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Reporting Nuclear Medicine Injection Extravasations as Medical Events

Comment On: NRC-2020-0141-0004
Reporting Nuclear Medicine Injection Extravasations as Medical Events; Notification of Docketing and Request for Comment

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Submitter Information

Name: Michael Peters
Organization: American College of Radiology (ACR)

General Comment

Please see the attached comments from the American College of Radiology (ACR) on NRC-2020-0141 / PRM-35-22.

Attachments

ACR_comments_NRC_PRM-35-22_11-25-20

November 25, 2020

Submitted via regulations.gov

Attn: Pamela Noto
Office of Nuclear Material Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Re: (Docket ID NRC-2020-0141; PRM-35-22) Petition for rulemaking; notification of docketing and request for comment; *Reporting Nuclear Medicine Injection Extravasations as Medical Events*; Comments of the American College of Radiology

The American College of Radiology (ACR)—a professional association representing nearly 40,000 diagnostic radiologists, interventional radiologists, nuclear medicine physicians, radiation oncologists, and medical physicists—appreciates the opportunity to provide input to the Nuclear Regulatory Commission (NRC) on the May 18, 2020 petition for rulemaking (PRM-35-22) filed by Ronald K. Lattanze of Lucerno Dynamics, LLC—the manufacturer of a device that would likely directly benefit financially if the petition is granted—and the corresponding request for comments published in the *Federal Register* on September 15, 2020 (85 FR 57148; Docket ID NRC-2020-0141). The following ACR comment submission was compiled under the leadership of the Commission on Government Relations-Federal Regulatory Committee, Commission on Medical Physics-Government Relations Committee, Commission on Nuclear Medicine and Molecular Imaging, and Commission on Radiation Oncology, with feedback from interested ACR members.

Historical Overview and Concordance of Terms

In PRM-35-22, the petitioner requested that NRC revisit its exemption policy for nuclear medicine intravenous (IV) injection extravasations¹ from medical event reporting requirements in 10 CFR 35.3045, and to further require reporting as medical events any extravasations that result in a localized dose equivalent exceeding 50 rem (0.5 Sv).

Historically, NRC has exempted nuclear medicine injection extravasation from medical event and previous misadministration reporting. The exemption policy was explicitly referenced in 1980 and has been reexamined by the NRC Advisory Committee on the Medical Uses of Isotopes (ACMUI) in accordance with the transparency requirements of the Federal Advisory Committee Act. In every periodic review, the

¹ We note that NRC's understanding of "extravasation" as synonymous with "infiltration" may differ from clinical usage of this terminology, which typically requires tissue damage or other injury more commonly associated with accidental infiltration of a vesicant or chemotherapeutic drug. We use the NRC terminology in this comment submission for consistency with PRM-35-22.

ACMUI has definitively supported the NRC’s 1980 exemption policy on extravasation, ensuring the continued relevance of the agency’s established approach.

Summary of the ACR’s Position

In accordance with universal feedback received from our membership, the ACR strongly recommends that NRC issue a formal denial of PRM-35-22. The agency’s established policy has been ACMUI-vetted and repeatedly reiterated and is the most appropriate oversight approach for nuclear medicine injection extravasation. It is aligned in principal with how NRC generally approaches other complex and unavoidable anatomical or physiological challenges to properly administered radioisotopes, such as shunting in yttrium-90 microsphere brachytherapy and seed migration in permanent implant brachytherapy. We discuss the various reasons for recommending denial of the petition in the section below titled, “ACR’s General Concerns and Comments on PRM-35-22.”

