is reevaluating this position. The reporting and analysis of events help the NRC to identify deficiencies in the safe use of radioactive material and ensure that corrective actions are taken to prevent recurrence. This report provides a brief summary of the NRC's activities related to extravasations, the considerations informing the NRC staff's ongoing evaluation, and planned next steps.

BACKGROUND

Extravasation is the infiltration of injected fluid into the tissue surrounding a vein or artery. It is a medical issue not limited to the injection of radiopharmaceuticals, and published studies indicate overall extravasation rates range from 0.10 to 16 percent of injections (Refs. 4–8). Common factors that contribute to the probability of extravasation include the anatomy of the patient; training, experience, and technique of the medical personnel administering the injection; catheter size; and patient activity (Ref. 9).

The NRC's mission, in part, is to regulate the nation's civilian use of byproduct, source, and special nuclear materials to provide reasonable assurance of adequate protection of public health and safety. This includes regulating the medical use of radioactive material to protect the health and safety of workers, the general public, and patients. The Commission's policy is not to intrude into medical judgments affecting patients, except as necessary to provide for the radiation safety of workers and the general public. The NRC's medical use regulations are guided by the Commission's Medical Policy Statement (Volume 65 of the *Federal Register* (FR), page 47654 (65 FR 47654)) (Ref. 10). In a 1980 rulemaking (45 FR 31701) (Ref. 11), the Commission made the policy decision not to require licensees to report extravasations to the NRC. The Commission stated that "Extravasation frequently occurs in otherwise normal intravenous or intraarterial injections. It is virtually impossible to avoid. Therefore, the Commission does not consider extravasation to be a misadministration."[1]

[1] In 2002, the NRC amended its medical use regulations and replaced the term "misadministration" with the term "medical event." This report uses the term "misadministration" only when referring to the Commission's 1980 policy decision.

DISCUSSION

More than 16 million diagnostic and about 100,000 therapeutic nuclear medicine procedures are performed in the United States each year (Ref. 12). Diagnostic procedures usually involve smaller amounts of radiopharmaceuticals for imaging organs. Therapeutic procedures deliver larger amounts of radiopharmaceuticals to treat cancer and other ailments. The NRC's review of published studies shows that extravasation of therapeutic radiopharmaceuticals is uncommon (Refs. 13–23). However, the likelihood of tissue damage around the injection site is higher in therapeutic extravasations (Ref. 24). A comprehensive study published in the *European Journal of Nuclear Medicine and Molecular Imaging* in 2017 (Ref. 24) reviewed 3,016 radiopharmaceutical extravasations: 3,006 involved diagnostic radiopharmaceuticals and 10 involved therapeutic radiopharmaceuticals. Three diagnostic extravasations required follow up because of skin irritation and tissue swelling around the injection site. Five therapeutic extravasations resulted in ulceration around the injection site.

The introduction of new diagnostic and therapeutic radiopharmaceuticals since the Commission's 1980 policy decision has prompted the NRC to reevaluate whether the extravasation of radiopharmaceuticals should be reported to the NRC as medical events.[2] Medical events may not necessarily result in harm to the patient or a safety violation for the medical facility, but they can indicate a potential problem in a medical facility's use of radioactive materials and administration as directed by the physician. The NRC analyzes each reported medical event to determine whether further action is needed. If there is a violation, the regulator may take enforcement action. The NRC also monitors trends in reported events to identify whether something in its regulations or guidance requires clarification. Medical event reporting allows the NRC to follow up on events, ensure licensees take appropriate corrective actions to prevent future occurrences, and share lessons learned with other licensees that might be experiencing similar challenges.

The Advisory Committee on the Medical Uses of Isotopes Assessments of Extravasations

The issue of whether to classify extravasation as a medical event and require reporting is not new. The Commission addressed the issue in its 1980 rulemaking on misadministrations, and the NRC staff addressed this issue again in 2008, 2009, and 2019 with input from the NRC's Advisory Committee on the Medical Uses of Isotopes (ACMUI).[3]

In 2008, the NRC staff asked the ACMUI to evaluate the 1980 policy of excluding extravasations from medical event reporting after learning of an extravasation with fluorine-18 fluorodeoxyglucose, a common diagnostic radiopharmaceutical. The licensee reported this to the NRC as a possible medical event because the dose to the tissue appeared to exceed the reporting criteria, but later retracted its report in accordance with the 1980 policy. In its December 2008 public teleconference (Refs. 25, 26), the ACMUI recommended that the NRC

[2] The NRC's medical event reporting requirements are contained in Title 10 of the *Code of Federal Regulations* (10 CFR) 35.3045, "Report and Notification of a Medical Event."

