

November 27, 2020

U.S. Nuclear Regulatory Commission
Rockville, Maryland

RE: Petition for Rulemaking, Request for Public Comments
10 CFR Part 35, Docket No. PRM-35-22, Docket ID NRC-2020-0141
Petition Title: "Reporting Nuclear Medicine Injection Extravasations as Medical Events"

TO WHOM IT MAY CONCERN:

The undersigned submits the following COMMENTS regarding Docket ID NRC-2020-0141, Reporting Nuclear Medicine Injection Extravasations as Medical Events

1. Is this an important issue for the Nuclear Regulatory Commission to address with 10CFR35 rulemaking?

COMMENT RESPONSE: Yes. The NRC has established formal dose limits for radiation protection to which all licensed users of medical byproduct materials are expected to honor and respect. When nuclear medicine diagnostic or therapeutic radiopharmaceuticals are improperly administered, resulting in extravasation, radiation doses can be imparted to sensitive skin and underlying tissues that exceed federal dose limits for skin and extremities. High doses to skin and extremity tissues can result in adverse tissue reactions and harmful biological damage in the patient. However, these extraordinary, high-dose events can be dismissed and go unreported by the clinic according to the NRC's 1980 medical event reporting policy on extravasations.

2. How frequently does radiopharmaceutical extravasation occur?

COMMENT RESPONSE: The undersigned has co-authored a scientific paper (Osborne D, Kiser JW, Knowland J, Townsend D, and Fisher DR, "Patient-specific extravasation dosimetry using uptake probe measurements," *Health Phys.* 2020; in press) that addresses extravasation event frequency in nuclear medicine. The authors report that extravasations occur relatively frequently (mean 10.4% of radiopharmaceutical infusions, n = 5418, covering 20 nuclear medicine centers). Most extravasations are not considered serious, but many serious cases have been documented in the published scientific literature. With increasing use of high-dose therapeutic infusions, the number of serious events associated with therapy has also been increasing.

3. Do you know of any extravasations that have resulted in harm to patients? If so and without including information that could lead to the identification of the individual, describe the circumstances, type of effect harm, and the impacts.

COMMENT RESPONSE: The manuscript cited above (Osborne et al., 2020) provides references on many cases in which radiopharmaceutical extravasation resulted in direct harm to patients. Adverse biological effects reported in the literature included local pain (burning sensation), erythema, swelling, lesions, wet and dry desquamation, severe tissue damage, and radiation necrosis. One case of local damage from a radium-223 therapy misadministration resulted in an aggressive squamous cell carcinoma at the injection site.

4. Do you expect that monitoring for extravasation and reviewing the results would improve radiopharmaceutical administration techniques at medical use licensee facilities? If so, how? If not, why not?

COMMENT RESPONSE: Yes, absolutely. The undersigned maintains that regardless of the serious nature of the dose, each extravasation to a patient's arm should be monitored and characterized as a proper health physics practice. Better understanding of the frequency and character of extravasation events can lead to procedure review, continuous learning, and improvement in administration quality.

5. Do you believe an NRC regulatory action requiring monitoring and review of extravasation would improve patient radiological health and safety? If so, how?

COMMENT RESPONSE: As with all other radiation protection practices, monitoring, characterization, dosimetry, and follow-up are essential radiation safety measures that are needed to ensure improve the technologist skill-set and to improve focus on patient radiological health and safety.

6. Are extravasations preventable?

COMMENT RESPONSE: Our independent research (Osborne et al., 2020, *op.cit.*) clearly shows that some clinics minimize radiopharmaceutical extravasations, while others do not. Inadvertent mis-administrations are largely avoidable with effort, improved quality, training, follow-up, and continuous improvement.

7. Is this a practice of medicine issue or a regulatory issue?

COMMENT RESPONSE: It is both! According to 10CFR35.3045, an accidental extravasation should become a medical event when a patient's radiation dose differs from the prescribed dose by more than 0.05 Sv (5 rem) effective dose equivalent, or imparts greater than 0.5 Sv (50 rem) to an organ or tissue, or imparts greater than 0.5 Sv (50 rem) shallow dose equivalent to the skin. Extravasation events often exceed these values for both diagnostic and therapeutic nuclear medicine procedures (Osborne et al., 2020, *op.cit.*)

8. Are patients receiving high radiation doses?

COMMENT RESPONSE: Radiation dose depends on severity, but in many cases, the answer is "yes". And the frequency of high-dose events is greater than most professionals might acknowledge. Some extravasations have resulted in serious tissue damage to patients.