If NRC determines that some manner of further action is warranted following denial of PRM-35-22, the agency could further clarify that extravasation should be handled as an unintentional form of “patient intervention” in §35.3045, including applicability of the significantly high harm standard stipulated under §35.3045(b) that *“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, as determined by a physician.”* This limited applicability of the reporting requirements would be aligned with the most recent NRC ACMUI recommendations on extravasation² and patient intervention.³

The ACR believes it would be extremely rare that extravasation of a nuclear medicine agent would meet the harm standard of §35.3045(b); however, this clarification would reflect how most licensees would currently handle hypothetical permanent injury cases in a manner that:

- Is reasonable, practicable, and generally aligned with clinical approaches to extravasation in the practice of medicine utilizing nonradioactive contrast media and pharmaceuticals;
- Does not set arbitrary thresholds requiring complex injection site dosimetry, novel technologies, and third-party services;
- Minimizes imposition on practice of medicine and avoids undue burden and penalization of healthcare providers for scenarios that are generally unpredictable and unpreventable when best IV practices are followed;
- Aligns with current NRC policy with regard to medical use of byproduct material and medical event reporting;
- Could address any marginal interest by Members of Congress, who may misunderstand or have been misled about the nature of extravasation and medical event reporting;
- Would potentially be implementable via sub-regulatory guidance without a rulemaking to revise §35.3045; and,
- Is aligned with the 2019 and 2020 public deliberations and recommendations of the NRC ACMUI.

² NRC ACMUI. ACMUI Subcommittee on Extravasation: Final Report. October 23, 2019. <https://www.nrc.gov/docs/ML1931/ML19316E067.pdf>

³ NRC ACMUI. ACMUI Subcommittee on Patient Intervention: Final Report. April 6, 2020. <https://www.nrc.gov/docs/ML2009/ML20097F476.pdf>

ACR's General Concerns and Comments on PRM-35-22

I. NRC's Medical Event Reporting Rationale Does Not Support This Change in Policy

The NRC's documented justification for the existence of medical event reporting and notification requirements under §35.3045 would be inapplicable to the petitioner's requested change in PRM-35-22. The NRC's April 24, 2002 final rule on medical use of byproduct material⁴ and corresponding enforcement policy revision⁵ made clear that medical event reporting is intended to capture deviations between prescribed and administered doses that may indicate a deficiency in the licensee's program, to determine what actions could be taken to prevent recurrence, and to enable decisions regarding remedial and prospective health care. §35.3045 includes stringent reporting timeframes as well as aggressive patient and referring physician notification requirements.

The NRC handles patient intervention-caused harms reportable under §35.3045(b) differently than medical events under §35.3045(a) that are primarily caused by errors, such as prescribed dose deviations, wrong radionuclides, wrong treatment sites, wrong routes of administration, wrong patients, and so on. §35.2 defines patient intervention as "*actions by the patient or human research subject, whether intentional or unintentional, such as dislodging or removing treatment devices or prematurely terminating the administration.*" The 2002 rule explained that the purpose of a "*significantly higher*" threshold for patient interventions reportable as medical events under §35.3045(b) was to capture only the most concerning scenarios.

The requested revisions in PRM-35-22 would be unjustifiable under the agency's rationale for medical events caused by provider error. Generally, nuclear medicine injection extravasations have the following characteristics:

- Typically caused by anatomical and/or physiological conditions or patient action, such as vein anatomy, obesity, vein collapse, involuntary or voluntary patient movement, history of drug abuse, and/or recent surgeries (e.g., lymph node dissection, dialysis access placement, vein harvests, burns, etc.);
- Are generally impossible to discern on a case-by-case basis whether a patient's movement, anatomy, physiology, or device issue was the root cause of a given extravasation instance;
- Not indicative that an administration deviated from the written directive or physician intent, as extravasation can occur during administrations provided as intended and still result in the intended clinical outcomes;
- Rarely significant from a radiation safety or clinical perspective;
- Unpredictable and unpreventable when best medical practices for IV access are followed;
- Do not indicate programmatic deficiencies and thus do not provide actionable lessons for NRC, state programs, or other medical licensees;
- Do not benefit from remedial or prospective medical care;
- Are of greater clinical concern for non-radiological, high volume contrast media, vesicants and other chemotherapy agents; and,

⁴ Medical Use of Byproduct Material, NRC final rule. April 24, 2002. <https://www.federalregister.gov/d/02-9663>