[3] The ACMUI advises the NRC on policy and technical issues that arise in the regulation of the medical uses of radioactive material in diagnosis and therapy. The ACMUI membership includes health care professionals from various disciplines who comment on changes to NRC regulations and guidance; evaluate certain nonroutine uses of radioactive material; provide technical assistance in licensing, inspection, and enforcement cases; and bring key issues to the Commission's attention for appropriate action.

maintain its policy of excluding diagnostic extravasations from medical event reporting, even if the resulting dose exceeds the reporting criteria. The ACMUI also agreed to continue its discussion of therapeutic extravasations.

During the May 2009 ACMUI meeting (Refs. 27, 28), the NRC staff noted that the 1980 policy decision did not make a distinction between diagnostic and therapeutic radiopharmaceutical extravasations. Intravenous administration of therapeutic radiopharmaceuticals was rare in 1980, but was becoming increasingly more common by 2009. The ACMUI members discussed the clinical aspects of extravasation and recommended that the NRC continue to also exempt therapeutic extravasations from the NRC's medical event reporting requirements.

During its April 2019 meeting (Refs. 29, 30), the ACMUI established a subcommittee to reevaluate the Commission's 1980 policy on extravasations and provide recommendations. The subcommittee presented its report (Ref. 31) and recommendations at the ACMUI's fall meeting on September 10, 2019 (Refs. 32, 33). The full ACMUI endorsed the following conclusions in the subcommittee's report:

- Extravasation is a practice of medicine issue and not an item that the NRC needs to regulate.

- Extravasations should be considered a type of "passive" patient intervention and should be added to the NRC's definition of patient intervention under 10 CFR 35.2, "Definitions."

- There is no evidence at this time for the subcommittee to recommend reclassifying extravasation as a medical event. However, the subcommittee recommends that extravasations that lead to unintended permanent functional damage be reportable as medical events under 10 CFR 35.3045(b).

Updates to Injection Quality Monitoring

In April 2019, an external stakeholder[4] informed the ACMUI and the NRC of a device that can monitor injection sites for excess radioactivity during and after a diagnostic radiopharmaceutical injection (Ref. 30). The device uses topical scintillation detectors to generate time-activity curves, which show the relative amount of local radioactivity over time. The stakeholder stated that this technology could allow for lower extravasation rates, thus reducing inaccurate diagnoses and treatments and protecting patients from unnecessary radiation exposure.

Under the NRC's Medical Policy Statement, the NRC regulates the medical use of radionuclides as necessary to provide for the radiation safety of workers and the public. While the NRC encourages licensees to use quality assurance tools and available technology to ensure that the licensee delivers the administration that the physician intended, the NRC does not require the use of such tools or technology. The ACMUI subcommittee's report on extravasation (Ref. 31) stated, "The prevention of extravasation is a medical training issue for the authorized user (AU) physician and the technologist under the supervision of the AU, which is considered medical practice and not something that needs NRC regulation."

[4] Lucerno Dynamics, LLC, attended the ACMUI's April 3, 2019, meeting and gave a presentation on its LARA infiltration (i.e., extravasation) detection technology. The Lucerno Dynamics presentation is on pages 69–106 and 214–252 of the ACMUI meeting transcript (Ref. 30).

Classification—Extravasations

Currently, the NRC excludes extravasation of radiopharmaceuticals from its medical event reporting regulations. Extravasations are not reported to the NRC and are not recorded in the NRC's Nuclear Material Events Database (NMED).[5]

The ACMUI subcommittee's October 23, 2019, report on extravasations (Ref. 31) stated there was "…no evidence at this time for the Subcommittee to recommend a reclassification of extravasation at the injection site for radiopharmaceuticals to be considered a medical event." In supporting this conclusion, the report indicated that it was common to have some remaining isotope at the injection site and it was difficult to assign a radiation dose to the extravasation. The ACMUI also commented that in the case of extravasation of diagnostic radiopharmaceuticals for positron emission tomography (PET) imaging, none of the total doses in those extravasations would meet the NRC's current medical event reporting criteria.