9. Please comment on the Position Statement submitted by the Health Physics Society.

COMMENT RESPONSE: The undersigned maintains that when a serious accidental or inadvertent misadministration of a radiopharmaceutical occurs to an unsuspecting medical patient--infiltrating subdermal tissues and irradiating both tissue and overlying skin--that the misadministration should be identified, measured, characterized, and documented in the patient's medical record, and not callously dismissed or concealed from the patient and others. The National Council on Radiation Protection and Measurements concurred and recommended that the occupational dose limit for the skin and extremities be applied to members of the public for certain medical procedures (NCRP Report No. 180, *Management of Exposure to Ionizing Radiation: Radiation Protection Guidance for the United States, 2018*, section 5.3.2.1, p. 62; 2018), that being 0.5 Gy to the most-exposed portion of the extremity or skin.

The International Commission on Radiological Protection (ICRP) specifically addressed the need to reduce or prevent medical errors involving misadministered radiopharmaceuticals (ICRP Publication 140, *Radiological Protection in Therapy with Radiopharmaceuticals*, Annals 48(1), pp. 61-62; 2019). ICRP acknowledged that extravasation can result in severe soft tissue lesions. The ICRP recommended that patients should be monitored for extravasation during infusion, that the extravasation should be characterized with dosimetry, and that records should be maintained in the patients' medical record.

Unfortunately, taking a polar opposite view, the Health Physics Society position statement embraced the idea that extravasations are not sufficiently serious considerations for patient radiation safety, that extravasation is a practice of medicine issue (not a regulatory responsibility), and that identifying, measuring, characterizing, and documenting this class of radiation accidents are *unnecessary and burdensome activities* for the clinic. The Society position statement directly contradicts standing NCRP and ICRP recommendations on these critical points.

Sincerely,



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Supporting Attachment: Fisher DR and Liverett MD, Extravasation Events in the Nuclear Medicine Clinic (white paper)

Extravasation Events in the Nuclear Medicine Clinic

INADVERTENT injections of radiopharmaceutical agents into a patient’s arm tissue instead of into the appropriate blood vessel can cause the injection to infiltrate underlying tissue and produce high-dose radiation localized to patients’ arm and skin tissue. When this type of misadministration occurs, called an extravasation event, it should be recognized, mitigated, and monitored for patient health and safety, as is the standard for other practices with radioactive materials.

A Petition submitted to the U.S. Nuclear Regulatory Commission (NRC) calls attention to nuclear medicine extravasation events and the need to improve existing state and federal regulations. The old NRC position that extravasation events are “virtually impossible to avoid” is based on a false assumption that a quality improvement process cannot be implemented in a clinical setting to reduce the frequency of radiopharmaceutical misadministrations. This document supports the Petition and provides background information to explain why it makes good sense for both clinicians and patients.

A legacy exemption dating back 40 years on reporting requirements for radiopharmaceutical misadministrations or “medical events” disregards the increasing use of some diagnostic and high-dose radionuclide therapy agents today that were not available in 1980, recommendations of national and international scientific advisory bodies, and extremity and skin dose limits that apply to radiation workers.

Petition for Rulemaking Docket

The Nuclear Regulatory Commission accepts petitions and comments from the public to consider changes to its standing rules and regulations. The rulemaking petition process is the system by which any member of the public can request that the NRC develop, modify, repeal, or rescind a federal regulation.

A petition on “Reporting Nuclear Medicine Injection Extravasations as Medical Events” (the Petition, Docket No. NRC-2020-0141, PRM-35-22) was submitted to the NRC by Mr. Ron Lattanze on June 8, 2020, on behalf of Lucerno Dynamics, LLC, Cary, North Carolina.

The Petition asks the Commission to revisit its policy established in a 1980 *Federal Register* notice (45 *Fed. Reg.* 31701; 1980) for exempting extravasations as reportable medical events. In light of contemporary evidence on the ability to reduce extravasation frequency, the Petition seeks to require that certain extravasation events not be exempted from reporting requirements; instead, these events should be characterized and documented. Experience shows that event frequency is reduced when clinics implement quality improvement procedures. Reporting of severe extravasations will alert the Commission to instances of potential misuse of nuclear byproduct material and incentivize practitioners to improve

injection and infusion practices. The Petition is intended to ensure that diagnostic and therapeutic nuclear medicine patients are better protected from avoidable irradiation, and that patients receive access to vital information to better understand when and how such medical events impact their health care.

The Petition submission follows in-person informational briefings in 2018 and 2019 by Mr. Lattanze to NRC senior staff and its Advisory Committee on the Medical Uses of Isotopes (ACMUI).

***VIEWPOINT** A private citizen concerned about the radiation safety of patients undergoing nuclear medicine procedures has recognized the need for regulatory reform to address certain cases where the injected radiopharmaceutical misses the vein and infiltrates arm tissue—potentially causing radiation damage to arm tissue and the skin.*

Extravasation and Infiltration Defined

Radiopharmaceuticals are typically administered intravenously. *Extravasation* refers to the unintentional or inadvertent injection of some of the injected solution into surrounding arm tissue. Escape from the intended vascular pathway and diffusion into surrounding tissue may also be referred to as an *infiltration*. Infiltration of a radiopharmaceutical into arm tissue can cause a localized radiation dose to the affected tissues.