⁵ NRC Enforcement Policy; Modification, Medical Use. April 24, 2002. <https://www.federalregister.gov/d/02-9992>

- Are already addressed through institutional processes, standards and best practices, technologist/personnel IV competency evaluation, and other quality assurance methods;

II. Practice of Medicine Imposition

The ACR agrees with the NRC ACMUI Extravasation Subcommittee's 2019 final report that extravasation should be viewed by the agency as a practice of medicine issue. IV access is broadly subject to medical standards and guidelines, institutional quality assurance policies, personnel proficiency/competency reviews, and other clinical safeguards. Extravasation of any IV injectable media can and will continue to occur as a function of the inherent friability of the vascular structures involved. Monitoring, assessment, evaluation, and relevant notification commensurate with the risk of any injected radiological or non-radiological materials is standard patient care regardless of NRC's current exemption policy. We also believe if the permanent injury standard of §35.3045(b) was reached in an extravasation case, that case would be reported to NRC or appropriate state agencies currently.

PRM-35-22 raises debatable suggestions regarding avoidance of extravasation and unsupported concerns of possible harm to patients. The petition and corresponding documentation cite literature related primarily to extravasations from non-radiological contrast media and cytotoxic chemotherapeutic instillations. These invariably consist of large volumes of substances with inherently tissue-damaging properties and are often administered with large-volume infusions over a long interval, often unattended. They are not analogous to administrations of radiopharmaceuticals, which are typically small volume, without inherent properties harmful to tissues, and—particularly with diagnostic nuclear medicine and molecular imaging agents—often administered by direct push by highly trained staff operating in a culture of safety. The literature, even as provided by petitioner, suggests rapid dissipation of radioactivity at the extravasation site and no reported permanent physical effects.

The ACR has the following practice of medicine concerns with the request in PRM-35-22:

(a) Concern regarding conflict with NRC medical policy statement

The requested change in PRM-35-22 would conflict with the NRC's Medical Use of Byproduct Material Policy Statement revised August 3, 2000, which states that "*NRC will not intrude into medical judgements affecting patients, except as necessary to provide for the radiation safety of workers and the general public.*" The policy goes on to state the underlying justification for medical event reporting that "*NRC will, when justified by the risk to patients, regulate the radiation safety of patients primarily to assure the use of radionuclides is in accordance with the physician's directions.*" NRC is obligated to consider the conflict with their current policy statement during the formal determination process per the requirements of §2.803(h)(vi).

Unquestionably, the requested change in PRM-35-22 would intrude into medical judgements affecting patients, thus implicating the medical policy statement; however, there is no indication that this imposition would provide any offsetting gains for the radiation safety of workers and the general public, as extravasation is typically of no consequence to either group. There is likewise no discernible data collection benefit to NRC for the purpose of determining whether an administration deviated from the physician's directions, as extravasation is unpredictable and unavoidable when best IV practices and the physician's directions are strictly adhered to. Moreover, the physics of byproduct material are such that the intended clinical outcome could occur regardless of the extravasate, such as a reviewable imaging study or successful treatment.

(b) Concern regarding punitive impact of reportable medical events

While NRC generally regards medical event reporting as a non-punitive information collection for identifying and addressing possible problems with the licensees' processes, the real-world impact of medical event reporting on providers is substantially different. The notification requirements in §35.3045(e) and (g), as well as the accessibility of medical event data, provide significant professional and medicolegal pressures and concerns. PRM-35-22 would unintentionally promote defensive medicine (see the subsection on "Concern regarding inappropriate regulatory influence on IV administration practices and protocols" below) and discourage treatments or types of administration that could result in regulatory and legal consequences even when administered appropriately.

(c) Concern regarding financial, clinical, and administrative burdens

The requested revision in PRM-35-22 would establish new and significant financial, practice, and administrative burdens for licensees and potentially cause extensive compliance-related patient care delays.