The ACMUI subcommittee report further stated the following:

> Extravasation frequently occurs in otherwise normal intravenous or intraarterial injections and is virtually impossible to avoid. While there are devices in the market today that can identify extravasation, not all [nuclear medicine] cameras (PET and SPECT [single photon emission computed tomography]) can quantify for all radiopharmaceuticals. These methods do not quantify the amount of activity that is infiltrated [extravasated] but it does alert medical personnel to the occurrence of an infiltrate [extravasation]. Members of this subcommittee are unaware of any cases where there has been patient harm due to extravasation as of today.

Medical Event Reporting Requirements

The NRC's regulations for medical events have evolved to be more risk-informed and performance-based over time. The agency has revised and clarified the reporting criteria to filter out less risk-significant medical events and instead focus regulatory attention on events that may indicate a potential problem in the use of radioactive materials. Medical event reporting assists the NRC and Agreement States[6] in performing their regulatory oversight functions, including timely reactive inspections and potential enforcement actions. The NRC is currently considering how reporting extravasations would contribute to this safety framework.

In 1980, the Commission amended its medical regulations in 10 CFR Part 35, "Medical Use of Byproduct Material," to require licensees to (1) keep records of all misadministrations of radioactive material, (2) promptly report therapy misadministrations to the NRC, the referring physician, and the patient or the patient's responsible relative (or guardian), and (3) report

[5] The NRC's NMED contains records of events involving nuclear material (including medical events) reported to the NRC by NRC licensees, Agreement States, and nonlicensees. The Idaho National Laboratory maintains the database. The NRC staff, Agreement State staff, and other users authorized by the NRC may access the NMED data. The NRC uses NMED to monitor trends and determine whether something in the NRC's regulations or guidance may need to be clarified.

[6] An Agreement State is a State that has signed an agreement with the NRC authorizing the State to regulate certain uses of radioactive materials within its border. There are currently 39 Agreement States that regulate the majority of medical licensees in the United States. Agreement State medical licensees report medical events to their Agreement State regulating agency, and the Agreement State enters medical event data into the NRC's NMED.

diagnostic misadministrations quarterly to the NRC (Ref. 11). In 1994, the NRC amended the threshold for reporting misadministrations and implemented dose-based criteria (59 FR 61767) (Ref. 34). In 2002, the NRC replaced the term “misadministration,” which could be read to imply negligence, with the term “medical event,” which better conveys that the radioactive material was not administered as directed by the physician (Ref. 35).

During the September 2019 ACMUI meeting (Refs. 32, 33), the ACMUI recommended that the NRC consider extravasations to be a type of passive “patient intervention” and include them in the NRC’s current definition of patient intervention under 10 CFR 35.2. While the ACMUI did not recommend reclassifying extravasations as medical events, it did recommend that extravasations that lead to unintended permanent functional damage be reportable as medical events. The NRC is currently evaluating ACMUI’s recommendations.

NEXT STEPS

The NRC staff is considering whether extravasations should be reported as medical events, but it has not made any conclusions. As part of its risk-informed approach to regulating medical uses of radioactive material, the NRC staff is examining the role of medical event reporting in implementing the Medical Policy Statement. If the NRC does decide extravasations should be reported, it will establish the reporting criteria, such as reporting those extravasations exceeding the current criteria for medical events, those extravasations causing permanent functional damage to an organ or physiological system, whether a different reporting threshold should be applied, and whether a distinction should be made between diagnostic and therapeutic extravasations.

As part of its review, the NRC staff is also examining past NRC rulemakings, NMED medical event data, and published studies that indicate some diagnostic extravasations could exceed the current reporting criteria (Refs. 13–15, 24). The NRC will also gather input from the Agreement States, the Conference of Radiation Control Program Directors, and the U.S. Food and Drug Administration. The NRC will continue to closely coordinate with the ACMUI and evaluate its additional insights. Related to the ACMUI’s recommendation that the NRC consider extravasation to be a form of “passive” patient intervention (Ref. 31), the ACMUI will provide the NRC staff with the results of its review of the regulatory definition of patient intervention. Additionally, the ACMUI extravasation subcommittee will review the NRC staff’s preliminary recommendation once it is drafted.

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