Why does this happen? Sometimes the radiopharmaceutical is improperly administered to a patient. Injected solution escaping from its intended vein or artery diffuses into and accumulates in perivascular tissue (cells, intercellular material, interstitial fluid, and interstitial compartments that are in the general vicinity of a blood vessel that may become infused with fluid from the needle or cannula). Unintended infusing may occur, for example, when the needle or cannula (i) causes a vein or artery to rupture, (ii) improperly punctures the vein or artery, (iii) backs out of the vein or artery, (iv) is improperly sized, (v) an infusion pump administers fluid at an excessive flow rate, or (vi) the infusate increases permeability of the vein or artery.

Adverse Consequences of Tissue Infiltration

Immediate symptoms of extravasation may include swelling, edema, pain, or numbness in the vicinity of the extravasation site; inflammation; and drainage from the site. Some infiltrations may go unnoticed until later. The principal concern for extravasation of radiopharmaceuticals is radiation dose and tissue damage. Another concern includes failure to deliver a prescribed amount of radiopharmaceutical. With the advent of high-dose theranostic agents (for both diagnostic and therapy), particular care must be exercised to ensure that high-activity therapy

agents are completely delivered into the artery or vein. An extravasation can result in a high-activity radiation dose remaining in the arm rather than reaching the intended target tissues.

How Common are Radiopharmaceutical Extravasation Events?

Recent studies show that extravasations in nuclear medicine occur relatively frequently (about 15% on average, where the typical range is 1.3% to 28%)¹ and can result in significant radiation dose to underlying tissues and skin². The resulting radiation effects on patients are rarely

¹ For example, see the following references:

Hall N, Zhang J, Reid R, Hurley D, Knopp M. Impact of FDG extravasation on SUV measurements in clinical PET/CT. Should we routinely scan the injection site? *J Nucl Med*. 2006;47:115P.

Krumrey S, Frye R, Tran I, Yost P, Nguyen N, Osman M. FDG manual injection verses infusion system: a comparison of dose precision and extravasation. *J Nucl Med*. 2009;50:2031.

Bains A, Botkin C, Oliver D, Nguyen N, Osman M. Contamination in ¹⁸F-FDG PET/CT: an initial experience. *J Nucl Med*. 2009;50:2222.

Muzaffar R, Frye SA, McMunn A, Ryan K, Lattanze R, Osman MM. Novel method to detect and characterize ¹⁸F-FDG infiltration at the injection site: a single-institution experience. *J Nucl Med Technol*. 2017;45:267-271.

Wong TZ, Benefield T, Masters S, et al. Quality Improvement Initiatives to Assess and Improve PET/CT Injection Infiltration Rates in Multiple Centers. *J Nucl Med Technol*. 2019;47:326-331.

Osman MM, Muzaffar R, Altinyay ME, Teymouri C. FDG dose extravasations in PET/CT: frequency and impact on SUV measurements. *Front Oncol*. 2011;1:41.

Currie G, Sanchez S. Topical Sensor for the Assessment of Injection Quality for ¹⁸F-FDG, ⁶⁸Ga-PSMA, ⁶⁸Ga-DOTATATE Positron Emission Tomography. *J Medical Imaging and Radiation Sciences*. 2020.

Silva-Rodriguez J, Aguiar P, Sanchez M, et al. Correction for FDG PET dose extravasations: Monte Carlo validation and quantitative evaluation of patient studies. *Med Phys*. 2014;41:052502.

McIntosh C, Abele J. Frequency of Interstitial Radiotracer Injection for Patients Undergoing Bone Scan. *The Canadian Association of Radiologists*. Montreal, Quebec.

² For example, see the following references:

Patton HS, Millar RG. Accidental skin ulcerations from radioisotopes: recognition, prevention, and treatment. *J Am Med Assoc*. 1950;143:554-555.

Bonta DV, Halkar RK, Alazraki N. Extravasation of a therapeutic dose of ¹³¹I-metaiodobenzylguanidine: prevention, dosimetry, and mitigation. *J Nucl Med*. 2011;52:1418-1422.

Goodman S, Smith J. Patient Specific Dosimetry of Extravasation of Radiopharmaceuticals using Monte Carlo. ANZSNM 2015; 2015.

Kawabe J, Higashiyama S, Kotani K, et al. Subcutaneous Extravasation of Sr-89: Usefulness of Bremsstrahlung Imaging in Confirming Sr-89 Extravasation and in the Decision Making for the Choice of Treatment Strategies for Local Radiation Injuries Caused by Sr-89 Extravasation. *Asia Ocean J Nucl Med Biol*. 2013;1:56-59.

Rhymer SM, Parker JA, Palmer MR. Detection of ⁹⁰Y Extravasation by Bremsstrahlung Imaging for Patients Undergoing ⁹⁰Y-ibritumomab Tiuxetan Therapy. *J Nucl Med Technol*. 2010;38:195-198.