Injection site dosimetry of the kind requested by PRM-35-22 would appear to implicitly require for every IV administration novel technology to quantitatively determine if the medical event reporting threshold has been reached. The petitioner offers a proprietary monitor device and accompanying services that would be expensive, unrecoverable financial costs for providers. The petitioner's product involves topical injection site sensors that need to be positioned prior to the administration and remain in place for a continual series of measurements over time. These sensors are not designed to be retroactively applied in the event of a clinically apparent extravasation; so, presumably, every site would need to purchase at least one device (or more to accommodate concurrent and sequential procedures) with no clinical rationale beyond demonstrating compliance with NRC regulations. Busy medical licensees that provide many diagnostic and therapeutic nuclear medicine procedures would be required by necessity to purchase and pay usage fees for numerous such compliance devices so that patient care is not drastically interrupted. Even in situations in which multiple compliance devices are available, delay of patient care is inevitable due to the additional post-administration time in which patients must remain connected to these devices, and the personnel resources needed to monitor outputs and conduct the novel calculations of equivalent dose to tissue requested by the petitioner. These technology acquisition expenses are unlikely to be recoverable by providers, and patient care delays and personnel commitments needed for injection site dosimetry would negatively impact the efficiency of nuclear medicine delivery across the board.

Compliance would also impact institutional policies and procedures, patient experience before and after radiopharmaceutical injections, IV preparation, and subsequent evaluation and documentation. Using monitoring/measurement technologies specifically for quantification in the event of an extravasation extends patient preparation and post-procedure evaluation time. Patients may be required to remain situated and hooked up to licensees' monitoring/measurement technologies for extended periods of time following administrations for no medical value beyond documenting compliance with NRC regulations, thus impacting all patients for an infinitesimally small number of extravasations in need of injection site dosimetry. Nonradioactive materials and agents that could cause clinically significant tissue damage are not subject to equivalent calculations, and have no reporting requirements to any state or federal agencies, and this would create an illogical focus on nuclear medicine injection extravasations in clinical environments.

In terms of administrative burden, the 24-hour notification timeline for medical event notification in §35.3045(e) is already unusually aggressive and disruptive for clinical environments. NRC requires

notification typically before facts and circumstances can be comprehensively verified by the licensee, and the benefit to NRC of these preliminary notifications are debatable. The appropriateness of the notification timeframe for NRC's limited purposes has been called into question many times before, and there are valid reasons to suggest that §35.3045 itself could be narrowed in scope to decrease the imposition on practice of medicine and provide more flexibility. The inherent burden of the §35.3045(e) timeline would be exacerbated by the complex injection site dosimetry and personnel commitments implicated by the request in PRM-35-22.

(d) Concern regarding inappropriate regulatory influence on IV administration practices and protocols

Healthcare providers could be influenced by the requested revisions in PRM-35-22 toward increased use of vesicant protocols⁶ and central venous catheters (“central lines”) for related administrations of radiological materials. Central lines would prevent extravasation in all instances, thereby avoiding the burdens and consequences associated with PRM-35-22, but patients with these lines are typically hospitalized and would be at risk of further medical complications beyond NRC's jurisdiction. The IV approaches would have major negative impacts on patient comfort, complexity of administration, and the cost of care, but may be increasingly viewed as the most reasonable option due to previously listed burdens and consequences.

III. Complex and Novel Dosimetry, Proprietary Devices, and Technical Considerations

The methodology to assess absorbed dose is insufficiently described in PRM-35-22 and impractical to implement in routine nuclear medicine because it is a lengthy process to accomplish, beyond the capability of healthcare professionals, requires proprietary information technology and services (including offsite calculation and analysis by the petitioner's company), and requires input from a proprietary monitor device. Concerns include:

