[7590-01-P]

NUCLEAR REGULATORY COMMISSION

10 CFR Part 35

NRC-2022-0218

RIN 3150-AK91

Reporting Nuclear Medicine Injection Extravasations as Medical Events

AGENCY: Nuclear Regulatory Commission.

ACTION: Proposed rule.

SUMMARY: The U.S. Nuclear Regulatory Commission (NRC) is proposing to amend its regulations to require reporting of certain nuclear medicine injection extravasations as medical events and to require medical licensees to develop, implement, and maintain written procedures for evaluating and reporting extravasations. This proposed rule would affect medical licensees that administer intravenous radiopharmaceuticals for diagnostic and therapeutic purposes. The NRC plans to hold a public meeting to promote full understanding of this proposed rule and facilitate public comments.

DATES: Submit comments by **[INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**. Comments received after this date will be considered if it is practical to do so, but the NRC is able to ensure consideration only for comments received on or before this date.

ADDRESSES: You may submit comments by any of the following methods; however, the NRC encourages electronic comment submission through the **Federal rulemaking website**:

- **Federal Rulemaking website:** Go to https://www.regulations.gov and search for Docket ID NRC-2022-0218. Address questions about NRC dockets to Dawn Forder; telephone: 301-415-3407; email: Dawn.Forder@nrc.gov. For technical questions contact the individuals listed in the FOR FURTHER INFORMATION CONTACT section of this document.
- **Email comments to:** Rulemaking.Comments@nrc.gov. If you do not receive an automatic email reply confirming receipt, then contact us at 301-415-1677.
- **Fax comments to:** Secretary, U.S. Nuclear Regulatory Commission at 301-415-1101.
- **Mail comments to:** Secretary, U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001, ATTN: Rulemakings and Adjudications Staff.
- **Hand deliver comments to:** 11555 Rockville Pike, Rockville, Maryland 20852, between 7:30 a.m. and 4:15 p.m. eastern time, Federal workdays; telephone: 301-415-1677.

You can read a plain language description of this proposed rule at https://www.regulations.gov/docket/NRC-2022-0218. For additional direction on obtaining information and submitting comments, see “Obtaining Information and Submitting Comments” in the SUPPLEMENTARY INFORMATION section of this document.

FOR FURTHER INFORMATION CONTACT: Irene Wu, Office of Nuclear Material Safety and Safeguards, telephone: 301-415-1951, email: Irene.Wu@nrc.gov and Daniel

DiMarco, Office of Nuclear Material Safety and Safeguards, telephone: 301-415-3303, email: Daniel.Dimarco@nrc.gov. Both are staff of the U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001.

SUPPLEMENTARY INFORMATION:

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I. Obtaining Information and Submitting Comments

A. Obtaining Information

Please refer to Docket ID NRC-2022-0218 when contacting the NRC about the availability of information for this action. You may obtain publicly available information related to this action by any of the following methods:

- **Federal Rulemaking Website:** Go to https://www.regulations.gov and search for Docket ID NRC-2022-0218.

- **NRC's Agencywide Documents Access and Management System (ADAMS):** You may obtain publicly available documents online in the ADAMS Public Documents collection at https://www.nrc.gov/reading-rm/adams.html. To begin the search, select "Begin Web-based ADAMS Search." For problems with ADAMS, please contact the NRC's Public Document Room (PDR) reference staff at 1-800-397-4209, at 301-415-4737, or by email to PDR.Resource@nrc.gov. For the convenience of the reader, instructions about obtaining materials referenced in this document are provided in the "Availability of Documents" section.

- **NRC's PDR**: The PDR, where you may examine and order copies of publicly available documents, is open by appointment. To make an appointment to visit the PDR, please send an email to PDR.Resource@nrc.gov or call 1-800-397-4209 or 301-415-4737, between 8 a.m. and 4 p.m. eastern time, Monday through Friday, except Federal holidays.

B. Submitting Comments

The NRC encourages electronic comment submission through the **Federal rulemaking website** (https://www.regulations.gov). Please include Docket ID NRC-2022-0218 in your comment submission.

The NRC cautions you not to include identifying or contact information that you do not want to be publicly disclosed in your comment submission. The NRC will post all comment submissions at https://www.regulations.gov as well as enter the comment submissions into ADAMS. The NRC does not routinely edit comment submissions to remove identifying or contact information.

If you are requesting or aggregating comments from other persons for submission to the NRC, then you should inform those persons not to include identifying or contact information that they do not want to be publicly disclosed in their comment submission. Your request should state that the NRC does not routinely edit comment submissions to remove such information before making the comment submissions available to the public or entering the comment into ADAMS.

II. Background

This section discusses the evolution of the existing regulatory framework for medical event reporting and the various requests for, and consideration of whether, certain extravasations should be included in medical event reporting to provide context for the proposed changes. 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.

A. NRC's Medical Event Reporting Regulations

In 1980, the NRC amended the medical use regulations in part 35 of title 10 of the *Code of Federal Regulations* (10 CFR), “Medical Use of Byproduct Material,” to require the reporting of medical misadministrations (later renamed medical events) (45 FR 31701). The reporting and analysis of medical events helps to identify deficiencies in the safe use of radioactive material and to ensure that corrective actions are taken to prevent recurrence. In the 1980 rulemaking, the NRC stated in a comment response that it did not consider an extravasation to be a misadministration because extravasations frequently occur in otherwise normal intravenous or intraarterial injections and that extravasations are virtually impossible to avoid. After the 1980 rulemaking, the medical event reporting requirements were subsequently updated in final rules published in the *Federal Register* in July 1991, April 2002, and July 2018 (56 FR 34104, 67 FR 20250, and 83 FR 33046). In 2002, the term and criteria for ‘‘misadministration’’ were replaced with ‘‘medical event’’ and several updates were made to § 35.3045, ‘‘Report and notification of a medical event.’’ None of these updates addressed extravasations. Consistent with the terminology currently used in 10 CFR part 35, the NRC will use the term “medical event” for the rest of this document.

B. Requests for and Consideration of Revisions to NRC’s Regulations

1. NRC’s Advisory Committee on the Medical Uses of Isotopes (ACMUI)

In 2008 and 2009, ACMUI evaluated whether extravasations should continue to be excluded from medical event reporting after a licensee reported (and later retracted) an extravasation involving a common diagnostic radiopharmaceutical. During ACMUI public meetings in December 2008 and May 2009, the ACMUI discussed diagnostic and therapeutic extravasations and recommended all extravasations should continue to be excluded from the medical event reporting requirements, and the staff agreed with the recommendation.

2. Lucerno Dynamics Petition

On May 18, 2020, Lucerno Dynamics, LLC, submitted a petition for rulemaking (PRM)-35-22, that requested the NRC to amend 10 CFR part 35 to require medical event reporting of radiopharmaceutical extravasations that lead to an irradiation resulting in a localized dose equivalent exceeding 50 rem (0.5 sievert). On September 15, 2020, the NRC published a notice of docketing and request for public comment in the *Federal Register* (85 FR 57148). The comment period closed on November 30, 2020, and the NRC received 488 comment submissions from the medical community, Agreement States, congressional representatives, and members of the public. The NRC heard from medical professionals strongly opposed to regulating extravasations. Some representatives of the medical community commented that no technology can prevent extravasations, although monitoring for extravasations could allow clinicians to begin mitigation measures sooner. Multiple commenters stated that requiring extravasations to be reported as medical events would create a significant regulatory burden on licensees with no added safety benefit. One commenter stated that the NRC did not need to regulate extravasations because many institutions already have initiatives for injection quality monitoring and improvement, and multiple mechanisms exist to evaluate and promote the safe medical use of radioactive materials.

3. NRC Evaluation

In a separate initiative, the NRC independently evaluated whether extravasations should be reported as medical events. To inform the independent evaluation, the NRC considered information from the petitioner, the ACMUI, Agreement States, and external stakeholders, as well as available published literature on extravasations. The NRC's preliminary evaluation of extravasations and medical event reporting resulted in the

consideration of several rulemaking options, all of which would require that certain extravasations be reported as medical events. The NRC provided its preliminary evaluation to the ACMUI extravasation subcommittee in April 2021. In September 2021, the subcommittee's recommendations were presented to the full ACMUI during a public meeting. At that meeting, the ACMUI endorsed a non-dose-based rulemaking option for reporting extravasations that result in a radiation injury.

4. NRC Rulemaking Plan and Commission Direction

On May 9, 2022, the NRC staff submitted to the Commission SECY-22-0043, "Petition for Rulemaking and Rulemaking Plan on Reporting Nuclear Medicine Injection Extravasations as Medical Events (PRM-35-22; NRC-2020-0141)," requesting approval to consider the issues raised in PRM-35-22 in the rulemaking process and to initiate rulemaking to require reporting of extravasations that require medical attention for a suspected radiation injury.

In staff requirements memorandum (SRM) to SECY-22-0043, dated December 12, 2022, the Commission approved the staff's recommendation to amend 10 CFR part 35 to include certain nuclear medicine injection extravasations as reportable medical events. Additionally, the Commission directed the staff to explore approaches to reduce reliance on patient reporting, develop regulatory guidance for all medical events, and look for opportunities to accelerate the rulemaking schedule without shortening public comment periods. On December 30, 2022, the NRC published a document in the *Federal Register* stating that the NRC would consider the issues raised in the petition in the rulemaking process and closed the petition docket (87 FR 80474).

5. Pre-rulemaking activities – Information Request

On April 19, 2023, the NRC staff published in the *Federal Register* an information request with preliminary proposed rule language and posed specific questions to obtain input from stakeholders (88 FR 24130). The questions were divided into three topics: definitions, procedures, and healthcare inequities. The NRC staff provided a 90-day public comment period, which the NRC staff later extended by 45 days to allow members of the public more time to develop and submit their input (88 FR 45824; July 18, 2023). On May 24, 2023, the NRC staff held a public meeting to facilitate stakeholder feedback on the preliminary proposed rule language and questions included in the information request. During the meeting, the NRC staff presented background on development of the NRC's medical event reporting requirements, the NRC's current regulations on medical event reporting, the basis for the preliminary proposed rule language, and the basis for the questions in the April 19, 2023, information request. Participants asked clarifying questions and were provided details on how to submit their feedback.

The NRC received over 200 submittals on the information request from members of the public, medical professionals, licensees, patient advocacy groups, nongovernmental organizations, and Agreement States. More than half of the submittals received were form letters that asked the NRC to reconsider the non-dose-based aspect of the extravasation rulemaking because it could put a burden on patients and stated the NRC should require providers to treat an extravasation like any other medical event (a threshold of 50 rem (0.5 sievert) localized dose). The NRC also received feedback that a rulemaking for extravasations was unnecessary because the NRC could instead clarify that the existing medical event regulations were inclusive of extravasations. (The NRC staff determined that extravasations do not fit under the current medical event criteria; therefore, 10 CFR Part 35 must be revised through the notice-and-comment rulemaking process in order to report them as medical events.) Copies of the submittals received on

the information request and preliminary proposed rule language may be viewed and downloaded from the Federal eRulemaking Website https://www.regulations.gov, under Docket ID NRC-2022-0218.

Since this comment period was outside the formal proposed rule notice-and-comment rulemaking process, formal responses to the submittals received on the information request were not prepared. However, the NRC considered these submittals in the development of this proposed rule and has made several modifications to the preliminary proposed rule language as a result of the public input. Those changes included:

- Revising the definition for “extravasation” to mean the unintentional presence of a radiopharmaceutical in the tissue surrounding the blood vessel following an injection;
- Removing the definition for “medical attention;”
- Changing “suspected radiation injury” to “radiation injury” and revising the definition to mean a deterministic health effect to the area around an injection site that can be attributed to radiation;
- Revising § 35.3045 to require that licensees report 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; and
- Revising the section on procedures for evaluating and reporting extravasations to clarify that licensees’ written procedures must provide high confidence that a reportable extravasation will be detected in a timely manner and reported in accordance with § 35.3045.

III. Discussion

A. What Action is the NRC Taking?

This NRC is proposing to amend 10 CFR part 35 to require that licensees report as a medical event an administration of byproduct material that results or has the potential to result in a radiation injury from an extravasation, as determined by a physician. The NRC is also proposing to amend 10 CFR part 35 to require that licensees have procedures in place for evaluating and reporting extravasations and that licensees retain a copy of those procedures for the duration of the license.

To support the implementation of these provisions, the NRC is proposing to add definitions of “extravasation” and “radiation injury” to the “Definitions” section of 10 CFR part 35. The NRC is also proposing changes that are corrective or of a minor or nonpolicy nature and do not substantially modify existing regulations in 10 CFR part 35 (e.g., inclusive language, plain language).

B. Who Would this Action Affect?

This proposed rule would affect all NRC and Agreement State medical licensees who administer intravenous radiopharmaceuticals for diagnostic and therapeutic purposes.

C. Why Do the Requirements Need to be Revised?

As noted in the “Background” section of this document, the NRC currently excludes radiopharmaceutical extravasations from its medical event reporting regulations in 10 CFR part 35. Therefore, extravasations that cause radiation injury, including those that meet the public health and safety significance criteria for an abnormal occurrence, are not required to be reported to the NRC for consideration in NRC’s evaluation of medical events. If extravasations that result or have the potential to

result in a radiation injury are reported to the NRC, the NRC can track and trend these events and collect information on their occurrence, detection, mitigation, and possible preventive strategies that would be available for licensee and public use.