Shapiro B, Pillay M, Cox PH. Dosimetric consequences of interstitial extravasation following i.v. administration of a radiopharmaceutical. *Eur J Nucl Med*. 1987;12:522-523.

Tylski P, Vuillod A, Goutain-Majorel C, Jalade P. Abstract 58, Dose estimation for an extravasation in a patient treated with ¹⁷⁷Lu-DOTATATE. *Phys Med*. 2018;56:32-33.

van der Pol J, Vöö S, Bucerius J, Mottaghy FM. Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review. *Eur J Nucl Med Mol Imaging*. 2017;44:1234-1243.

studied. We maintain that extravasations should be more fully evaluated, and efforts should be dedicated to reducing the frequency of extravasation events.

VIEWPOINT *Extravasation events can result in radiation doses to arm tissue and skin that are harmful to patients. Although most diagnostic agents impart relatively small radiation doses, the increasing use of some diagnostic and high-dose theranostic agents in nuclear medicine requires a new look at the old problem of radiopharmaceutical administrations into arm tissue instead of the blood vessel.*

Standards for Radiation Protection of Medical Patients

Recommendations for radiation protection are promulgated by national and international scientific committees, including the National Council on Radiation Protection and Measurements (NCRP), and the International Commission on Radiological Protection (ICRP). As a general practice, recommendations by these groups are codified into federal law under Title 10, Code of Federal Regulations, Part 20.

ICRP Publication 140, “Radiological Protection in Therapy with Radiopharmaceuticals” (2019, page 62)³ specifically addresses extravasation events, as follows:

Intravenous infusion of therapeutic radiopharmaceuticals must take place via an appropriate venous access device to ensure safe administration and prevent extravasation (Tennvall, 2006)⁴. Patients should be monitored for extravasation during infusion. In the event of extravasation, the infusion must be halted immediately. Extravasation can result in severe soft tissue lesions (van der Pol, 2017)⁵. Although there is no specific treatment, local hyperthermia, elevation of the extremity, and gentle massage may promote spreading of the radiopharmaceutical and reduce the local absorbed dose. The event must be recorded, and follow-up is advised.

³ ICRP 2019, International Commission on Radiological Protection, Publication 140, *Radiological Protection in Therapy with Radiopharmaceuticals*,” ICRP Publications, Ann. ICRP 48(1); 2019.

⁴ Tennevall J, Fischer M, Bischof Delaloye A, et al. 2007. EANM Procedure Guideline of Radioimmunotherapy for B-Cell Lymphoma with ⁹⁰Y-radiolabeled Ibritumomab Tiuxetan (Zevalin®). Eur. J. Nucl. Med. Mol. Imaging 34: 1324-1327.

⁵ Van der Pol J, Vöö S, Bucerius J, et al., 2017. Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review. Eur. J. Nucl. Med. Mol. Imaging 44: 1234-1243.

Important points from the above ICRP recommendations include:

- Extravasations by radiopharmaceuticals can cause severe soft-tissue lesions
- Extravasations should be characterized and followed for adverse reactions
- Patients should be monitored for extravasation during infusion of radionuclide therapy agents
- If an extravasation occurs, the infusion should be halted

“Patients should be monitored for extravasation during infusion.”

-- ICRP Publication 140, “Radiological Protection in Therapy with Radiopharmaceuticals,” page 62; 2019.

According to recent guidance from NCRP (Publication 180)⁶, the recommended dose limit for members of the general public for skin and extremities is the same as recommended for occupational exposure (radiation workers): 0.5 Gy absorbed dose to extremities or skin per year, averaged over the most highly exposed 10 cm² area of skin.

Since adverse biological effects correlate directly with the amount of radiation imparted, an important part of extravasation event characterization is radiation dosimetry by medical or health physicists to evaluate the total radiation dose to patient arm tissue and overlying skin. Radiation doses cannot be determined accurately without carefully monitoring the extravasation event uptake and assessing infiltrated fluid clearance rates.

VIEWPOINT *National and international scientific advisory bodies have provided specific recommendations and dose limits for patient radiation safety to protect against inadvertent extravasation events involving the extremities and skin.*

Radiation Dose Limits

The national and international scientific guidance is incorporated within federal law as radiation dose limits specified in 10 CFR Part 20, Section §20.1201, Occupational Dose Limits for Adults. According to Section §20.1201(a)(2)(ii), the dose limit is:

A shallow-dose equivalent of 50 rem (0.5 Sv) to the skin of the whole body or to the skin of any extremity⁷. The assigned shallow-dose equivalent is the dose averaged over the contiguous 10 square centimeters of skin receiving the highest exposure.

⁶ NCRP 2018, National Council on Radiation Protection and Measurements, NCRP Report No. 180, *Management of Exposure to Ionizing Radiation: Radiation Protection guidance for the United States (2018)*. Bethesda, Maryland.