- Extravasation dosimetry estimations are generally novel, complex, resource intensive, and of debatable clinical or practical value to nuclear medicine providers and patients;
- It is generally inappropriate to apply occupational dose limits to patients;
- With respect to the specific compliance device in question, outputs from what is essentially a small area scintillation survey meter (counts per second) are converted to tissue absorbed dose (gray) without a detailed description of how those outputs can be independently verified;
- Critical input variables are assumed instead of directly measured—including the essential inputs of infiltrate activity and tissue volumes—which would result in high dose estimates and over-reporting of medical events;
- It is unclear how the device assesses efficiency, assesses true sensitivity, or tests for a distributed source like an infiltrate;
- The significant post-procedural time commitment for patients to enable the dosimetry monitoring and analyses are unduly burdensome in clinical environments;
- Bidirectional connectivity with an additional third-party device manufacturer may introduce additional cybersecurity concerns in hospital environments that are increasingly the focus of ransomware and other

⁶ ACR–ACNM–ASTRO–SNMMI Practice Parameter for the Performance of Therapy with Unsealed Radiopharmaceutical Sources. Revised 2019 (Resolution 41). <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/UnsealedSources.pdf>

cybercrime—often, breaches are enabled by web-exposed medical devices, and this is an area of increased scrutiny and tightening by provider institutions;⁷ and,

- Reasonable compliance alternatives are not discussed for licensees unable or unwilling to acquire the petitioner’s specific products and services.

IV. Financial Conflict of Interest of Petitioner

Per NRC’s obligation under §2.803 to consider the merits of the petition, the NRC should review the financial conflict of interest of the petitioner and all documentation supporting PRM-35-22. As of this writing, PRM-35-22 is the only petition among twenty-one PRMs under active NRC consideration that has been filed by a private company.⁸ The four PRMs attributed by NRC’s data collection to “industry representatives” were filed by trade associations acting on behalf of the interests of multiple entities, and were not implicitly or explicitly seeking policy changes to create or expand market demand for specific products and services. The NRC’s handling of PRM-35-22—in addition to its previous handling of SECY-20-0005—would create a precedent and roadmap for future private companies interested in wielding NRC’s regulatory authority to sell their wares.

The practical effect of PRM-35-22 would be to require clinical use of injection site dosimetry technologies during all relevant administrations to enable novel dosimetry in the rare event of extravasation which would not demonstrate actual patient harm or radiation safety significance. The petitioner’s company manufactures, distributes, and/or licenses monitoring devices and services of the kind implicitly required for compliance with the requested regulatory revision. The petitioner’s device or a similar competing product would need to be in place during each relevant injection to quantitatively demonstrate compliance in case of extravasation. In many cases, a busy licensee would need to acquire multiple compliance products from the petitioner to handle all relevant nuclear medicine injections in case of a hypothetical need for quantification. These are not inexpensive nor widely adopted products.

The transparent financial conflict of interest of the petitioner would immediately call to question the propriety of any future regulatory changes resulting from PRM-35-22. If a new medical device is perceived to be of value by its vendor, that value should be subjected to competitive utilization in the marketplace rather than required by regulations of questionable public value. Many stakeholders have been surprised to learn §2.803(b) does not permit NRC to prohibit or discourage petitions from private companies establishing de facto mandates for specific compliance products during docketing review. NRC should reconsider the requirements of §2.803(b) to provide the agency staff with ample flexibility to evaluate such conflicts prior to docketing petitions and expending limited agency and stakeholder resources.

V. Apparent Contradiction with Justification for Rulemaking Plan Described in SECY-20-0005

On January 13, 2020, the NRC staff recommended to the Commission in SECY-20-0005 elimination of authorized user (AU) training and experience requirements for diagnostic and therapeutic unsealed materials under 10 CFR Subparts D and E, and to instead rely on revised board recognition criteria to more readily enable non-radiological boards to provide AU eligibility to their physicians. If the plan is approved by the Commission—and depending on implementation of the board recognition criteria component—the effect would be to move certain radiopharmaceutical therapies out of licensees’ current nuclear medicine

⁷ U.S. Food and Drug Administration Cybersecurity Safety Communications. <https://www.fda.gov/medical-devices/digital-health-center-excellence/cybersecurity#safety>

⁸ Excel spreadsheet of Current Petition for Rulemaking Data, NRC. <https://www.nrc.gov/reading-rm/doc-collections/rulemaking-ruleforum/active/Data/Petitions%20Export.csv>; accessed October 29, 2020.

and radiation oncology departments and into referring specialty departments, with therapeutic administrations being handled by associated nursing staff instead of nuclear medicine, radiation oncology, or nuclear radiology teams that provide these therapies currently.