D. Why Does the NRC Believe a Non-Dose-Based Criterion is Appropriate for Extravasations?

The NRC supports a non-dose-based criterion for the reporting of certain extravasations in order to gain further understanding of the extravasations that have potential radiation safety concerns. The severity of the extravasation may depend on a multitude of factors, and an extravasation may result from a nuclear medicine injection that was correctly administered. Extravasation is a known risk in all medical injections because a vessel is being punctured and fluid may leak from the puncture site inadvertently. In response to the NRC's information request, commenters generally noted that extravasations may be prevalent, but extravasations tend to be of low volume and do not affect patient safety or care. Some commenters from the medical community agreed that extravasations that result in patient harm or compromise patient care are very rare and typically associated with therapeutic radiopharmaceuticals. However, as noted above, the NRC does not currently possess data on the extent to which extravasations may result in patient harm or compromise patient care because there is currently no reporting requirement for extravasations. The NRC expects that if finalized, the proposed reporting requirement would further the NRC's understanding of extravasations by providing information on radiation-safety-significant extravasations. As with all reporting requirements, such information could help the NRC understand the radiation safety risk posed by extravasations and collect and share information on extravasation trends, prevention, mitigation, and best practices. Because available information suggests that extravasations that result in patient harm or otherwise

compromise patient care are rare, the NRC does not see a need for a dose-based criterion at this time. 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 risks posed by extravasations of radiopharmaceuticals, the NRC believes such a dose-based requirement would be inappropriate.

Further, a reporting requirement that does not include a dose-based threshold comports with the approach the NRC has taken for certain other reportable medical events. While medical reportable medical events under § 35.3045(a) include a dose-based threshold, other portions of § 34.3045 do not. The criteria in § 35.3045(a) are primarily based on human error (i.e., wrong radioactive drug or radionuclide, wrong route of administration, wrong individual, wrong mode of treatment); however, to be reportable, these errors must result in a dose that exceeds 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin. The NRC also requires reporting of events where skin, organ, or tissues other than the treatment site receive doses that exceed by 0.5 Sv (50 rem) or more the expected dose to that site from the procedure and 50 percent or more the expected dose to that site from the procedure.

The NRC is proposing a criterion for reporting an extravasation in § 35.3045(a)(3) that is different from the other medical event reporting criteria in § 35.3045(a) because there is no method to assess whether the extravasation resulted from human error or from other factors outside the licensee's control. Unintentional presence of radiopharmaceutical in the tissue surrounding a blood vessel may be observed even when the prescribed dosage of a radiopharmaceutical as indicated in the

written directive and intended by an authorized user (AU) is administered to a patient. While there may be some delay time, normal biological processes will transport the dose to the intended target.

Although the proposed criterion in § 35.3045(a)(3) may differ from the other medical event criteria in § 35.3045(a), NRC does have provisions for medical event reporting criteria that are not based on human error or a dose threshold. For example, § 35.3045(b) requires reporting of medical events resulting from patient intervention. This reporting requirement is not predicated on a medical error having occurred or on a dose threshold being exceeded; rather, under § 35.3045(b) an event is reportable if due to intervention of a patient the administration or radiation from byproduct material results in unintended permanent functional damage to an organ or physiological system, as determined by a physician.

Additionally, there does not yet exist a standardized dosimetry model for extravasations. The NRC has determined that a reporting criterion for nuclear medicine injection extravasations that does not rely on a dose differential strikes the appropriate balance between the dosimetry required to properly characterize an extravasation and the potential for a radiation effect on a patient, regardless of whether the extravasation results from human error.

E. What is the Status of the Dosimetry Model?

Although the proposed reporting criterion for extravasations is not based on dose, licensees may want to perform a dose assessment of an extravasation because knowing the estimated dose to tissue could help licensees assess a suspected radiation injury. In SECY-22-0043, the staff indicated that it would develop a dosimetry model to assist licensees in characterizing reportable nuclear medicine injection extravasations. The NRC is currently developing a dosimetry methodology as a module in the

VARSKIN+ computer code. VARSKIN+ is currently free to use and will allow interested stakeholders to use the code for dose assessments or research. This model is expected to be complete in early 2025.

F. Why Does the Reportable Threshold Require Reporting for an Extravasation that Results or Has the Potential to Result in a Radiation Injury from an Extravasation?

The reporting threshold in the proposed rule resulted from extensive interactions with ACMUI, medical professionals, and other members of the public. In its preliminary evaluation of nuclear medicine injection extravasations (July 30, 2021), the NRC assessed several options related to the potential reporting of extravasations as medical events. One of the options considered by the NRC was for licensees to report to the NRC as medical events extravasations that require medical attention due to radiation-induced tissue damage near the administration site. This reporting criterion would have captured extravasations from both diagnostic and therapeutic radiopharmaceuticals, while ensuring extravasations that pose a risk to the patient be reported and assessed. In its preliminary evaluation, the NRC also stated that this criterion would not require monitoring of any radiopharmaceutical injection because only those extravasations significant enough to merit medical attention would need to be reported. Licensees could elect to perform dosimetry if they suspected that the extravasation would be significant enough to result in a radiation injury. The ACMUI, in the final report from the extravasation subcommittee, recommended that the NRC revise this option to report extravasations that require medical attention for a suspected radiation injury, in consideration of a comment from the American Society for Radiation Oncology. The ACMUI stated that this approach would provide the NRC with information related to the potential types of radiation injuries and frequency. The staff considered the ACMUI's recommendation, and also considered that the Organization of Agreement States and

several Agreement States also supported its recommendation that extravasations that require medical attention for a suspected radiation injury be reported as medical events because it would focus on the extravasations that pose the greatest risk to the patient while ensuring the National Materials Program is gathering and sharing data related to extravasation medical events. The Commission ultimately approved the staff's recommended option.

In Section II.e of the information request, the NRC issued preliminary proposed rule language and sought public comment on this specific reporting criterion. Responses were generally mixed on the definition of medical attention. Some commenters pointed to the definitions provided by the Common Terminology Criteria for Adverse Events (CTCAE) or deferred to the expertise of the medical community. Other commenters stated that the definition of medical attention was too ambiguous, as it was unclear who is providing the attention, what attention is being provided, and whether the care is preventative or reactive. Commenters also stated that some types of non-invasive or minor medical attention should not be included in the definition. The NRC has decided to revise the reporting requirements to remove "medical attention" due to the ambiguity of the term. Additionally, healthcare providers may already have mitigative measures for when a patient experiences an extravasation. Regardless of the severity of the extravasation, the NRC has determined that the application of medical care should not itself be a trigger for medical event reporting.

Some commenters suggested that the NRC require the reporting of an extravasation that results in an observable radiation injury. The commenters stated that only objective criteria can be used for uniform and fair implementation of the regulations. However, the NRC decided to keep the reporting criterion based on the potential for radiation injury in § 35.3045(a)(3) because deterministic effects of radiation to the skin often manifest days to weeks after exposure to radiation, depending on the dose. By

focusing on the potential for radiation injury, the licensee does not need to wait for deterministic effects to manifest to ensure appropriate assessment and reporting of an extravasation that could result in risk to the patient. This places the responsibility of reporting on the licensee and reduces reliance on patient involvement in the identification of a reportable extravasation. Additionally, focusing on the potential for harm ensures that licensees have adequate procedures to detect and assess extravasations while the patient is still in the care of the licensee.

Many commenters stated that the NRC should only require reporting of extravasations of therapeutic radiopharmaceuticals because extravasations from diagnostic radioactive drugs rarely result in harm to patients. There have been cases reported in scientific literature that show that certain radiopharmaceutical extravasations may have significant health effects for patients, including those from diagnostic administrations. For example, extravasations from I-131-iodocholesterol resulting in an erythematous plaque and Thallium-201 resulting in a radiation ulcer have been reported in the literature. Because radiation damage from all types of radiopharmaceutical administrations, although rare, continues to be documented in the literature, the NRC determined that including diagnostic radiopharmaceutical administrations in extravasation medical event reporting is consistent with the NRC's Medical Use of Byproduct Material policy statement (65 FR 47654; August 3, 2000), which states that the NRC will regulate the radiation safety of patients primarily to assure the use of radionuclides is in accordance with the physician's directions, when justified by the risk to the patients. The ACMUI, in their final report, agreed that the NRC may be interested in all radiopharmaceutical extravasations that can cause radiation damage from a public health and safety perspective. Therefore, the NRC is not limiting the reporting criterion to only therapeutic administrations of radioactive drugs to ensure that the NRC captures risk to the patient from any radiopharmaceutical administration.

Several commenters recommended that the NRC align its reporting criterion with the CTCAE[1] developed by the National Cancer Institute. Specifically, commenters suggested that reporting be required if the extravasation results in a CTCAE Grade 3 or 4 event that can be attributed to radiation. The NRC's proposed reporting criterion is analogous to a potential for a CTCAE Grade 2 event. The NRC determined that the reportable level of potential radiation injury is appropriate because radiation injury to the injection site is not a typical risk in radiopharmaceutical injections like it is in other medical applications of radiation. The relative risk is well understood in machine produced radiation and the link between dose and tissue injury is well defined. In radiopharmaceutical extravasation, the amount of material extravasated, the time the material dwells in the area, and a multitude of other physical and patient-related factors complicate the potential for radiation injury.

In the proposed reporting criterion for extravasations, the NRC replaced "suspected radiation injury" with "an extravasation that results or has the potential to result in a radiation injury" and removed the requirement for medical attention. The NRC determined that the definition of "radiation injury" should not be ambiguous since the deterministic effects of radiation to tissue are well defined. Similarly, removing the more ambiguous term "medical attention" would provide more clarity and not impose additional burden to a licensee that is responding to an extravasation appropriately.

G. Why Does the Proposed Reporting Criterion Include a Determination by a Physician?

The proposed criterion in § 35.3045(a)(3) requires that the potential for radiation injury be determined by a physician. The NRC received input from a number of stakeholders, and the ACMUI recommended in their final report, that determination of a

[1] https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

suspected radiation injury should be made by an AU. The NRC agrees that a complex issue such as a determination of a radiation injury from an extravasation should be made by a physician, but the NRC considers all physicians, not just those that are AUs, to have the expertise to make this determination. The expertise and experience required to make a determination of a radiation injury is not exclusive to AUs; some guidelines, such as the American College of Radiology's Manual on Contrast Media, recommend a surgical consult for severe extravasation injuries. Some commenters also stated that patients may not have regular access to a licensee's physician or an AU, such as patients who travel for medical treatments. The NRC recognizes that the complexity of diagnosing and treating a radiation injury is a matter of medical practice. The NRC considered whether other healthcare professionals (e.g., nurses, nuclear medicine technologists, physicists) could assess and determine whether an extravasation results or has the potential to result in a radiation injury. However, the NRC concluded that physicians are best suited to make this determination based on their training and experience, as well as their knowledge of a patient's condition, medical history, and plan of care.

H. What Definitions Did the NRC Update?

As discussed in the background section of this document, the NRC initially proposed defining "extravasation" as the leakage of a radiopharmaceutical from the blood vessel into the surrounding tissue. In response to the NRC's request for information and comment on preliminary proposed rule language, the NRC received feedback on this definition of extravasation, including as to whether the NRC should (1) use the term "extravasation" or "infiltration," (2) limit the definition to therapeutic radiopharmaceuticals, and (3) use the term "leakage" in the definition. Commenters noted that the definition of extravasation implied tissue damage from a vesicant, and that

radioisotopes could be considered as a type of vesicant. Some commenters noted that infiltration may also mean the leakage of pharmaceutical around the injection site, but that this leakage does not result in tissue damage. Comments from the public stated that the NRC's preliminary proposed definition did not take into account extravasations that miss the blood vessel entirely and inject the radiopharmaceutical into the interstitial volume directly.

Upon consideration of this feedback, in this proposed rule the NRC defines the term "extravasation" in § 35.2 as the unintentional presence of a radiopharmaceutical in the tissue surrounding the blood vessel following an injection. The NRC has replaced the text "leakage" with the phrase, "presence of radiopharmaceutical surrounding the blood vessel". "Unintentional presence" captures injections that miss the blood vessel entirely in addition to injections that result in extravasations. As discussed in section III F. of this proposed rule, the NRC does not believe that the definition of extravasation should be limited to therapeutic radiopharmaceuticals. While the risk of deterministic effects from extravasations of diagnostic and therapeutic radiopharmaceuticals is different, diagnostic radiopharmaceutical extravasations have been shown in scientific literature to have caused radiation injury. Therefore, the NRC has determined that limiting the definition of extravasations to therapeutic uses of radiopharmaceuticals is not appropriate. The NRC also considered but has excluded from the definition of extravasation unsealed byproduct materials that are not radiopharmaceuticals, such as microspheres. The NRC determined that because a treatment site must be specified in the written directive for these administrations, any events would be captured under the wrong treatment site criteria.

In the preliminary proposed rule language, the NRC defined "suspected radiation injury" as a potential or observable deterministic health effect to the area around an injection site that can be attributed to radiation. As part of its information request, the

NRC received feedback on this definition of “suspected radiation injury.” Commenters questioned the utility of the qualifiers “potential” and “suspected” and requested clarification of the term “deterministic health effect.” There were also comments stating that the “suspected radiation injury” determination should be made by some medical authority.