⁷ For a relative biological effectiveness where RBE = 1, the absorbed dose in Gy and the dose equivalent in rem or sievert (Sv) are numerically equivalent for purposes of radiation protection. Thus, an absorbed dose of 0.5 Gy is approximately equivalent to 50 rem or 0.5 Sv.

Medical Event Reporting Requirements

The medical use of diagnostic and therapeutic radionuclides by licensed clinicians and hospitals is regulated under 10 CFR, Part 35, Medical Use of Byproduct Materials. Some aspects of the occupational dose limits are applied to protection of medical patients in 10 CFR Part 35. Under Subpart M, Section §35.3045 on Report and Notification of a Medical Event, the NRC requires that:

- (a) A licensee shall report any event as a medical event, except for an event that results from patient intervention, in which—
 - (1) The administration of byproduct material or radiation from byproduct material, except permanent implant brachytherapy, results in—
 - (i) A dose that differs from the prescribed dose or dose that would have resulted from the prescribed dosage by more than 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; and (A) The total dose delivered differs from the prescribed dose by 20 percent or more; (B) The total dosage delivered differs from the prescribed dosage by 20 percent or more or falls outside the prescribed dosage range; or (C) The fractionated dose delivered differs from the prescribed dose for a single fraction, by 50 percent or more.
 - (ii) 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 from any of the following—
 - (A) An administration of a wrong radioactive drug containing byproduct material or the wrong radionuclide for a brachytherapy procedure;
 - (B) An administration of a radioactive drug containing byproduct material by the wrong route of administration;
 - (C) An administration of a dose or dosage to the wrong individual or human research subject;
 - (iii) A dose to the skin or an organ or tissue other than the treatment site that exceeds by:
 - (A) 0.5 Sv (50 rem) or more the expected dose to that site from the procedure if the administration had been given in accordance with the written directive prepared or revised before administration; and
 - (B) 50 percent or more the expected dose to that site from the procedure if the administration had been given in accordance with the written directive prepared or revised before administration.

Exceptions to Medical Event Reporting

Medical practice allows for diagnostic and therapeutic uses of radionuclides for diagnosing and treating diseases. Although by statute, extravasations leading to extremity doses exceeding the

dose limits described above should be reported as “medical events,” that is not the current practice due to two exceptions:

First, the reporting requirement exemption under 10 CFR Part 35 §35.3045 states: “except for an event that results from patient intervention.” Patient intervention is defined in Part 35:

“Patient intervention means actions by the patient or human research subject, whether intentional or unintentional, such as dislodging or removing treatment devices or prematurely terminating the administration.”

According to Section §35.3045 (a)(1)(iii)(D)(b), a licensee shall report any event resulting from intervention of a patient or human research subject in which the administration of byproduct material or radiation from byproduct material results or will result in unintended permanent functional damage to an organ or a physiological system.

Second, a May 14, 1980, *Federal Register* notice⁸ on “10 CFR Part 35 Misadministration Reporting Requirements” exempted extravasations from misadministration reporting requirements:

“The final rule will require reporting of all diagnostic misadministrations to NRC. Several commenters questioned whether extravasation is considered a misadministration. Extravasation is the infiltration of injected fluid into the tissue surrounding a vein or artery. Extravasation frequently occurs in otherwise normal intravenous or intraarterial injections. It is virtually impossible to avoid. Therefore, the Commission does not consider extravasation to be a misadministration.”

However, we maintain that misadministration frequency can be substantially reduced. The exemption policy disregards the increasing use of some diagnostic and high-dose radionuclide therapy agents today that were not available in 1980, current recommendations of national and international scientific advisory bodies, and the extremity and skin dose limits that apply to radiation workers and the public.

VIEWPOINT *For more than 40 years, the Commission has exempted extravasation events from those classes of misadministrations of radioactive materials that must be characterized and reported, even though the radiation dose to a patient’s arm tissue or sensitive skin layer may exceed a dose equivalent of 0.5 Sv (50 rem), the limit set for radiation workers and the public.*

⁸*Federal Register*, 45(95):31701-31704, May 14, 1980.

Responsibility to Establish Sound Radiation Protection Programs

Under Title 10, Code of Federal Regulations, Part 20 §20.1101, each licensee is required to develop, document, and implement a sound radiation protection program commensurate with the scope and extent of licensed activities, and sufficient to ensure compliance with the provisions of this part. Section §20.2102 adds recordkeeping requirements under this program.

***VIEWPOINT** Timely measurements of radioactivity are needed to adequately characterize the significance of a tissue infiltration so that radiation dose may be determined to assess the severity of an extravasation event.*

Each licensee is required to use, to the extent practical, procedures and engineering controls based upon sound radiation protection principles to achieve occupational doses “and doses to members of the public” that are as low as is reasonably achievable (ALARA). To determine internal radiation dose, Section §20.1204 requires “suitable and timely measurements for assessing dose” to determine compliance with occupational dose equivalent limits, including “quantities of radionuclides in the body.” By extension, and for determining compliance with public dose limits stated in 10 CFR 20, suitable and timely activity measurements should also be performed when necessary to characterize event severity.