The basis for the NRC staff-recommended rulemaking plan in SECY-20-0005 was an assumption that unitized dose delivery systems are intrinsically safe to be managed by referring physicians and nursing staff without nuclear materials sub-specialization or expertise. In direct opposition to this understanding, PRM-35-22 calls for complex injection site dosimetry and expertise that would be infeasible for the type of nominally-trained personnel that would be providing therapeutic radiopharmaceuticals at licensed facilities in the future paradigm. This inconsistency is perplexing.

We note that the Organization of Agreement States (OAS) has publicly indicated support for both SECY-20-0005 and PRM-35-22 without healthcare provider input and despite the inherent contradiction of these two documents. However, the OAS' stated understanding in their comments on SECY-20-0005 assumed nuclear medicine technologists and other allied health professionals specific to radiological subspecialties would be handling unsealed materials in that paradigm, and that only the supervising physician specialties would change. While the basis for OAS' understanding here is unclear, it should be noted for NRC's purposes that allied health professionals handling and administering unsealed materials under the supervision of nontraditional AUs should always be assumed to be specialty nurses or other allied health professionals associated with that given specialty, unless there are relevant scope of practice requirements for supervised personnel within a given state. Many states unfortunately do not have stringent scope or licensure requirements for supervised personnel, and some do not have minimum qualifications of any kind. In contrast, PRM-35-22 assumes current levels of radiation expertise and an ability to conduct complex and novel injection site dosimetry by those using radiopharmaceuticals—expertise which would not exist for certain therapeutic agents in that future paradigm.

§2.803(h)(vi) obligates NRC to consider “*relevant past decisions and current policies*,” including the previously discussed Medical Policy Statement, 2002 final rule, 1980 extravasation exemption, subsequent revisitations and reaffirmations by ACMUI, as well as the rulemaking plan described in SECY-20-0005 (should it be approved by the Commission).

ACR Responses to NRC Questions

Q: *How frequently does radiopharmaceutical extravasation occur?*

A: Radiopharmaceutical extravasations of *radiation safety significance* are hypothetically possible, but extremely rare. Of all physician and medical physicist members who responded to the ACR's solicitation for input in advance of this comment submission, none were professionally aware of extravasation from a nuclear medicine imaging agent that resulted in a clinical or radiation concern. Radiopharmaceutical therapies pose the most realistic risk of local skin damage, but therapeutic radiopharmaceutical extravasation cases are the rarest kind due to protocols and routes of IV access.

While trustworthy data is difficult to find on frequency of *insignificant* extravasation, there have been international studies unaffiliated with the petitioner that perhaps provide NRC with a more accurate baseline of reasonable expectations.

One officially-documented example is an Australian study with sponsorship from the national government that reported an incidence of 8–9 “maladministrations” of any kind per 100,000 procedures. The Australian Radiation Protection and Nuclear Safety Agency has been operating the Australian Radiation Incident Register as a national repository of data on incidents and events where radiation or radioactivity was implicated. The study reviewed reported maladministrations from 2007 through 2011. Type 5 maladministrations included extravasations, among other subtypes. In that five-year period, 2,552,513 procedures were performed (337,999 for diagnostic non-imaging studies, 2,194,063 for diagnostic nuclear medicine procedures, and 20,451 for therapeutic radiopharmaceutical procedures). 149 maladministrations (0.0058%) reported (ave. 29.8/Y). The incidence of maladministration was 5.8/100,000. About half of these maladministrations were found to be caused by incorrectly prepared or dispensed radiopharmaceuticals, and roughly half of those inaccuracies were found to be the fault of a commercial radiopharmacy laboratory (i.e., a “commercial nuclear pharmacy” in U.S. vernacular). Nearly all maladministrations found to be the fault of providers were the result of nuclear medicine specialists not being involved in the review. Approximately 88% of maladministrations involved the use of Technetium-99m or Molybdenum-99. Only 2 total maladministrations involved therapeutic radiopharmaceuticals. Importantly for PRM-35-22, only 7 total Type 5 maladministrations over the course of the five-year study were extravasations, all of which were less than 10 mSv and of no discernable or projected radiation safety consequence.⁹

Q: 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.