Upon consideration of this feedback, the NRC is proposing to define the term “radiation injury” in § 35.2 as a deterministic health effect to the area around an injection site that can be attributed to radiation. The potential for radiation injury is more appropriate in the reporting requirement, rather than the “Definitions” section. This proposed rule would require licensees to assess the risk to the patient in a prompt manner. This provision will ensure that the patient has sufficient information in the event that a radiation injury manifests after the patient has been released from the licensee's care. Licensees will also be able to glean additional and more accurate information from an early assessment of an extravasation, such as the specific timing of symptoms, any patient or clinician actions during the extravasation, and estimates of the volume of radiopharmaceutical extravasated. This information could be less accurate or unavailable if time is given to allow an observable effect to manifest.

Several commenters stated that deterministic effects of radiation injury should be well defined in the regulation. The NRC, however, determined that a specific deterministic effect should not be included in the definition for radiation injury. While the deterministic effects to the skin and tissues are well understood, these effects do not manifest consistently in patient populations. Therefore, the NRC determined that the potential for these effects is best determined on a case-by-case basis by a physician as proposed in § 35.3045(a)(3).

I. Why is the NRC Requiring that Licensees Have Procedures to Detect and Report Extravasations?

In SRM-SECY-22-0043, the Commission directed the staff to evaluate whether the NRC should require licensees to develop, implement, and maintain written procedures to provide high confidence that radiation-safety-significant extravasations will be detected and reported. As part of the preliminary proposed rule language, the NRC included a requirement for licensees to have procedures that address extravasations. In the information request, the NRC asked questions regarding what steps licensees can take to minimize, detect, assess, and characterize radiopharmaceutical extravasations. Many commenters agreed that licensees should be required to have procedures to address extravasations and that licensees should be provided the flexibility to institute their own policies for detecting and monitoring radiopharmaceutical extravasations.

The proposed requirements in new § 35.42 ensure that extravasations are being properly evaluated and managed during patient care. The proposed requirements in § 35.42 concerning written procedures would also ensure that licensees detect and report reportable extravasations as they happen, and the model procedures referenced in the implementation guidance provide information that licensees can give to patients so that patients can identify symptoms or signs of a radiation injury that manifests after being released from the licensee's care. The NRC determined that licensees should handle minimizing extravasations as part of their quality management and injection quality programs. The proposed procedures would also require that licensees take steps to document how licensees implement these procedures in their evaluation of extravasations that may meet the proposed reporting criteria in § 35.3045(a)(3). The NRC has determined that documentation of the assessment of these incidents will ensure that licensees are evaluating potentially reportable extravasations in accordance with their written procedures and that regulators have the information necessary to

determine if further inquiry of incidents involving potential radiation injury from an extravasation is needed.

IV. Specific Requests for Comments

The NRC is seeking advice and recommendations from the public on this proposed rule.

- The NRC is seeking feedback on the term “high confidence,” as used in § 35.41 and proposed § 35.42 with respect to procedures for written directives and for detecting and reporting extravasation medical events. Specifically, the NRC is seeking input on whether the NRC should include a definition of “high confidence” in § 35.2. Please provide the rationale for your response.

- The NRC is seeking feedback related to the procedures for detecting and reporting extravasation medical events. Currently, the proposed § 35.42(b) would require a licensee’s written procedures to address how the licensee will determine that a reportable extravasation has occurred and how the licensee documents this determination. The NRC is seeking feedback on what elements should be included as part of these procedures. Additionally, the NRC is seeking feedback on whether licensees should be required to document and keep records of their assessments, including the process and determination of whether an extravasation is reportable. We are also seeking feedback on what steps the NRC can take to ensure that licensees are implementing these procedures. Please provide the rationale for your responses.

- The NRC is seeking feedback on whether the proposed procedures in § 35.42 should also include monitoring of patients, rather than only requiring monitoring of injections, to ensure licensees are detecting extravasations as defined in § 35.3045 in a timely manner.

- The NRC is seeking feedback on the assumptions used in developing the cost-benefit estimates in the regulatory analysis. Specifically, the NRC is seeking feedback related to the assumptions regarding extravasation rates and the costs licensees would incur to obtain additional methodologies or equipment or both to comply with this proposed rule. Please provide the rationale or specific numerical support for your response.

V. Section-by-Section Analysis

The following paragraphs describe the specific changes proposed by this rulemaking.

Section 35.2 Definitions

This proposed rule would add definitions for *Extravasation* and *Radiation injury*.

Section 35.8 Information collection requirements: OMB approval

This proposed rule would add new §§ 35.42 and 35.2042 to the approved information collection requirements contained in § 35.8(b) for Office of Management and Budget (OMB) control number 3150-0010.

Section 35.42 Procedures for evaluating and reporting extravasations

This proposed rule would add new § 35.42 to require written procedures for evaluating and reporting extravasations.

Section 35.2042 Records for procedures for evaluating and reporting extravasations

This proposed rule would add new § 35.2042 to require a copy of the procedures required by § 35.42(a) for the duration of the license.

Section 35.3045 Report and notification of a medical event

This proposed rule would add new paragraph (a)(3) to require the report and notification of a medical event that results or has the potential to result in a radiation injury from an extravasation, as determined by a physician.

In addition, this proposed rule would replace “shall” with “must” in § 35.3045 and make minor editorial and conforming changes to include gender-inclusive language.

VI. Regulatory Flexibility Certification

The NRC has prepared a draft regulatory analysis of the impact of this proposed rule on small entities. This proposed rule would affect 5,933 medical licensees that administer radiopharmaceuticals, some of which may qualify as small business entities as defined by § 2.810, “NRC size standards.” On the basis of the draft regulatory analysis conducted for this action, the estimated costs of this proposed rule for affected licensees are one-time implementation costs of $2,393 per licensee and annual costs of $26 per licensee. The NRC determined that the selected alternative reflected in the proposed rule is the least burdensome and most flexible alternative that would accomplish the NRC's regulatory objective. The draft regulatory flexibility analysis is included as a section in the draft regulatory analysis.

The NRC is seeking public comment on the potential impact of this proposed rule on small entities. The NRC particularly desires comments from licensees who qualify as small businesses, specifically as to how the proposed regulation will affect them and how the regulation may be tiered or otherwise modified to impose less stringent requirements on small entities while still adequately protecting the public health and safety and common defense and security. Comments on how the regulation could be modified to take into account the differing needs of small entities should specifically discuss:

(a) The size of the business and how the proposed regulation would result in a significant economic burden upon it as compared to a larger organization in the same business community;

(b) How the proposed regulation could be further modified to take into account the business's differing needs or capabilities;

(c) The benefits that would accrue, or the detriments that would be avoided, if the proposed regulation was modified as suggested by the commenter;

(d) How the proposed regulation, as modified, would more closely equalize the impact of NRC regulations as opposed to providing special advantages to any individuals or groups; and

(e) How the proposed regulation, as modified, would still adequately protect the public health and safety and common defense and security.

Comments should be submitted as indicated under the ADDRESSES caption.

VII. Regulatory Analysis

The NRC has prepared a draft regulatory analysis on this proposed regulation. The analysis examines the costs and benefits of the alternatives considered by the NRC. 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 intravenous radiopharmaceuticals for diagnostic and therapeutic purposes), the NRC, and Agreement States of $29,357,000 using a 7-percent discount rate and $35,889,000 using a 3-percent discount rate. Though the regulatory analysis indicates the proposed rule would not be quantitatively beneficial, the NRC plans to proceed with the proposed rule because it concluded that these costs would be outweighed by the qualitative public health benefits of the rulemaking, as discussed in the regulatory

analysis. The NRC requests public comment on the draft regulatory analysis. The regulatory analysis is available as indicated in the “Availability of Documents” section of this document. Comments on the draft regulatory analysis may be submitted to the NRC as indicated under the ADDRESSES caption of this document.

VIII. Backfitting and Issue Finality

The NRC's backfitting provisions (which are found in the regulations at §§ 50.109, 70.76, 72.62, and 76.76) and issue finality provisions of 10 CFR part 52 do not apply to this rule. Part 35 of 10 CFR does not contain a backfitting provision, and this rulemaking will not impact activities authorized by parts 50, 52, 70, 72, or 76. As a result, this rulemaking cannot constitute "backfitting" as defined in 10 CFR Chapter I or otherwise affect the issue finality of a 10 CFR part 52 approval.

IX. Cumulative Effects of Regulation

The NRC seeks to minimize any potential negative consequences resulting from the cumulative effects of regulation (CER). The CER describes the challenges that licensees, or other impacted entities such as State partners, may face while implementing new regulatory positions, programs, or requirements (e.g., rules, generic letters, backfits, inspections). The CER is an organizational effectiveness challenge that may result from a licensee or impacted entity implementing a number of complex regulatory actions, programs, or requirements within limited available resources.

The NRC is following its CER process by engaging with external stakeholders throughout this proposed rule and related regulatory activities. Public involvement has included a public meeting to facilitate feedback on the April 19, 2023, information

request and publication of preliminary proposed rule language. The NRC is considering holding additional public meetings during the remainder of the rulemaking process.

To better understand the potential CER implications incurred due to this proposed rule, the NRC is requesting comment on the following questions. Responding to these questions is voluntary, and the NRC will respond to any comments received in the final rule.

1. In light of any current or projected CER challenges, does the proposed rule's effective date provide sufficient time to implement the new proposed requirements, including changes to programs, procedures, and the facility?

2. If CER challenges currently exist or are expected, what should be done to address them? For example, if more time is required for implementation of the new requirements, what period of time is sufficient?

3. Do other (NRC or other agency) regulatory actions (e.g., orders, generic communications, license amendment requests, inspection findings of a generic nature) influence the implementation of the proposed rule's requirements?

4. Are there unintended consequences? Does the proposed rule create conditions that would be contrary to the proposed rule's purpose and objectives? If so, what are the unintended consequences, and how should they be addressed?

5. Please comment on the NRC's cost and benefit estimates in the regulatory analysis that supports the proposed rule.

X. Plain Writing

The Plain Writing Act of 2010 (Pub. L. 111-274) requires Federal agencies to write documents in a clear, concise, and well-organized manner. The NRC has written this document to be consistent with the Plain Writing Act as well as the Presidential

Memorandum, “Plain Language in Government Writing,” published June 10, 1998 (63 FR 31885). The NRC requests comment on this document with respect to the clarity and effectiveness of the language used.

XI. National Environmental Policy Act

The NRC has determined that this proposed rule is the type of action described in § 51.22(c)(3)(iii). Therefore, neither an environmental impact statement nor environmental assessment has been prepared for this proposed rule.

XII. Paperwork Reduction Act

This proposed rule contains (a) new or amended collection(s) of information subject to the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 et seq). This proposed rule has been submitted to the OMB for review and approval of the information collection(s).

Type of submission, new or revision: Revision.

The title of the information collection: Reporting Nuclear Medicine Injection Extravasations as Medical Events, Proposed Rule.

The form number if applicable: N/A.

How often the collection is required or requested: On occasion.

Who will be required or asked to respond: NRC and Agreement State licensees who administer intravenous radiopharmaceuticals for diagnostic and therapeutic purposes.

An estimate of the number of annual responses: 6,650 (489 reporting responses + 5,933 recordkeepers + 228 third-party disclosure responses).

The estimated number of annual respondents: 5,933 (547 NRC licensees + 5,386 Agreement State licensees).

An estimate of the total number of hours needed annually to comply with the information collection requirement or request: 20,193.15 hours (652 reporting + 19,085.15 recordkeeping + 456 third-party disclosure).

Abstract: The NRC is proposing to amend 10 CFR part 35 to require reporting of certain nuclear medicine injection extravasations as medical events. The proposed changes would help staff track and trend extravasation medical events and collect information on their occurrence, detection, mitigation, and possible preventive strategies that would be available for licensee and public use. The proposed rule would also require licensees to develop, implement, and maintain written procedures for evaluating and reporting extravasations. These procedures are necessary to provide high confidence that these extravasations will be detected in a timely manner and reported to the NRC.

The NRC is seeking public comment on the potential impact of the information collection(s) contained in this proposed rule and on the following issues:

1. Is the proposed information collection necessary for the proper performance of the functions of the NRC, including whether the information will have practical utility?

2. Is the estimate of the burden of the proposed information collection accurate?

3. Is there a way to enhance the quality, utility, and clarity of the information to be collected?

4. How can the burden of the proposed information collection on respondents be minimized, including the use of automated collection techniques or other forms of information technology?

A copy of the OMB supporting statement is available in ADAMS under Accession No. ML24017A137 or can be obtained free of charge by contacting the NRC's PDR reference staff at 1-800-397-4209, at 301-415-4737, or by email to PDR.resource@nrc.gov. You may obtain information and comment submissions related to the OMB clearance package by searching on https://www.regulations.gov under Docket ID NRC-2022-0218.

You may submit comments on any aspect of these proposed information collection(s), including suggestions for reducing the burden and on the above issues, by the following methods:

- **Federal rulemaking website:** Go to https://www.regulations.gov and search for Docket ID NRC-2022-0218.
- **Mail comments to:** FOIA, Library, and Information Collections Branch, Office of Information Services, Mail Stop: T6-A10M, U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001 or to the OMB reviewer at: Office of Information and Regulatory Affairs (3150-0010), Attn: Desk Officer for the Nuclear Regulatory

Commission, 725 17th Street, NW, Washington, DC 20503; telephone: 202-395-1741, email: oira_submission@omb.eop.gov.