Although the Commission does not regulate the practice of medicine, the ALARA principle does apply to licensee medical facilities, radiation workers who administer and handle radioactive materials, and members of the public—including medical patients—that undergo diagnostic and therapeutic nuclear medicine procedures. The ALARA principle holds that incidental radiation exposures to normal organs and tissues should be minimized to the extent possible to prevent adverse tissue reactions and to minimize the possibility of late effects (such as cancer) in exposed individuals. The ALARA principle serves the best interest of nuclear medicine patients and helps to ensure that they receive only the medically administered radiation that they need for their personal welfare and medical benefit.

***VIEWPOINT** Patient radiation safety is a principal concern of the Nuclear Regulatory Commission. Clinical users of radioactive materials are required to implement safety practices that minimize radiation dose to the extent practicable.*

The Principle of Safety Culture

The NRC has adopted a formal position on safety culture for licensees that use and work with radioactive materials (NUREG-BR-0500, 2018). The *Safety Culture Policy Statement* (2018) sets forth the Commission’s expectation for licensees, that “all individuals and organizations performing regulated activities establish and maintain a positive safety culture commensurate with the safety and security significance of their activities and the nature and complexity of their organizations and functions.”

Three of the nine elements of the NRC safety culture policy include problem identification and resolution, continuous learning, and a questioning attitude:

- Problem identification: Issues potentially impacting safety are promptly identified, fully evaluated, and addressed and corrected commensurate with their significance
- Continuous learning: Opportunities to learn about ways to ensure safety are sought out and implemented
- Questioning attitude: Individuals avoid complacency and continuously challenge existing conditions and activities to identify discrepancies that might result in error or inappropriate action

VIEWPOINT *The principle of safety culture espoused by the Commission means that medical licensees must take the initiative to identify, address, and correct errors that may lead to significant radiation doses to patients. Institutions should also make “continuous learning” a priority to reduce the frequency of radiopharmaceutical misadministrations.*

Advisory Committee on the Medical Uses of Isotopes

The Commission regularly seeks the advice of its Advisory Committee on the Medical Uses of Isotopes (ACMUI). The Advisory Committee guides the NRC on policy, technical issues, and rulemaking that arise in the regulation of the medical uses of radioactive materials for diagnosis and therapy. Committee membership includes health care professionals from various medical and radiation safety specialties, plus a designated patients’ rights advocate.

The Advisory Committee has periodically reviewed the NRC policy exempting extravasations as reportable medical events. In 2009, the Advisory Committee recommended keeping the 1980 exemption policy⁹. In 2019, the Advisory Committee was again asked to review the policy of exempting radiopharmaceutical infiltrations and extravasations from classification as

⁹ See footnote 8.

misadministrations (now called “medical events”). In its final report¹⁰ on *Extravasation* dated October 23, 2019, the Subcommittee concluded that extravasations and infiltrations should “not be reported as a Medical Event¹¹ at the current time.” The Subcommittee also stated in its report that:

- The Subcommittee recommends that extravasations that lead to “unintended permanent function damage” be reportable as a Medical Event under 10 CFR 35.3045(b).
- Extravasation frequently occurs in otherwise normal intravenous or intra-arterial injections and is virtually impossible to avoid¹².
- Prevention of extravasation is a medical training issue . . . considered medical practice and not something that needs NRC regulation.
- It is difficult to quantify . . . (radioactive) drugs left at the injection site and difficult to assign the radiation dose attributable.
- None of the total doses in these extravasations meet the NRC’s medical event criteria of a discrepancy of a total dosage of $\pm 20\%$ delivered dose criteria¹³.
- The Subcommittee recommends . . . extravasations be considered a type of “passive patient intervention”¹⁴.

The Subcommittee conclusion that extravasations should not be reported as a Medical Event contradicts their recommendation that certain extravasations be reportable as a Medical Event. Their finding on event frequency and inability to avoid extravasations contradicts the Subcommittee conclusion that prevention of extravasations is a medical training issue. Their suggestion that extravasations do not meet a $\pm 20\%$ delivered dose criteria would be incorrect if more than 20% of the injection were extravasated. The Subcommittee recommendation that extravasation be considered a type of “passive patient intervention” was flawed in two ways:

1. The NRC definition of patient intervention does not include any reference to “passive patient intervention” (a contradiction in terms).
2. Implying that an extravasation misadministration is the fault of the patient, not the administering medical technologist, contradicts their statement that extravasations are a training and medical practice issue.