A: We are unaware of extravasations of byproduct material that resulted in permanent physical harm to patients in practice, although this outcome is possible with therapeutic radiopharmaceuticals. A study into reports of extravasation found that less than 0.001 percent of diagnostic nuclear medicine extravasations result in temporary symptoms of any kind—the same study found that the most severe symptom associated with rare therapeutic extravasations was temporary ulceration.¹⁰ As with the aforementioned Australian study, the Van der Pol study is most noteworthy for demonstrating the extreme rarity of noteworthy extravasations.

Documentation corresponding with PRM-35-22 cited an example of a radiopharmaceutical extravasation “leading directly” to a highly localized cancerous lesion involving Radium 223 Dichloride.¹¹ It was claimed that an aggressive squamous cell carcinoma manifested within 120 days of extravasation, and that it was caused by the incident. However, radiation experts reviewing the report consider this claim to be highly suspicious, as the latent period for radiation-induced malignancies is typically seven to ten years for hematologic cancers and over ten years for solid tumors. With the radioisotope in question, one would anticipate some absorption with subsequent bone deposition. Adding to the suspiciousness of the claim, the specific radiopharmaceutical therapy in question is administered via five to six fractions with four-week intervals between the fractions. Squamous cell carcinoma often presents on sun-exposed areas of the body,

⁹ George S Larcos, GS, Collins, LT, Georgiou, A et al. Maladministrations in nuclear medicine: revelations from the Australian Radiation Incident Register. MJA 2014; 200: 37–40

¹⁰ Van der Pol, J., Voo, S., Bucerius, J. et al. Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review. Eur J Nucl Med Mol Imaging (2017) 44:1234–1243

¹¹ Benjegerdes KE, Brown SC, Housewright CD. Focal Cutaneous Squamous Cell Carcinoma Following Radium-223 Extravasation. Proc Bayl Univ Med Cent. 2017;30:78-79

including the hands, and it is far more likely that manifestation of the lesion in the cited case was coincidental rather than being directly caused by the extravasate.

Extravasation cases involving nonradioactive agents or contrast media are generally of much greater clinical significance, and accepted practices are in place to help physicians evaluate and respond to such incidents. The ACR's Committee on Drugs and Contrast Media maintains the popular publication, "ACR Manual on Contrast Media," which includes a chapter on extravasation of nonradioactive contrast. Radiology residents are well-trained on IV quality practices and extravasation concerns in general. Also, the ACR administered its Intravascular Contrast Extravasation (ICE) registry until it was discontinued in December 2016. The ICE registry did not collect data on nuclear medicine and molecular imaging agents as these were considered insignificant from a clinical perspective compared to nonradioactive contrast media.^{12, 13}

Nuclear medicine injection extravasation is generally not considered to be a practical concern beyond what is appropriately addressed through quality and safety processes within a given institution. In almost all cases, administered material is small volume and without inherent risk to tissue, and in most cases, dissipated and absorbed from the tissues—therefore, it should not be automatically assumed that diagnostic nuclear medicine injection extravasation would necessitate repeat imaging. IV access is secured prior to injection of byproduct material, and sites are observed during and after administrations. Depending on facility or institutional policies and procedures, personnel IV competency is often reviewed on an annual basis and technologists are trained to ask for help if needed and to avoid use of any uncertain access site. For therapeutic radiopharmaceuticals, injection sites are assessed routinely prior to use by flushing with saline and observing for physical and subjective signs/symptoms of extravasation prior to administering pharmaceuticals. Depending on the specific agent, it may also be diluted in the IV bag for slower infusion over time rather than using syringe push or injector.