Submit comments by **[INSERT DATE 30 DAYS AFTER PUBLICATION IN THE *FEDERAL REGISTER*]**. Comments received after this date will be considered if it is practical to do so, but the NRC staff is able to ensure consideration only for comments received on or before this date.

Public Protection Notification

The NRC may not conduct or sponsor, and a person is not required to respond to, a collection of information unless the document requesting or requiring the collection displays a currently valid OMB control number.

XIII. Criminal Penalties

For the purposes of Section 223 of the Atomic Energy Act of 1954, as amended (AEA), the NRC is issuing this proposed rule that would amend part 35 under one or more of Sections 161b, 161i, or 161o of the AEA, except as noted in § 35.4002(b). Willful violations of the part 35 regulations not listed in § 35.4002(b) would be subject to criminal enforcement. Criminal penalties as they apply to regulations in part 35 are discussed in § 35.4002.

XIV. Coordination with NRC Agreement States

The working group that prepared this proposed rule included a representative from the Organization of Agreement States. A draft of the proposed rule was provided to

the Agreement States for review. Comments from Agreement States were taken into consideration during the development of this proposed rule.

XV. Coordination with the Advisory Committee on the Medical Uses of Isotopes

On [DATE], a draft of the proposed rule was provided to the ACMUI for a 90-day review. The draft was made public to facilitate the ACMUI's review in a public forum. The ACMUI established a subcommittee to review and comment on the draft proposed rule. The subcommittee discussed their report on the draft proposed rule at a publicly held teleconference on [DATE], and the report was unanimously approved by the full committee. The ACMUI provided its final report on [DATE].

XVI. Compatibility of Agreement State Regulations

On the basis of the "Agreement State Program Policy Statement" approved by the Commission on October 2, 2017, and published in the *Federal Register* (82 FR 48535; October 18, 2017), NRC program elements can be placed into six categories (A, B, C, D, NRC, or health and safety (H&S)) to form the basis for evaluating and classifying the program elements. Under the Policy Statement, a program element means any component or function of a radiation control regulatory program, including regulations and other legally binding requirements imposed on regulated persons, which contributes to implementation of that program.

Compatibility Category A are those program elements that include basic radiation protection standards and scientific terms and definitions that are necessary to understand radiation protection concepts. Compatibility Category A program elements

adopted by an Agreement State should be essentially identical to those of the NRC to provide uniformity in the regulation of agreement material on a nationwide basis.

Compatibility Category B pertains to a limited number of program elements that cross jurisdictional boundaries and should be addressed to ensure uniformity of regulation on a nationwide basis. For Compatibility Category B, the Agreement State program element shall be essentially identical to that of NRC. Program elements in Compatibility Category C include those program elements that are important for an Agreement State to have in order to avoid conflict, duplication, gaps, or other conditions that would jeopardize an orderly pattern in the regulation of agreement material on a national basis. An Agreement State program shall embody the essential objectives of the Category C program elements.

Under Category C, Agreement State program elements may be more restrictive than NRC program elements; however, they should not be so restrictive as to prohibit a practice authorized by the Atomic Energy Act of 1954 (AEA), as amended, and in the national interest without an adequate public health and safety or environmental basis related to radiation protection.

Compatibility Category D are those program elements that do not meet any of the criteria of Category A, B, or C, above, and are not required to be adopted by Agreement States for purposes of compatibility. An Agreement State has the flexibility to adopt and implement program elements within the State's jurisdiction that are not addressed by the NRC or that are not required for compatibility (*i.e.,* Compatibility Category D). However, such program elements of an Agreement State relating to agreement material shall (1) not create conflicts, duplications, gaps, or other conditions that would jeopardize an orderly pattern in the regulation of agreement material on a nationwide basis; (2) not preclude a practice authorized by the AEA and in the national interest; and (3) not

preclude the ability of the NRC to evaluate the effectiveness of Agreement State programs for agreement material with respect to protection of public health and safety.

Compatibility Category NRC are those program elements that address areas of regulation that cannot be relinquished to the Agreement States under the AEA, or provisions of Title 10 of the of the *Code of Federal Regulations*. The NRC maintains regulatory authority over these program elements and the Agreement States must not adopt these NRC program elements. However, an Agreement State may inform its licensees of these NRC requirements through a mechanism under the State's administrative procedure laws, as long as the State adopts these provisions solely for the purposes of notification and does not exercise any regulatory authority as a result.

Category H&S program elements embody the basic health and safety aspects of the NRC's program elements. Although H&S program elements are not required for purposes of compatibility, they do have particular health and safety significance. The Agreement State must adopt the essential objectives of such program elements to maintain an adequate program.

The proposed new definition for "extravasation" in § 35.2 would be designated as Compatibility Category B. The NRC has determined that this definition needs to be adopted to ensure a consistent regulatory approach across the National Materials Program and inconsistent definitions of this term would have direct and significant transboundary implications.

The proposed new definition for "radiation injury" in § 35.2 would be designated as Compatibility Category H&S because the essential objectives of this provision have health and safety significance and need to be adopted by the Agreement States.

Proposed new requirements related to procedures for evaluating and reporting extravasations in § 35.42(a) and (b) would be designated as Compatibility Category H&S

because the essential objectives of these provisions have health and safety significance and need to be adopted by the Agreement States.

Proposed new requirements related to procedures for evaluating and reporting extravasations in § 35.42(c) would be designated as Compatibility Category D. Compatibility Category D are those program elements that do not meet any of the criteria of Category A, B, or C, above, and, therefore, do not need to be adopted by Agreement States for purposes of compatibility. The proposed Compatibility Category D designation for this provision would provide the flexibility for Agreement States insofar as requiring licensees to retain the copy of the procedures for a time period other than the duration of the license as specified in proposed § 35.2042. Proposed new requirements for maintaining records for procedures for evaluating and reporting extravasations in § 35.2042 would be designated as Compatibility Category D. Compatibility Category D are those program elements that do not meet any of the criteria of Category A, B, or C, above, and, therefore, do not need to be adopted by Agreement States for purposes of compatibility. The proposed Compatibility Category D designation for this provision would provide the flexibility for Agreement States insofar as requiring licensees to retain the copy of the procedures for a time period other than the duration of the license as specified in the proposed regulations.

Proposed new requirements for report and notification of a medical event in § 35.3045(a)(3) would be designated as Compatibility Category C because the NRC has determined that the essential objectives of these provisions need to be adopted by the Agreement States. The proposed compatibility category of this provision is to maintain consistency with the compatibility category designation for the current § 35.3045, which is Compatibility Category C.

Compatibility categories for other provisions that are subject to amendment would remain unchanged.

The final rule would be a matter of compatibility between the NRC and the Agreement States, thereby providing consistency among Agreement State and NRC requirements. The compatibility (A, B, C, D, and NRC) and adequacy (H&S) categories are designated in the following table:

Compatibility Table

Section	Change	Subject	Compatibility	
			Existing	New
10 CFR 35.2	New	Definition: Extravasation	-	B
10 CFR 35.2	New	Definition: Radiation injury	-	H&S
10 CFR 35.8(b)	Amend	Information collection requirements: OMB approval	D	D
10 CFR 35.42(a)	New	Procedures for evaluating and reporting extravasations	-	H&S
10 CFR 35.42(b)	New	Procedures for evaluating and reporting extravasations	-	H&S
10 CFR 35.42(c)	New	Procedures for evaluating and reporting extravasations	-	D
10 CFR 35.2042	New	Records for procedures for evaluating and reporting extravasations	-	D
10 CFR 35.3045(a)	Amend	Report and notification of a medical event	C	C
10 CFR 35.3045(a)(3)	New	Report and notification of a medical event	-	C
10 CFR 35.3045(b)	Amend	Report and notification of a medical event	C	C
10 CFR 35.3045(c)	Amend	Report and notification of a medical event	C	C
10 CFR 35.3045(d)	Amend	Report and notification of a medical event	C	C
10 CFR 35.3045(e)	Amend	Report and notification of a medical event	C	C
10 CFR 35.3045(g)	Amend	Report and notification of a medical event	C	C

XVII. Voluntary Consensus Standards

The National Technology Transfer and Advancement Act of 1995, Pub. L. 104-113, requires that Federal agencies use technical standards that are developed or adopted by voluntary consensus standards bodies unless the use of such a standard is inconsistent with applicable law or otherwise impractical. In this proposed rule, the NRC will revise the regulations to require reporting of certain nuclear medicine injection extravasations as medical events. This action does not constitute the establishment of a standard that contains generally applicable requirements.

XVIII. Availability of Guidance

The NRC is issuing new draft guidance, Draft Regulatory Guide DG-8062, "Medical Event Evaluation and Reporting," for the implementation of the proposed requirements in this rulemaking. The guidance is available in ADAMS under Accession No. ML24016A109. You may obtain information and comment submissions related to the draft guidance by searching on https://www.regulations.gov under Docket ID NRC-2022-0218.

The draft regulatory guide describes an approach acceptable to NRC staff to meet the requirements for evaluating and reporting all medical events, including extravasation events as described in this proposed rule. The draft regulatory guide provides licensees with guidance on when medical event reports are required, how reports should be made, and what is required to be in the report. In addition, the draft regulatory guide provides guidance for procedures for administrations requiring a written directive and for evaluating and reporting extravasation events as described in this proposed rule.

You may submit comments on this draft regulatory guidance by the method outlined in the ADDRESSES section of this document.

XIX. Public Meeting

The NRC will conduct a public meeting on this proposed rule to promote full understanding of the proposed rule and associated guidance document.

The NRC will publish a notice of the location, time, and agenda of the meeting on the NRC's public meeting website within at least 10 calendar days before the meeting. Stakeholders should monitor the NRC's public meeting website for information about the public meeting at: https://www.nrc.gov/public-involve/public-meetings/index.cfm.

XX. Availability of Documents

The documents identified in the following table are available to interested persons through one or more of the following methods, as indicated.

DOCUMENT	ADAMS ACCESSION NO. / WEB LINK / *FEDERAL REGISTER* CITATION
Proposed Rule and Draft Guidance Documents	
Draft Regulatory Analysis for the Reporting Nuclear Medicine Injection Extravasations as Medical Events Proposed Rule	ML24016A293
Draft Supporting Statement for Information Collections Contained in the Reporting Nuclear Medicine Injection Extravasations as Medical Events Proposed Rule	ML24017A137
Draft Regulatory Guide DG-8062, "Medical Event Evaluation and Reporting"	ML24016A109
SECY-24-0XXX, "Proposed Rule: Reporting Nuclear Medicine Injection Extravasations as Medical Events (RIN 3150-AK91; NRC-2022-0218)," [DATE]	ML24016A294

Related Documents	
ACMUI Meeting Transcript, December 18, 2008	ML090340745
ACMUI Meeting Transcript, May 7, 2009	ML092090034
ACMUI Meeting Summary, September 2, 2021	ML21267A021
ACMUI Extravasation Subcommittee, Final Report, [DATE]	[MLXXXXXXXXX]
Final Rule: Misadministration Reporting Requirements, May 14, 1980	45 FR 31701
Final Rule: Quality Management Program and Misadministrations, July 25, 1991	56 FR 34104
Final Rule: Medical Use of Byproduct Material, April 24, 2002	67 FR 20250
Final Rule: Medical Use of Byproduct Material – Medical Event Definitions, Training and Experience, and Clarifying Amendments, July 16, 2018	83 FR 33046
Preliminary Evaluation of Radiopharmaceutical Extravasation and Medical Event Reporting for ACMUI Review, July 30, 2021	ML21223A085
PRM-35-22, Petition for Rulemaking, Reporting Nuclear Medicine Injection Extravasations as Medical Events, May 18, 2020	ML20157A266
PRM-35-22, Reporting Nuclear Medicine Injection Extravasations as Medical Events, Petition for Rulemaking, Notification of Docketing and Request for Comment, September 15, 2020	85 FR 57148
PRM-35-22, Reporting Nuclear Medicine Injection Extravasations as Medical Events, Petition for Rulemaking, Consideration in the Rulemaking Process, December 30, 2022	87 FR 80474
Reporting Nuclear Medicine Injection Extravasations as Medical Events, Preliminary Proposed Rule Language, Notice of Availability and Public Meeting, April 19, 2023	88 FR 24130
Reporting Nuclear Medicine Injection Extravasations as Medical Events, Preliminary Proposed Rule Language, Extension of Comment Period, July 18, 2023	88 FR 45824
SECY-22-0043, “Petition for Rulemaking and Rulemaking Plan on Reporting	ML21268A005 (package)

Nuclear Medicine Injection Extravasations as Medical Events (PRM-35-22; NRC-2020-0141)," May 9, 2022	
SRM-SECY-22-0043, "Staff Requirements – SECY-22-0043 – Petition for Rulemaking and Rulemaking Plan on Reporting Nuclear Medicine Injection Extravasations as Medical Events (PRM-35-22; NRC-2020-0141)," December 12, 2022	ML22346A112 (package)
Plain Language in Government Writing, June 10, 1998	63 FR 31885
Agreement State Program Policy Statement, October 18, 2017	82 FR 48535

The NRC may post materials related to this document, including public comments, on the Federal rulemaking website at https://www.regulations.gov under Docket ID NRC-2022-0218. In addition, the Federal rulemaking website allows members of the public to receive alerts when changes or additions occur in a docket folder. To subscribe: 1) navigate to the docket folder (NRC-2022-0218); 2) click the "Subscribe" link; and 3) enter an email address and click on the "Subscribe" link.