¹⁰ Nuclear Regulatory Commission (NRC) Advisory Committee on the Medical Use of Isotopes (ACMUI) Subcommittee on Extravasation Final Report, October 23, 2019; Subcommittee Members: Vasken Dilsizian, M.D., Richard Green, Melissa Martin (Chair), Michael Sheetz, Megan Shober, Laura Weil; NRC Staff Resource: Said Daibes, PhD (formerly Maryann Ayoade); available at: <https://www.nrc.gov/docs/ML1931/ML19316E067.pdf>, (accessed June 22, 2020).

¹¹ This statement contradicts the first bullet item

¹² This statement contradicts the next bullet item

¹³ This statement is likely incorrect if an extravasation exceeds 20% of the administered activity designated in the therapy written directive.

¹⁴ Implying that the misadministration or extravasation is the fault of the patient, not the administering medical technologist; this statement directly contradicts the second and third bullets in the list above, which state that extravasation is a “training issue” and a “medical practice” matter.

The Patients' Rights member of the Advisory Committee (Ms. Laura Weil) dissented with the Subcommittee Final Report, quoting directly as follows:

“One member of the Subcommittee expressed concern with the existing 1980 exclusion of extravasation events from ME status. This member acknowledges the Subcommittee consensus that there would be only rare incidence of extravasation triggering ME criteria of >50 rem tissue dose or <80% of prescribed dose delivered to the patient, and believes the extravasation exemption in the 1980 language is unnecessary. Only rare gross discrepancies in delivered dose or tissue exposure would be reportable, and this member believes that those rare instances should be reported just as any other misadministration of such magnitude would be reported as MEs. The fact that they may result in no patient harm should have no bearing on the requirement to report. This would be consistent with the fact that all other ME's that cause no patient harm are currently required to be reported. When/if NRC decides to redefine ME criteria to exclude events that do not cause patient harm, then extravasation incidents would be included in such exclusion. But this member believes that the current specific exclusion of extravasation is inconsistent with other regulation and unwarranted.

--Respectfully submitted, Laura Weil.”

VIEWPOINT *The interests of patient safety are safeguarded by a Patient's Rights Advocate, who is a member on the Commission's Advisory Committee on Medical Uses of Isotopes (ACMUI), who represents the best interests of medical patients, and who dissented from findings of the ACMUI Subcommittee on Extravasation; she wrote that “the current specific exclusion of extravasation is inconsistent with other regulation(s) and (is) unwarranted.”*

Organization of Agreement States Position

The Organization of Agreement States is a voluntary, nonprofit, scientific, and professional society comprising state radiation control directors and staff from the 39 Agreement States who are responsible for implementation of their respective Agreement State programs. The purpose of the Organization is to facilitate cooperation between these Agreement States and the Nuclear Regulatory Commission on regulatory issues associated with their respective agreements. In a letter from the Organization to the NRC Chairman and Commissioners dated February 26, 2020, Organization Board Chair Terry Derstine commented on the Advisory Committee's Final Report on *Extravasation* and concurred with the position taken by the Committee's Patient Advocate representative:

“The Board is happy to hear the Commission has directed an independent review of extravasations. We support the ACMUI’s dissenting opinion in their final report, dated October 23, 2019, that MEs (medical events) are possible by the injection of a radiopharmaceutical into an unintended tissue and should be reported upon occurrence. Whether there is immediate harm or not has no bearing on the reporting criteria; it is only a matter of dose with the current ME rule.”

The Nuclear Medicine Technologist Perspective

Extravasations represent a serious quality issue for nuclear medicine departments. Nuclear medicine technologists strive to avoid misadministrations that can negatively impact patient imaging, clinical outcomes, and the overall patient experience. Technologist training emphasizes basic radionuclide handling techniques and administrative controls to prevent adverse events. The technologist receives training on intervention and mitigation in the event of and to reduce the frequency of unintentional infusion extravasations. Preventative measures include training and techniques under the Nuclear Medicine Technologist Scope of Practice and Performance Standards¹⁵, as follows:

1. I B 1&2 – A nuclear medicine technologist (NMT) provides patient care by the use and monitoring of intravenous lines (central lines or peripherally inserted central catheters)...and inserting and monitoring peripheral intravenous catheters.
2. I B 10 – A NMT provides patient care by recognizing, responding to, reporting, and documenting adverse events.
3. III A 1-3 – A NMT performs imaging procedures by preparing, evaluating, and properly administering the prescribed amount of various radiopharmaceuticals, adjunctive medications, and imaging medications.
4. VII A 3 – A NMT properly prepares and administers therapeutic radiopharmaceuticals...by observing prescribed radiation safety using FDA and USP Standards.

Additional training is specified in 10 CFR Part 35, including Section §35.290 on training for imaging and localization studies, §35.390 on training for use of unsealed byproduct material for which a written directive is required, and §35.396 on training for the parenteral administration of unsealed byproduct material requiring a written directive.