List of Subjects in 10 CFR Part 35

Biologics, Byproduct material, Criminal penalties, Drugs, Health facilities, Health professions, Labeling, Medical devices, Nuclear energy, Nuclear materials, Occupational safety and health, Penalties, Radiation protection, Reporting and recordkeeping requirements.

For the reasons set out in the preamble and under the authority of the Atomic Energy Act of 1954, as amended; the Energy Reorganization Act of 1974, as amended; and 5 U.S.C. 552 and 553, the NRC is proposing to amend 10 CFR part 35 as follows:

PART 35– MEDICAL USE OF BYPRODUCT MATERIAL

1. The authority citation for part 35 continues to read as follows:

Authority: Atomic Energy Act of 1954, secs. 81, 161, 181, 182, 183, 223, 234, 274 (42 U.S.C. 2111, 2201, 2231, 2232, 2233, 2273, 2282, 2021); Energy Reorganization Act of 1974, secs. 201, 206 (42 U.S.C. 5841, 5846); 44 U.S.C. 3504 note.

2. In § 35.2, add definitions for *Extravasation* and *Radiation injury* in alphabetical order to read as follows:

§ 35.2 Definitions.

* * * * *

Extravasation means the unintentional presence of a radiopharmaceutical in the tissue surrounding the blood vessel following an injection.

* * * * *

Radiation injury means a deterministic health effect to the area around an injection site that can be attributed to radiation.

* * * * *

§ 35.8 [Amended]

3. In § 35.8(b), add in numerical order, “35.42” and “35.2042.”

4. Add § 35.42 to read as follows:

§ 35.42 Procedures for evaluating and reporting extravasations.

(a) For any administration in which an extravasation can occur, the licensee must develop, implement, and maintain written procedures to provide high confidence that an extravasation that results or has the potential to result in a radiation injury, as determined by a physician, will be detected in a timely manner and reported in accordance with § 35.3045.

(b) The written procedures required by paragraph (a) of this section must address how the licensee determines that an extravasation meets the criteria in § 35.3045(a)(3) for a medical event and how the licensee documents this determination.

(c) A licensee must retain a copy of the procedures required under paragraph (a) of this section in accordance with § 35.2042.

5. Add § 35.2042 to read as follows:

§ 35.2042 Records for procedures for evaluating and reporting extravasations.

A licensee must retain a copy of the procedures required by § 35.42(a) for the duration of the license.

6. In § 35.3045:

a. Remove the word “shall” wherever it may appear, and add in its place, the word “must”;

b. Add paragraph (a)(3); and

c. In paragraph (e) remove the phrase “he or she” and add in its place the phrase “the referring physician”.

The addition to read as follows:

§ 35.3045 Report and notification of a medical event.

(a) * * *

(1) * * *

(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.

* * * * *

Dated: <Month XX, 2024>.

For the Nuclear Regulatory Commission.

Carrie M. Safford,
Secretary of the Commission.

U.S. NUCLEAR REGULATORY COMMISSION

DRAFT REGULATORY GUIDE DG-8062

Proposed new Regulatory Guide 8.16

Issue Date: Month 2024
Technical Lead: Katie Tapp
Daniel Dimarco

MEDICAL EVENT EVALUATION AND REPORTING

A. INTRODUCTION

Purpose

This regulatory guide (RG) describes an approach that is acceptable to the U.S. Nuclear Regulatory Commission (NRC) staff to meet the requirements in Title 10 of the *Code of Federal Regulations* (10 CFR) Part 35, "Medical Use of Byproduct Material," for evaluating and reporting medical events (Ref. 1). This RG provides licensees with guidance on when medical event reports should be filed, how reports should be made, and what reports should contain. In addition, this RG provides guidance on procedures for administrations of byproduct material for medical procedures requiring a written directive and on procedures for evaluating and reporting extravasation events.

Applicability

This RG applies to all NRC medical licensees authorized to administer byproduct material subject to 10 CFR Part 35.

Applicable Regulations

- 10 CFR Part 35 includes requirements and provisions for the radiation safety of workers, the public, patients, and human research subjects.
    - 10 CFR 35.2, "Definitions," defines the terms "authorized user," "extravasation," "patient intervention," "physician," "prescribed dosage, "prescribed dose," "radiation injury," "treatment site," and "written directive."
    - 10 CFR 35.27, "Supervision," provides the requirements for individuals supervised by an Authorized User (AU). This regulation requires the supervised individuals to be instructed in and to follow the licensee's written radiation protection and written directive procedures.
    - 10 CFR 35.40, "Written directives," states when written directives are required and what information they must contain.

- 10 CFR 35.41, "Procedures for administrations requiring a written directive," provides the requirements for procedures to provide high confidence that the patient's or human research subject's identity is verified before each administration and that each administration is in accordance with the written directive. This regulation requires all licensees to develop, implement, and maintain written procedures to determine whether a medical event has occurred, as well as to determine, for permanent implant brachytherapy, the total source strength administered outside of the treatment site compared to the total source strength documented in the post implantation portion of the written directive.

- 10 CFR 35.42, "Procedures for evaluating and reporting extravasations," provides the requirement
  for
  licensees to develop, implement, and maintain procedures to provide high confidence that an extravasation that has resulted in, or has the potential to result in, a radiation injury will be detected promptly and reported in accordance with 10 CFR 35.3045, "Report and notification of a medical event."

- 10 CFR 35.2041, "Records for procedures for administrations requiring a written directive," requires licensees to retain a copy of procedures required by 10 CFR 35.41 for the duration of the license.

- 10 CFR 35.2042, "Records for procedures for evaluating and reporting extravasations," requires licensees to retain a copy of procedures required by 10 CFR 35.42 for the duration of the license.

- 10 CFR 35.3045 requires licensees to report medical events that meet certain. The regulation specifies when and how to report a medical event and what information a medical event report needs to include.

- 10 CFR 35.3047, "Report and notification of a dose to an embryo/fetus or a nursing child," requires licensees to report an unplanned dose to an embryo or fetus from administration to a pregnant individual, or a dose to a nursing child as a result of administration to a breastfeeding individual. The regulation specifies when and how to report these exposure events and what information a medical event report needs to include.

Related Guidance

NUREG-1556, "Consolidated Guidance about Materials Licenses," Volume 9, "Program -Specific Guidance about Medical Use Licenses," (Ref. 2), includes program -specific guidance and information intended to help applicants and licensees prepare applications for materials licenses for the medical use of byproduct material.

Purpose of Regulatory Guides

The NRC issues RGs to describe methods that are acceptable to the staff for implementing specific parts of the agency's regulations, to explain techniques that the staff uses in evaluating specific issues or postulated events, and to describe information that the staff needs in its review of applications for permits and licenses. Regulatory guides are not NRC regulations and compliance with them is not required. Methods and solutions that differ from those in RGs are acceptable if supported by a basis for the issuance or continuance of a permit or license by the Commission.

Paperwork Reduction Act

This RG provides voluntary guidance for implementing the mandatory information collections in 10 CFR Part 35 that are subject to the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 et seq.). These information collections were approved by the Office of Management and Budget (OMB), under control number 3150-0132. Send comments regarding this information collection to the FOIA, Library, and Information Collections Branch (T6-A10M), U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001, or by email to Infocollects.Resource@nrc.gov, and to the OMB reviewer at: OMB Office of Information and Regulatory Affairs, NEOB-10202 (3150-0132), Attn: Desk Officer for the Nuclear Regulatory Commission, 725 17th Street, NW, Washington, 20503; email: oira_submissions@omb.eop.gov.

Public Protection Notification

The NRC may not conduct or sponsor, and a person is not required to respond to, a collection of information unless the document requesting or requiring the collection displays a currently valid OMB control number.

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B. DISCUSSION

Reason for Issuance

This RG provides guidance to licensees for complying with and implementing the requirements associated with medical event evaluation and reporting in 10 CFR Part 35. The RG also includes guidance for reporting extravasation events, a new requirement included in 10 CFR Part 35 which was developed in conjunction with this RG as described in SRM-SECY-22-0043, "Staff Requirements—SECY-22-0043—Petition for Rulemaking and Rulemaking Plan on Reporting Nuclear Medicine Injection Extravasations as Medical Events (PRM-35-22; NRC-2020-0141)," dated December 12, 2022 (Agencywide Documents Access and Management System (ADAMS) Accession No. ML22346A112) (Ref. 3).

Background

The NRC's policy statement on the medical use of byproduct material (65 FR 47654; August 3, 2000) (Ref. 4) specifies that the NRC will not intrude into medical judgments affecting patients, except as necessary to provide for the radiation safety of workers and the general public. The policy statement also specifies that the NRC will regulate the radiation safety of patients, when this is justified by the risk to the patients, primarily to ensure that the use of radionuclides is in accordance with the physician's directions.

To meet this intent, the NRC also established regulations to ensure that physicians who use byproduct material in medicine are adequately trained in radiation safety (10 CFR 35.190, 10 CFR 35.290, 10 CFR 35.390, 10 CFR 35.490, 10 CFR 35.590, 10 CFR 35.690, and 10 CFR 35.1000). Physicians with this training are known as Authorized Users (AUs). When justified by the risk of use, AUs are required to provide written directives for the medical use of byproduct material. Finally, NRC regulations require licensees to develop, implement, and maintain written procedures to provide high confidence that administrations of byproduct material are in accordance with these written directives. If an administration is not in accordance with the physician's directions and meets specific criteria listed in 10 CFR 35.3045, the NRC requires the reporting of the administration as a medical event.

Medical event reports provide the NRC with operational experience to ensure that the medical use of byproduct material is in accordance with physicians' directions and that corrective actions are taken to prevent recurrence when possible. Medical events do not necessarily result in harm to the patient or mean an error in standard of care occurred during treatment. However, while some medical events cannot be prevented because of current limitations in the practice of medicine, a medical event may indicate a problem in a medical facility's use of radioactive materials. Medical event reporting also allows the NRC to follow up on events and determine whether other licensees might be experiencing similar challenges. The NRC assesses trends or patterns, identifies generic issues or concerns, and evaluates any inadequacy or unreliability in specific equipment or procedures. When the NRC identifies similarities in the root causes of medical events reported from multiple facilities, it may issue a generic communication to help prevent additional incidents. Generic communications related to medical events are listed in appendix A. The NRC also provides information about medical events to the industry through presentations, communication with professional societies, and direct communication with manufacturers and other regulators to minimize the risk of recurrence and to ensure that the use of byproduct material in medicine is in accordance with the physician's directions.

Consideration of International Standards

The International Atomic Energy Agency (IAEA) works with member states and other partners to promote the safe, secure, and peaceful use of nuclear technologies. The IAEA develops Safety Requirements and Safety Guides for protecting people and the environment from harmful effects of

ionizing radiation. This system of safety fundamentals, safety requirements, safety guides, and other relevant reports reflects an international perspective on what constitutes a high level of safety. To inform its development of this RG, the NRC considered IAEA Safety Requirements and Safety Guides pursuant to the Commission's International Policy Statement (Ref. 5) and Management Directive and Handbook 6.6, "Regulatory Guides" (Ref. 6).

The following IAEA Safety Requirements and Guides were considered in the update of this RG:

- IAEA Specific Safety Guide No. 46, "Radiation Protection and Safety in Medical Uses of Ionizing Radiation," issued 2018 (Ref. 7), provides IAEA recommendations for investigating and reporting unintended and accidental medical exposures and discusses how regulators can use the reports to disseminate information to avoid future events at other licensees.

- IAEA Human Health Series No. 33, "QUANUM 3.0: An Updated Tool for Nuclear Medicine Audits," Third Edition, issued August 2021 (Ref. 8), recommends that nuclear medicine services have procedures to prevent, monitor for, manage, and document misadministrations.[1] It also provides recommendations for classification of extravasations.

In addition, when developing specific guidance for reporting extravasation events, the NRC considered recommendations from several other sources, including the International Commission on Radiological Protection (ICRP), the IAEA, and the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA):

- According to ICRP Publication 140, "Radiological Protection in Therapy with Radiopharmaceuticals," issued September 2019 (Ref. 9), any infusion of therapeutic radiopharmaceuticals should be monitored to ensure safe administration, and the infusion should be stopped if an extravasation occurs. ICRP Publication 140 also recommends best practices for reducing dose to tissue, and therefore risk of radiation injury, by improving radiopharmaceutical uptake.

- The IAEA considers complete extravascular injections to be misadministrations by wrong route of administration. The IAEA states that an extravasation can result in a very high absorbed dose, especially if the extravasant has a long retention time and involves a high activity in a small volume. The IAEA recommends reporting of all misadministrations, regardless of the effect on the patient, to enable providers to learn from prior misadministrations and thus prevent future incidents. Reports should describe the incident, any methods used to estimate whole-body and organ doses received by the patient, medical consequences of the misadministration, and recommendations for corrective measures.

- ARPANSA 14.2, "Safety Guide for Radiation Protection in Nuclear Medicine," issued 2008 (Ref. 10), states that misadministration of diagnostic radiopharmaceuticals is unlikely to result in radiation injury or other complications. The guide calls out a possible exception for extravasations where the extravasant has a long retention time and involves a high activity in a small volume. It also states that licensees should internally investigate any misadministrations and in some cases should report them to the regulatory authority.

1 Although the term "misadministration" was replaced with "medical event" in 2002 (67 FR 20250; April 24, 2002), other entities still use "misadministration" to describe what the NRC refers to as a "medical event."

C. STAFF REGULATORY GUIDANCE

This section provides detailed descriptions of methods and approaches the NRC staff considers acceptable for meeting the requirements of the applicable regulations cited in the introduction.

1. Medical Event Criteria (10 CFR 35.3045)

The medical event criteria listed in 10 CFR 35.3045 are divided into four categories: (1) events not associated with permanent implant brachytherapy, (2) events associated with permanent implant brachytherapy; (3) events associated with patient intervention, and (4) events associated with extravasations. The following sections provide guidance for each of these categories. Appendix B provides examples of medical events and events that do not meet the criteria.

1.1 Medical Events Not Associated with Permanent Implant Brachytherapy or Patient Intervention

The criteria for medical events associated with administration of byproduct material or radiation from byproduct material, except for events that result from patient intervention or are associated with permanent implant brachytherapy, are listed in 10 CFR 35.3045(a)(1). These criteria are broken down into three parts, described below.

1.1.1 Wrong Dose or Dosage

An incident associated with wrong dose or dosage should be evaluated using the criterion of 10 CFR 35.3045(a)(1)(i). This criterion requires reporting of events that involve a dose that differs from the prescribed dose, or from the dose that would have resulted from the prescribed dosage, by more than 0.05 sievert (Sv) (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin; and where one of the following is true:

- The total dose delivered differs from the prescribed dose by 20 percent or more.
- The total dosage delivered differs from the prescribed dosage by 20 percent or more or falls outside the prescribed dosage range.
- The fractionated dose delivered differs from the prescribed dose for a single fraction, by 50 percent or more.

The following equation should be used to calculate the percent difference between prescribed dose and actual delivered dose:

$$\%\ difference = \frac{D - P}{P} \times 100\%,$$

where D = delivered dose or dosage, and
P = prescribed dose or dosage.

Events that meet the dose criteria and differ from the prescribed dose or dosage by more than 20 percent, whether negative or positive, must be reported in accordance with 10 CFR 35.3045.

"Prescribed dosage" is defined in 10 CFR 35.2 as the specified activity or range of activity of unsealed byproduct material, as documented either in a written directive or in accordance with the directions of the AU, for procedures performed pursuant to 10 CFR 35.100, "Use of unsealed byproduct

material for uptake, dilution, and excretion studies for which a written directive is not required," and 10 CFR 35.200, "Use of unsealed byproduct material for imaging and localization studies for which a written directive is not required."

The directions of an AU for procedures performed pursuant to 10 CFR 35.100 and 10 CFR 35.200 may be documented in patient-specific prescriptions, licensee standardized dosage charts, or electronic orders. If a dosage range is used, the event must be reported if the administered dosage is not within the prescribed range and the dose criteria are met. To determine the difference between the delivered dose and the dose that would have resulted from the prescribed dosage range, licensees can use the minimum dosage for an underdose event and the maximum dosage for an overdose event. While most incidents involving uses under 10 CFR 35.100 and 10 CFR 35.200 do not meet the minimum dose threshold for reporting, some could meet the threshold (e.g., if a batch dosage is inadvertently administered). Therefore, for events in which the wrong dosage is given for a diagnostic study, licensees should still evaluate whether the dose threshold for reporting is met. For most incidents, licensees can use dosimetry information provided in the package inserts approved by the U.S. Food and Drug Administration to determine whether the dose threshold for reporting is met.

"Prescribed dose" is defined differently in 10 CFR 35.2 for different modalities. For manual brachytherapy, the total dose is given by either the total source strength and exposure time or the total dose as documented in the written directive. For temporary implant manual brachytherapy, licensees must document the prescribed dose on the written directive before implantation in accordance with 10 CFR 35.41. This dose should be used to evaluate whether an incident needs to be reported as a medical event.

For high dose-rate remote afterloader brachytherapy, the written directive contains the prescribed dose per fraction, number of fractions, and prescribed total dose. When an incident with a fraction is discovered, it should be evaluated against the criteria in 10 CFR 35.3045(a)(1)(i)(A) and (a)(1)(i)(C) to determine whether a medical event occurred. If an incident with a fraction is discovered before the entire treatment protocol is complete, the AU can revise the written directive in accordance with 10 CFR 35.40(c)(1) to modify the prescribed fraction dose for future fractions and total dose before administration of the remaining fractions. In this case, the prescribed total dose used for the medical event evaluation should be the sum of the original prescribed dose(s) of the fraction(s) where the incident occurred and the revised prescribed dose for the later fractions.

For therapeutic dosages of unsealed byproduct material, the prescribed dosage is defined as the specified activity or range of activity as documented in the written directive. As 10 CFR 35.40 does not require that fractions be included for written directives involving administrations under 10 CFR 35.300, "Use of unsealed byproduct material for which a written directive is required," incidents involving unsealed byproduct material licensed under 10 CFR 35.300 should be evaluated using the total dosage difference described in 10 CFR 35.3045(a)(1)(i)(B), even if the administration is part of a multiple administration regimen.

1.1.2 Wrong Treatment

An incident associated with an administration that was not performed as intended by the AU should be evaluated using the criteria of 10 CFR 35.3045(a)(1)(ii), as described in the subsections below.

1.1.2.1 Wrong Radioactive Drug or Radionuclide

An incident involving the administration of the wrong radioactive drug or wrong radionuclide for a brachytherapy procedure, excluding permanent implant brachytherapy, should be evaluated using the criterion of 10 CFR 35.3045(a)(1)(ii)(A). If the incident involved the administration of the wrong radioactive drug or radionuclide and resulted in a dose exceeding 0.05 Sv (5 rem) effective dose

equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin, it must be reported as a medical event.

When the dose criteria are met, a report is required if a radioactive drug or radionuclide was administered that was not directed or intended by the AU. This includes incidents where the intended radioactive drug or radionuclide administration would not require a written directive if the dose criteria are met. For example, under this criterion, a licensee would need to report an incident in which an AU intended to give a patient a diagnostic drug that did not require a written directive, but a different therapeutic drug was administered to the patient. In addition, if the dose criteria are met, an incident in which the written directive inadvertently specified the wrong drug or radionuclide must be reported if the administration was not given as intended. For example, an incident where a patient was intended to receive a diagnostic dosage of I-123 but instead received a therapeutic dosage of I-131 under written directive created in error would be a medical event if the dose criteria were met. An AU's intent is based on their medical judgment; deviation from the usage described in a package insert is not considered a medical event if the administration was in accordance with the AU's intent.

1.1.2.2 Wrong Route of Administration

In accordance with 10 CFR 35.40, the written directive must include the AU's intended route of administration.[2] Common examples of routes of administration include oral, intravascular, intravascular bolus, intravascular drip, and parenteral. If a radioactive drug containing byproduct material is administered by the wrong route, the incident should be evaluated using the criterion of 10 CFR 35.3045(a)(1)(ii)(B). If the incident resulted in a dose exceeding 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin, it must be reported as a medical event.

Incidents should be reported as medical events under this criterion even if no written directive was required, or the written directive specified the wrong route of administration, if the dose criteria was met and the route of administration was not as intended by the AU. Deviation from the usage described in a package insert is not considered a medical event if the administration was in accordance with the AU's intended route of administration.

1.1.2.3 Wrong Individual

An incident involving the administration of a dose or dosage to the wrong individual or human research subject should be evaluated using the criterion of 10 CFR 35.3045(a)(1)(ii)(C). If the incident resulted in a dose exceeding 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin, it must be reported as a medical event. Incidents should be reported as medical events under this criterion in cases where there is no written directive, or the written directive specified the wrong patient or human research subject, if the administration was not intended by the AU.

1.1.2.4 Wrong Mode of Treatment

An incident involving the administration of a dose or dosage delivered by the wrong mode of treatment should be evaluated using the criterion of 10 CFR 35.3045(a)(1)(ii)(D). If the incident resulted in a dose exceeding 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin, it must be reported as a medical event. Examples of

2 Licensees should use medically appropriate terms for routes of administration. At the time of publication of this document, the FDA has defined various routes of administration at https://www.fda.gov/drugs/data-standards-manual-monographs/route-administration.

modes of treatment include gamma stereotactic radiosurgery therapy versus linear accelerator therapy, high-dose-rate versus pulsed-dose-rate brachytherapy, and rotational versus fixed teletherapy.

1.1.2.5 Leaking Sealed Source

An incident involving a leaking sealed source should be evaluated using the criterion of 10 CFR 35.3045(a)(1)(ii)(E). If the incident resulted in a dose exceeding 0.05 Sv (5 rem) effective dose equivalent, 0.5 Sv (50 rem) to an organ or tissue, or 0.5 Sv (50 rem) shallow dose equivalent to the skin, it must be reported as a medical event.

1.1.3 Wrong Treatment Site

An incident involving a dose to the wrong treatment site should be evaluated using the criterion of 10 CFR 35.3045(a)(1)(iii). The incident must be reported as a medical event if both of the following are met:

- The wrong treatment site receives 0.5 Sv (50 rem) or more than the expected dose to that site from the procedure if the administration had taken place in accordance with the written directive prepared or revised before administration.

- The dose is 50 percent or more than the expected dose to that site from the procedure if the administration had taken place in accordance with the written directive prepared or revised before administration.

"Treatment site" is defined in 10 CFR 35.2 as the anatomical description of the tissue intended to receive a radiation dose, as described in a written directive. As 10 CFR 35.40 does not require a treatment site to be defined for administrations of unsealed byproduct material, incidents involving radiopharmaceuticals used under 10 CFR 35.300 cannot meet this criterion. For extravasation events, see section 1.4 below.

For uses where a treatment site is documented in the written directive, this criterion may be met if the treatment location shifts significantly, as well as if the dose is delivered to a completely different site. If the treated site is located a significant distance away from the intended treatment site—for example, on the wrong side of the body or of a larger organ—the expected dose to that wrong treatment site can likely be assumed to be minimal, and any incident leading to a dose of 50 rem or more must be reported.

To determine whether an incident is reportable when the treatment was administered close to the expected treatment site, or even with a small shift in treatment site, licensees should determine what the expected dose to the wrong treatment site would have been if the administration had taken place in accordance with the written directive. Licensees should report an event if any volume of tissue received sufficient dose to meet the criteria for a medical event.

1.2 Medical Events Associated with Permanent Implant Brachytherapy but Not Patient Intervention

The criteria for medical events associated with permanent implant brachytherapy, except for events that result from patient intervention, are listed in 10 CFR 35.3045(a)(2). Unlike medical events for other modalities described above, there is no dose threshold for permanent implant brachytherapy medical events except in the case of a leaking source. The medical event criteria for permanent implant brachytherapy are broken down into three parts, described below.

1.2.1 Incorrect Source Strength to Treatment Site

An incident associated with incorrect total source strength should be evaluated using the criterion of 10 CFR 35.3045(a)(2)(i). This criterion requires reporting of events involving an administration where the total source strength administered differs by 20 percent or more from the total source strength documented in the post-implantation portion of the written directive. In accordance with 10 CFR 35.40, the post-implantation portion of the written directive must be completed after implantation, but before the patient leaves the post-treatment area. It must include the treatment site, the number of sources implanted, the total source strength implanted, and the date.

1.2.2 Incorrect Source Strength outside Treatment Site

Licensees must determine the total source strength administered outside the treatment site, compared to the total source strength documented in the post-implantation portion of the written directive, within 60 calendar days from the date of implantation, unless a written justification of patient unavailability is documented. In accordance with 10 CFR 35.41, licensees must develop, implement, and maintain written procedures for making this determination. If the licensee determines that the total source strength administered outside the treatment site exceeds 20 percent of the total source strength documented in the post-implantation portion of the written directive, the licensee must report the incident as a medical event in accordance with 10 CFR 35.3045(2)(ii). However, under 10 CFR 35.3045(a)(2), the reporting criteria exclude permanent implant brachytherapy events associated with sources that were implanted into the correct site but migrated outside the treatment site.

1.2.3 Wrong Treatment

An incident associated with an administration of permanent implant brachytherapy that was not performed as intended by the AU should be evaluated using the criteria in 10 CFR 35.3045(2)(iii). All administrations of a wrong radionuclide and all administrations to the wrong individual or human research subject must be reported in accordance with 10 CFR 35.3045(2)(iii)(A)–(B). In accordance with 10 CFR 35.3045(2)(iii)(D), licensees must also report incidents of a leaking sealed source that results in a dose exceeding 0.5 Sv (50 rem) to an organ or tissue. These incidents should be evaluated against both the pre- and post-implantation portions of the written directive.

In addition, in accordance with 10 CFR 35.3045(2)(iii)(C), licensees must report incidents where a sealed source is implanted directly into a location discontiguous from the treatment site, as documented in the post-implantation portion of the written directive. Licensees must report such incidents even if only one seed is implanted into a location discontiguous from the treatment site, as this criterion does not have a minimum dose or percent difference threshold. In general, the term discontiguous describes things that are not adjacent or touching, or that are disconnected or have a gap between them. In the context of the medical event criteria for permanent implant brachytherapy, a discontiguous location is one that is not physically adjacent to or touching the treatment site.