Palliative Care for a Radiopharmaceutical Extravasation or Infiltration

Typical mitigation treatments after an infiltration or extravasation event include:

- Applying an appropriate warm or cold compress
- Massaging the tissue around the affected site

¹⁵ June 2017 Nuclear Medicine Technologists Scope of Practice and Performance Standards

- Elevating the affected limb
- Fasciotomy (a surgical procedure to relieve swelling and pressure in a compartment of the body; during fasciotomy, tissue that surrounds the infiltrated area is cut open to relieve pressure)
- (In rare cases) plastic surgery or amputation may also be required

***VIEWPOINT** Training in radiopharmaceutical injections is of central importance to qualifying a nuclear medicine technologist for administering radioactive materials to patients. The frequency of extravasation events can be minimized, but when they occur, those events should be adequately characterized and monitored.*

Characterization of Extravasations and Infiltrations

The medical community recognizes that radiopharmaceutical misadministrations range in severity from trivial to serious, depending on radionuclide, administered activity, and fraction of infusion that infiltrates tissue. Characterization means measuring the radioactivity that infiltrates extravascular tissue, measuring changes in localized activity with time, determining the mass of tissue infiltrated, imaging the infiltration, determining fraction or percent of the administered activity in the affected tissue, calculating radiation dose to infiltrated tissue and the overlying layer of sensitive skin, and keeping records of the measurements, dose, and mitigation steps taken for the patient. These data may be supplemented with photographs and observation notes. Since adverse biological tissue reactions may appear several weeks or months post-infusion, the patient should be followed and provided longer-term observation and care, as needed.

Radiation Dose to Infiltrated Tissues and Overlying Skin

A forthcoming scientific article¹⁶ prepared for publication in the peer-reviewed literature will show that moderate infiltrations¹⁷ of the diagnostic agent ¹⁸F-FDG can lead to arm tissue doses of 2.6 to 3.5 Gy, and contiguous 10-cm² area of sensitive skin doses of 1.5 Gy. The referenced Petition cites 23 significant extravasations involving diagnostic radiopharmaceuticals. Radiation doses to infiltrated tissue from high-dose radionuclide therapies, including alpha-emitter products, can produce much higher radiation doses than those estimated for ¹⁸F-FDG. In some cases, tissue absorbed doses can exceed 20 Gy. These values far exceed the federal dose limit of 0.5 Sv (0.5 Gy).

¹⁶ Josh Knowland, Lucerno Dynamics, personal communication, June 19, 2020.

¹⁷ About 25% of administered activity.

Physician Reluctance to Embrace Additional Regulatory Obligation

We understand that clinicians may be hesitant to submit to misadministration oversight and reporting requirements, and that preferably, regulatory burdens on licensees should be reduced and not added upon. This reluctance is reflected in the Advisory Committee final report. However, as we work with and support nuclear medicine clinics, we observe several experiencing difficult extravasation events. Some have asked for technical support to calculate local tissue doses, characterize event severity, or prepare standard operating procedures for managing cases. We typically advise clinics in favor of well-documented assessments for communication with patients and institutional liability protection.

Summary

We support the Petition of June 8, 2020, because it provides meaningful recommendations and does not simply extend *ad infinitum* the ongoing discussion within the NRC. The 1980 exemption policy needs to be reversed. Our review confirms that radiopharmaceutical extravasations can produce localized, high-dose radiation to patients' arm and skin tissue. Serious extravasations should not be automatically exempted from medical event reporting requirements. Instead, extravasations should be recognized, mitigated, and monitored for patient health and safety. Indeed, recommended dose limits for members of the public for skin and extremities dose are the same as those applicable to radiation workers, and dose to patients from inadvertent misadministrations should not be disregarded as a medical practice error.

The Advisory Committee on Medical Uses of Isotopes issued a contradictory set of findings and conclusions, together with recommendations inconsistent with existing NRC regulations and recent recommendations of national and international scientific committees. That being the case, the Advisory Committee's patient rights' advocate dissented from the final report and highlighted inconsistencies in the NRC medical event reporting requirements. The Organization of Agreement States concurred with the *Extravasation* report dissenting opinion.

While the Nuclear Regulatory Commission mandates strict extremity radiation dose limits for occupational workers, it appears to overlook those same limits for medical patients who, by no fault of their own, may receive an inadvertent tissue or skin infiltration from a misadministered radiopharmaceutical at a licensee medical facility. While the NRC mandates ALARA for both occupational workers and members of the public, its policies seemingly disregard potentially severe extravasation events that might lead to high radiation doses to tissue and overlying sensitive skin--potentially resulting in adverse tissue damage and other complications. And while the NRC publicly advocates for institutional safety culture, it may be falling short in the way it views applicability of its own policies and regulations for extravasation event characterization, assessing radiation dose against established limits, and record keeping--on the 40-year-basis that extravasations are "virtually impossible to avoid," and whose oversight belongs only to the realm of medical practitioners.

In the best interest of patient safety, we maintain that extravasation and infiltration event frequencies can be reduced through improved training and practice. If and when they occur, and for the protection of both patients and institutions, those events should be adequately characterized and documented.

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