1.3 Medical Events Associated with Patient Intervention

In accordance with 10 CFR 35.3045, events due to patient intervention must be reported if the administration results or will result in unintended permanent functional damage to an organ or a physiological system, as determined by a physician. “Patient intervention” is defined in 10 CFR 35.2 as an action by the patient or human research subject, whether intentional or unintentional.

Emergent patient conditions that do not result from an action by the patient are not considered patient intervention. For example, if a patient experiences a medical emergency and the AU decides to stop treatment, this would not be considered patient intervention. Instead, the licensee should evaluate this

event against other medical event criteria and report it accordingly. The NRC is aware that in many cases of emergent patient conditions, necessary medical actions could result in a dose being less than intended, leading to a medical event. However, as stated earlier, the occurrence of a medical event does not necessarily mean a patient was harmed or there was an error in standard of care. The purpose of medical event reporting is to minimize recurrence of events. Therefore, in its report of a medical event, the licensee should include any actions the licensee identified that could prevent recurrence, so the NRC can share this information with the medical community as necessary.

Examples of patient intervention are when a patient dislodges or removes a treatment device or prematurely terminates the administration. Patient intervention does not include cases in which a device is not appropriately fixed into place and therefore becomes dislodged by patient movement, or in which administration continues after noticeable patient movement. Information Notice 2006--11, "Applicability of Patient Intervention in Determining Medical Events for Gamma Stereotactic Radiosurgery and Other Therapy Procedures," dated June 12, 2006 (ML061360026) (Ref. 11), provides more information on determining whether an event is due to patient intervention.

1.4 Medical Events Associated with Extravasations

An administration that results in, or has the potential to result in, a radiation injury from an extravasation should be evaluated using the criterion in 10 CFR 35.3045(a)(3). "Extravasation" is defined in 10 CFR 35.2 as the unintentional presence of a radiopharmaceutical in the tissue surrounding the blood vessel following an injection. While some amount of a radiopharmaceutical is expected to remain in the tissue around an administration site following all injections because of the nature of vascular injections, extravasations occur when the presence of the radiopharmaceutical in the tissue is unintended. For example, an extravasation could occur if a blood vessel is missed during injection or is blown or ruptured after needle insertion.

"Radiation injury" is defined in 10 CFR 35.2 as a deterministic health effect to the area around an administration site that can be attributed to radiation. The deterministic effects of radiation to the tissue around an administration site are well known; they range from severe ulceration and necrosis from high exposures to erythema from low exposures. For the purposes of this proposed rule, all deterministic effects reasonably attributable to radiation as determined by a physician must be reported, including radiation -induced erythema. Although deterministic effects near the site of the administration could be caused by many different factors, to determine whether the reporting criterion is met, licensees should evaluate such effects to determine whether they can be attributed to an extravasation. The regulations require reporting of extravasation events with potential deterministic effects, as well as effects that have already appeared. This enables licensees to report extravasation events promptly, without having to wait for symptoms to appear; to provide appropriate medical care to patients as quickly as possible; and to take corrective actions, as necessary, to prevent recurrence. It also minimizes the burden on the affected patient, relieving them of the need to return to a healthcare provider solely for reporting purposes. While not all extravasations are severe enough for a physician to make a determination of the potential for radiation injury before an injury actually develops, this provision allows for expediting of the reporting process.

The determination of whether an extravasation has the potential to result in a radiation injury is a medical determination. Any physician, as defined in 10 CFR 35.2, who has the proper medical knowledge and has experience with radiation injuries should be able to make this determination, regardless of AU status or licensee affiliation. If a physician not affiliated with a licensee notifies the licensee of an extravasation meeting the reporting criterion, then the licensee must report the event. If a physician notifies the licensee of an extravasation that may meet the reporting criteria, but for which the physician

has not made a determination, the licensee should evaluate further the incident further to determine if it is reportable.

Notably, an extravasation is not necessarily reportable under 10 CFR 35.3045 if it does not have the potential to result in a radiation injury. There are several case-specific factors that affect the potential for radiation injury from an extravasation, including the type (i.e., alpha, beta, or gamma) and amount of radiation, actions taken to reduce the dose to the affected area, and patient-specific conditions that affect radiosensitivity. Licensees should take these factors into account when determining whether an extravasation is reportable.

2. Embryo and Fetus Events (10 CFR 35.3047)

In accordance with 10 CFR 35.3047(a), licensees must report any dose to an embryo/fetus exceeding 50 mSv (5 rem) dose equivalent that results from an administration of byproduct material or radiation from byproduct material to a pregnant individual, unless the AU specifically approved the dose to the embryo/fetus prior to the administration. Moreover, a licensee must report a discovered event that meets these criteria even if the licensee could not have known at the time of administration that the individual was pregnant. Licensees can use RG 8.36, "Radiation Dose to the Embryo/Fetus (Ref. 12)," or manufacturer dosimetry information to determine the dose to the embryo/fetus.

In accordance with 10 CFR 35.3047(b), licensees must report any dose to a nursing child that results from an administration of byproduct material to a breastfeeding individual, if it exceeds 50 mSv (5 rem) total effective dose equivalent or has resulted in unintended permanent functional damage to an organ or a physiological system of the child, as determined by a physician. A licensee must report any event that meets these criteria, even if the licensee provided guidance on to interrupt or discontinue breastfeeding at the time of the patient's release, as required by 10 CFR 35.75, "Release of individuals containing unsealed byproduct material or implants containing byproduct material." In accordance with 10 CFR 35.75(b), upon releasing a patient from its control, a licensee must provide certain instructions to the patient if the total effective dose equivalent to a nursing child could exceed 1 mSv (0.1 rem). These instructions must include guidance on the interruption or discontinuation of breastfeeding and information on the potential consequences, if any, of failure to follow the guidance.

In accordance with 10 CFR 35.3047(c), the licensee must notify the NRC Operations Center by telephone no later than the next calendar day after discovery of a dose to an embryo/fetus or nursing child that meets the criteria in 10 CFR 35.3045(a) or (b). In accordance with 10 CFR 35.3047(d), licensees must submit a written report to the appropriate NRC regional office within 15 days after discovery of the event by the appropriate method listed in 10 CFR 30.6(a). The written report must include the licensee's name; the name of the prescribing physician; a brief description of the event; why the event occurred; the effect, if any, on the embryo/fetus or nursing child; what actions, if any, have been taken or are planned to prevent recurrence; and either certification that the licensee notified the pregnant individual or mother (or the mother's or child's responsible relative or guardian), or an explanation of the reason if the licensee did not do so.

While some events of this type are unavoidable, licensees should still perform evaluations after such events to determine actions to be taken to prevent recurrence. For example, licensees could consider instructing patients to avoid sexual activity for a specified period of time before treatment, to prevent the possibility that an embryo too young to be detected will receive a dose from a patient's administration.

3. Procedures for Administrations

3.1 Procedures for Administrations That Require a Written Directive

In accordance with 10 CFR 35.41, for any administration requiring a written directive, licensees must develop, implement, and maintain written procedures to provide high confidence of the following:

- The identity of the patient or human research subject is verified before each administration.
- Each administration is in accordance with the written directive.

The regulation at 10 CFR 35.41(b) lists items that these procedures must address at a minimum. In addition to steps to prevent medical events, the procedures must address how the licensee will determine whether a medical event has occurred. Licensees' procedures should be specific to the treatment they are performing, their staffing, and facilities, to ensure that the licensee can implement them. Appendix S of NUREG-1556, Volume 9, Revision 3, provides guidance and model procedures for administrations that require written directives.

3.2 Procedures for Evaluating and Reporting Extravasations

In accordance with 10 CFR 35.42, for any administration in which an extravasation could occur, licensees must develop, implement, and maintain written procedures to provide high confidence that an extravasation that results in, or has the potential to result in, a radiation injury will be detected in a timely manner and reported in accordance with 10 CFR 35.3045. These written procedures must address how the licensee will determine whether an extravasation results in, or has the potential to result in, a radiation injury. Serial imaging of the area surrounding the administration site, physical examination, and dosimetric assessment can aid in characterizing an extravasation. Model procedures for evaluating and reporting extravasations are part of the implementation guidance for the extravasations rule. The model procedures are currently available at ML24047A272 and will be added as a new appendix to NUREG-1556, Volume 9, when NUREG-1556 is next revised.

4. Reporting

In accordance with 10 CFR 35.3045(c), licensees must notify the NRC Operations Center by telephone, at 301-816-5100, no later than the next calendar day after discovery of a medical event. Discovery occurs when a licensee identifies an administration that appears not to have gone in accordance with the written procedure or the AU's intent. As many medical events are complex, the NRC recognizes that the licensee may not have all of the necessary information the day an event is discovered. However, if the licensee suspects that a medical event has occurred, to ensure compliance and to allow the NRC and the licensee to respond appropriately, the licensee should report the event no later than the next calendar day. To allow the NRC to respond quickly to any generic issues, the report should contain as much information as the licensee knows at the time of reporting.

An extravasation that results or has the potential to result in, a radiation injury, as determined by a physician, must be reported as a medical event under 10 CFR 35.3045(a)(3), and therefore the licensee must meet all reporting requirements outlined in 10 CFR 35.3045. In accordance with 10 CFR 35.3045(c), the licensee must report medical events resulting from an extravasation no later than the calendar day following discovery of the event. In the context of medical events arising from an extravasation, an event is discovered when the licensee makes or is notified of a final determination made by a physician that the event satisfies the criteria in 10 CFR 35.3045(a)(3). This may be the day the administration occurred or sometime afterwards. Examples include the following:

- Immediately after the administration, a licensee physician determines that the extravasation is severe enough to have already resulted in deterministic effects, or that it has the potential to result in a radiation injury.

- A patient's physician notifies the licensee, or a licensee physician determines, that the criteria for a medical event have been met.

- A patient's physician notifies the licensee that the criteria for a medical event may have been met, and further evaluation by the licensee has confirmed that the criteria have been met.

In all of the above cases, the licensee must notify the NRC Operations Center no later than the next calendar day after discovery. The report should contain as much information as the licensee knows at the time of reporting; however, the NRC recognizes that not all information may be available to the licensee at this point.

In accordance with 10 CFR 35.3045(d), the licensee must submit a written report to the appropriate NRC regional office within 15 days after discovery of the medical event by a method listed in 10 CFR 30.6(a). The licensee's report must include the information listed in 10 CFR 35.3045(d)(1). The regulation at 10 CFR 35.3045(d)(1)(v) requires the report to include the effect, if any, on the individual(s) who received the administration. In the case of a medical event resulting from an extravasation, the effect on the individual who received the administration may not present until weeks or months after the event. If the report is based on a determination that the extravasation has the potential to result in a radiation injury, the report should describe the potential deterministic effects anticipated (e.g., erythema, necrosis).

The NRC uses the reported information to assess trends or patterns, identify generic issues or generic concerns, and recognize any inadequacies or unreliability in specific equipment or procedures. The reported information is critical, because it helps the NRC gain a timely and effective understanding of why the event occurred and identify any actions necessary to minimize the risk that similar events will occur. While the regulations identify specific information that must be included, medical event reports submitted by licensees range from minimally to highly detailed. Reports that provide only the minimum required information often lack useful narratives that would allow the NRC staff to fully assess medical events and identify trends or patterns. Therefore, to help prevent future medical events, the NRC recommends that licensees consider the best practices for reporting described in appendix E to the Nuclear Material Events Database Annual Report for 2021, issued January 2022 (ML22049B538) (Ref. 13).

5. Recordkeeping

In accordance with 10 CFR 35.2041, "Records for procedures for administrations requiring a written directive," and 10 CFR 35.2042, "Records for procedures for evaluating and reporting extravasations,", a licensee must retain a copy of the procedures required by 10 CFR 35.41(a) and 10 CFR 35.42(a) for the duration of its license. If the licensee changes the procedures for any reason, it must also keep all previous versions of the procedures for the duration of the license. The licensee should annotate each version of each procedure with the dates during which that version was used.

D. IMPLEMENTATION

The NRC staff may use this regulatory guide as a reference in its regulatory processes, such as licensing, inspection, or enforcement. Backfitting and issue finality considerations do not apply to 10 CFR Part 35 licensees and applicants, because 10 CFR Part 35 does not include backfitting or issue finality provisions. The forward fitting policy in Management Directive 8.4, "Management of Backfitting, Forward Fitting, Issue Finality, and Information Requests" (Ref. 14), also does not apply to these licensees and applicants.

REFERENCES[3]

1. U.S. *Code of Federal Regulations*, "Medical Use of Byproduct Material," Part 35, Chapter I, Title 10, "Energy."

2. U.S. Nuclear Regulatory Commission (NRC), NUREG-1556, "Consolidated Guidance about Materials Licenses," Volume 9, "Program Specific Guidance about Medical Use Licenses Specific Guidance about Medical Use Licenses," Washington, DC.

3. NRC, "Staff Requirements—SECY-22-0043—Petition for Rulemaking and Rulemaking Plan on Reporting Nuclear Medicine Injection Extravasations as Medical Events, Washington, DC, December 12, 20222.

4. NRC, "Medical Use of Byproduct Material; Policy Statement, Revision," *Federal Register*, Vol. 65, No. 150, pp. 47654–47660 (65 FR 47654), Washington, DC, August 3, 2000.

5. NRC, "Nuclear Regulatory Commission International Policy Statement," *Federal Register*, Vol. 79, No. 132, pp. 39415–39418 (79 FR 39415), Washington, DC, July 10, 2014.

6. NRC, Management Directive 6.6, "Regulatory Guides," Washington, DC.

7. International Atomic Energy Agency (IAEA), Specific Safety Guide No. 46, "Radiation Protection and Safety in Medical Uses of Ionizing Radiation," Vienna, Austria, 2018.

8. IAEA, Human Health Series No. 46, "QUANUM 3.0: An Updated Tool for Nuclear Medicine," 3rd Edition, Vienna, Austria, August 2021.

9. International Council of Radiation Protection, Publication 140, "Radiological Protection in Therapy with Radiopharmaceuticals," September 2019.

10. Australian Radiation Protection and Nuclear Safety Agency (ARPANSA), Radiation Protection Series No. 14.2, "Safety Guide for Radiation Protection in Nuclear Medicine," Chief Executive Officer of ARPANSA, Yallambie, Victoria, August 2008.

11. NRC, Information Notice 2006-11, "Applicability of Patient Intervention in Determining Medical Events for Gamma Stereotactic Radiosurgery and Other Therapy Procedures", Washington, DC, June 12, 2006.

12. NRC, Regulatory Guide 8.36, "Radiation Dose to the Embryo/Fetus," Washington, DC, July 1992.

13. NRC, "Nuclear Material Events Database, Annual Report, Fiscal Year 2021," Washington, DC, January 2022.

3 Publicly available NRC published documents are available electronically through the NRC Library on the NRC's public website at http://www.nrc.gov/reading-rm/doc-collections/ and through the NRC's Agencywide Documents Access and Management System (ADAMS) at http://www.nrc.gov/reading-rm/adams.html. For problems with ADAMS, contact the Public Document Room staff at 301-415-4737 or (800) 397-4209, or email pdr.resource@nrc.gov. The NRC Public Document Room (PDR), where you may also examine and order copies of publicly available documents, is open by appointment. To make an appointment to visit the PDR, please send an email to PDR.Resource@nrc.gov or call 1-800-397-4209 or 301-415-4737, between 8 a.m. and 4 p.m. eastern time (ET), Monday through Friday, except Federal holidays.

14. NRC, Management Directive 8.4, "Management of Backfitting, Forward Fitting, Issue Finality, and Information Requests," Washington, DC.

APPENDIX A

LIST OF GENERIC COMMUNICATIONS ON MEDICAL EVENTS

Below is a list of generic communications on medical events issued between 2002 and the time of publication of this document. More recent generic communications are available at the U.S. Nuclear Regulatory Commission medical use licensee toolkit webpage at https://www.nrc.gov/materials/miau/med-use-toolkit.html.

- Information Notice (IN) 2019-12, "Recent Reported Medical Events Involving the Administration of Yttrium-90 Microspheres for Therapeutic Medical Procedures," dated December 31, 2019, includes information on yttrium-90 microsphere medical events so that licensees can evaluate the possibility of such events at their facilities and consider actions, as appropriate, to avoid similar events.

- IN 2019-07, "Methods to Prevent Medical Events," dated August 26, 2019, provides the results of an evaluation of medical events, as well as strategies to reduce or prevent medical events.

- IN 2019-06, "Patient Skin Contamination Events Associated with I-131 Metaiodobenzylguanidine [MIBG] during Neuroblastoma Treatments," dated August 26, 2019, gives an overview of patient contamination risks associated with therapeutic treatments using iodine (I)-131 MIBG.

- IN 2012-08, "High Dose-Rate Remote Afterloader (HDR) Physical Presence Requirements," dated April 10, 2012, informs licensees about several high-dose-rate remote afterloader administration medical events, to demonstrate the importance of verifying treatment parameters before treatment.

- IN 2009-17, "Reportable Medical Events Involving Treatment Delivery Errors Caused by Confusion of Units for the Specification of Brachytherapy Sources," dated August 28, 2009, informs licensees of treatment delivery errors and associated medical events caused by confusion of units for the specification of low-energy photon-emitting brachytherapy sources implanted into patients.

- IN 2009-15, "Varian Medical Systems Varisource High Dose-Rate Remote Afterloader Events: Source Retraction Problems," dated August 28, 2009, alerts licensees about events reported at three locations where service engineers experienced problems with the VariSource HDR during source retractions.

- IN 2007-35, "Varian Medical Systems Varisource HDR Events: Iridium-192 Source Pulled from Shielded Position," dated October 17, 2007, alerts licensees about events when the use of the emergency manual retract hand wheel on the VariSource HDR had caused the active iridium-192 source to be pulled out of the shielded position.

- IN 2007-03, "Reportable Medical Events Involving Patients Receiving Dosages of Sodium Iodide Iodine-131 Less than the Prescribed Dosage Because of Capsules Remaining in Vials after Administration," dated February 2, 2007, describes events in which I-131 capsules remained in vials after administration. Similar events have continued to occur in more recent years.

- IN 2006-11, "Applicability of Patient Intervention in Determining Medical Events for Gamma Stereotactic Radiosurgery and Other Therapy Procedures," dated June 6, 2006, describes the applicability of patient intervention in two events related to gamma stereotactic radiosurgery use.

- IN 2005-27, "Low-Dose-Rate Manual Brachytherapy—Equipment-Related Medical Events," dated October 7, 2005, informs licensees of recently reported medical events that occurred during a licensee's implementation of low-dose-rate manual brachytherapy procedures.

- IN 2005-17, "Manual Brachytherapy Source Jamming," dated June 23, 2005, informs licensees of medical events involving ruptured seeds that had occurred at different facilities during manual brachytherapy as a result of seed jamming.

APPENDIX B

EXAMPLES OF MEDICAL EVENTS

This appendix provides examples that do and do not meet the medical event criteria. An overview of recent medical events appears on the U.S. Nuclear Regulatory Commission (NRC) medical use licensee toolkit webpage at https://www.nrc.gov/materials/miau/med-use-toolkit.html.

Wrong Dosage Event

A patient was prescribed 3.7 gigabecquerels (GBq) (100 millicuries (mCi)) of lutetium (Lu)-177 (Lutathera) on a written directive but received 7.62 GBq (206 mCi). Although this occurred at the patient's third treatment of a four-treatment protocol, the licensee used separate written directives for each administration; therefore, only this administration needs to be considered for the medical event evaluation. The percent difference between the total dosage delivered and the total prescribed dosage was

$$\%\ difference = \frac{7.62 - 3.7}{3.7} \times\ 100\% = 107\%.$$

The licensee calculated that the difference between the administered dosage and the prescribed dosage resulted in an additional organ dose of 256 centigrays (cGy) (rad) to the kidney. As the percent difference in dosage and the dose threshold are greater than the limits listed in Title 10 of the *Code of Federal Regulations* (10 CFR) 35.3045(a)(1)(i), this event is reportable as a medical event.

Wrong Treatment Site

A licensee discovered that a tandem and ovoid applicator had shifted inside a patient's pelvis during administration, causing several dwell positions to shift slightly from the treatment plan. As a result, the licensee evaluated the administered dose to nontreatment sites to determine whether it met the criteria in 10 CFR 35.3045(a)(1)(iii). As the criteria in 10 CFR 35.3045(a)(1)(iii) are based on the difference between the expected and the administered dose to the wrong treatment site, the licensee compared the original treatment plan to a treatment plan created to model the administered dose. In this example, the licensee model found that the administered dose to 5 cubic centimeters of nontarget bowel tissue was 550 cGy (rad), instead of the 220 cGy (rad) planned. Thus, this tissue received 330 cGy (rad) more than expected, a difference of 150 percent. As these doses are greater than the thresholds in the criteria in 10 CFR 35.3045(a)(1)(iii), this event is reportable as a medical event.

Wrong Treatment Site for Permanent Implant Brachytherapy

A patient's prescribed treatment plan was to have 54 iodine (I)-125 seeds with a total activity of 1.01 GBq (27.4 mCi) implanted into the prostate. As the licensee believed that the administration had gone as planned, the post-implantation portion of the written directive matched the pretreatment written directive containing the prescribed treatment plan. However, the patient's follow-up CT scan revealed that 28 seeds with a total activity of 0.52 GBq (14.2 mCi) had been implanted into the patient's penile bulb. This meant that more than 20 percent of the total source strength documented in the post-implantation portion of the written directive had been administered outside the treatment site. Therefore, this event is reportable as a medical event under the criteria in 10 CFR 35.3045(a)(2)(ii).

Wrong Treatment Configuration within the Treatment Site for Permanent Implant Brachytherapy

A patient's prescribed treatment plan was to have 61 I-125 seeds permanently implanted into the prostate. The Authorized User (AU) intended to place the seeds in a uniform distribution to achieve the

intended dose distribution within the treatment site. However, during administration, the seeds were inadvertently placed with higher distribution in the center of the treatment site, so that the absorbed dose in the center was higher than intended. In accordance with 10 CFR 35.3045, the NRC does not consider this a medical event, because the NRC's regulations on medical event reporting do not consider the details of source placement within the treatment site or dose for permanent implant brachytherapy. Therefore, the licensee is not required to report this event to the NRC. However, since the treatment did not conform to the AU's intentions, the NRC would recommend that the licensee evaluate the cause of the error and take corrective actions as necessary.

Radiopharmaceutical Extravasation Determined to Have the Potential for Radiation Injury

A patient was prescribed 3.7 GBq (100 mCi) of Lu-177 (Lutathera), administered by infusion. During the administration, the patient complained of pain in the arm, and examination of the injection site showed clear swelling. The administration was halted, and the patient was given a warm compress to hold to the site and told to elevate the arm above their head. Post-treatment imaging of the site showed a significant amount of activity remaining in the arm, and the physician determined that this extravasation had the potential to result in a radiation injury. Based on the physician's determination, this event is reportable as a medical event under the criteria in 10 CFR 35.3045(a)(3) and must be reported no later than the next calendar day after the physician made the determination.

Radiopharmaceutical Extravasation Discovered after the Fact

A patient had undergone an administration of radium (Ra) (Xofigo) at licensee X. The treatment was initially thought to have Ra-223 (Xofigo) at licensee X. The treatment was initially thought to have been completed without incident, and the patient was given leave to return home. Two days after the administration, the patient returned to their primary care physician, reporting a rash and blistering at the injection site. Using the information card given to the patient by licensee X, the patient's primary care physician contacted the licensee and shared their suspicions of radiation induced injury. In collaboration, the two physicians ultimately concluded that the injury was not likely due to radiation from a suspected extravasation of the original radiopharmaceutical. Their medical opinion was that the symptoms were from an allergic reaction. This is not a reportable event, since the physicians determined that the injury was not due to radiation from the radiopharmaceutical administration.

Draft Model Procedures for Evaluating and Reporting Extravasation Medical Events

This draft model provides acceptable procedures for administrations in which an extravasation could occur. Applicants may either adopt this model procedure or develop their own procedure to meet the requirements of Title 10 of the *Code of Federal Regulations* (10 CFR) 35.42.

Procedures for Evaluating and Reporting Extravasations

This model provides guidance to license and applicants for developing, maintaining, and implementing written procedures for evaluating and reporting extravasation medical events. This model does not restrict use of other guidance in developing, maintaining, and implementing written procedures for evaluating and reporting extravasation medical events. These procedures are to provide high confidence that the objectives specified in 10 CFR 35.42 will be met.

The written procedures must contain the information described in 10 CFR 35.42 and be retained in accordance with 10 CFR 35.2042, “Records for procedures for evaluating and reporting extravasations.”

Discussion

Before an administration of radioactive materials for diagnostic or therapeutic purposes, the authorized user (AU) should inform the patient about what the procedure will involve, including any possible complications, feelings, or sensations arising from an extravasation. The AU should inform the patient of what steps to take if they feel a symptom that could indicate a possible extravasation (e.g., unexpected burning sensations near the injection site).

During the administration, the licensee should monitor the patient to detect an extravasation as soon as it happens. Examples of monitoring include frequent contact with the patient during longer administrations, consideration of patient feedback, observation of symptoms such as swelling, and use of monitoring technologies. If the licensee identifies that an extravasation has occurred, the licensee must determine whether it has resulted in, or could potentially result in, a radiation injury in accordance with 10 CFR 35.42(b). If a physician determines that the extravasation has resulted in, or has the potential to result in, a radiation injury, the licensee should report the extravasation to the NRC in accordance with 10 CFR 35.3045.

To ensure that a radiation injury from a delayed reaction will be detected in a timely manner, the licensee should inform the patient about the potential complications of the treatment and let the patient know how to contact the licensee if a potential radiation injury occurs. The licensee should give the patient an information card to minimize the burden to the patient of having to remember the information. The information card should include the name of the physician, the radiopharmaceutical or treatment given, the location of the treatment, the date of the treatment, and a way of contacting the clinic providing the treatment.

Because radiation effects may be delayed, a patient may go to another healthcare provider if effects occur. The licensee should use any information provided by other healthcare providers as necessary to determine whether a radiation injury has resulted from an extravasation. If a physician later determines that an extravasation resulted in, or has the potential to result in, a radiation injury, the licensee should report the extravasation to the NRC in accordance with 10 CFR 35.3045.

Figure AA.1 Patient Information Card. Licensees should provide information to patients after their treatment to assist patients if they develop symptoms posttreatment and seek medical care for a potential radiation injury.