Q: For medical use licensees, does your facility currently monitor for radiopharmaceutical extravasation? If so, why and how do you monitor? If not, why not?

A: Respondents to the ACR's solicitation for information on this question indicated that healthcare facilities monitor for extravasation in general as standard medical practice, primarily out of concern for more clinically significant non-radioactive contrast and agents that have a greater potential for patient harm if extravasated. Managing IV access and related quality assurance is best handled broadly without regard for the presence of radioactivity. There are widely applicable processes, standards, and procedures for handling extravasation occurrences, including but not limited to regular IV proficiency or competency reviews with relevant allied healthcare personnel. Nuclear medicine technologists and others in the clinical environment are aware of the potential for extravasation, and any clinically apparent extravasation would be reviewed immediately by the AU to determine any subsequent course of action, such as repeat imaging.

Q: 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?

¹² American College of Radiology Committee on Drugs and Contrast Media. ACR Manual on Contrast Media. Accessed October 30, 2020. https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf

¹³ ACR-SPR Practice Parameter for the Use of Intravascular Contrast Media. Revised 2017 (Resolution 5). <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/ivcm.pdf>

A: Providers currently monitor for extravasation in general as a routine standard of care. Extravasations of non-radioactive contrast and pharmaceuticals have a substantially greater potential to cause harm to the patient. There is no practical need or radiation safety benefit to be gained from specifying radiopharmaceutical extravasation monitoring or reviewing requirements in NRC’s regulations.

Medical technique generally falls outside NRC’s regulatory jurisdiction. However, it is also important to note that technique improvements and adoption of best practices do not prevent extravasation. The petitioner’s own sponsored study demonstrated that anatomical/physiological variables and other involuntary patient interventions are often the primary contributing factors. Institutions participating in that sponsored study focused on mitigations of patient-level factors in efforts to marginally reduce infiltration rates. These mitigations included drastic changes to type of IV access for patients of a certain weight or age. Despite these focused efforts, and despite using the petitioner’s products and services, infiltrations continued to occur at noteworthy rates within all institutions.¹⁴ Moreover, the lead author of that sponsored study filed comments strongly opposing PRM-35-22.¹⁵

Indeed, novel injection site dosimetry of the kind needed for PRM-35-22, including product acquisition costs, patient wait times, personnel commitments, IV access changes, and other resource allocation requirements, would have a substantial negative impact on nuclear medicine services provided within licensed facilities (see the previous section, “ACR’s General Concerns and Comments on PRM-35-22”).

Q: Do you believe an NRC regulatory action requiring monitoring and review of extravasation would improve patient radiological health and safety? If so, how? If not, why not?

A: NRC regulatory action would be unable to improve patient radiological health and safety beyond current standard medical practice, as extravasation is unpredictable and unavoidable even when applicable IV access standards and protocols are followed. Nuclear medicine injection extravasation of any radiation safety significance is more hypothetical than practical, and rare anecdotes or theoretical possibilities that are unheard of in practice do not offset the real world negative impacts and consequences of the request in PRM-35-22, which, as previously mentioned, would be unduly disruptive and problematic. Moreover, regulatory action making certain extravasations a medical event could negatively impact patients’ health and safety as certain at-risk patients would be subjected to more intrusive, higher risk IV access procedures to reduce the extravasation risk.

Q: Are there any benefits, not related to medical techniques, to monitoring and reporting certain extravasations as medical events? What would be the burden associated with monitoring for and reporting certain extravasations as medical events?

A: We do not see the benefit of the request in PRM-35-22, or in any other arbitrary percentage or threshold-based reporting of extravasation cases as medical events. The measurement-based reporting of medical events under §35.3045(a) were created to determine if an administration of byproduct material was delivered in accordance with the written directive or physician’s intent, and to what extent it deviated. This rationale would be ill-suited to extravasation scenarios, as these occur regardless of whether the administration proceeded as intended and in accordance with best practices.

¹⁴ T. Z. Wong, et al., Quality Improvement Initiatives to Assess and Improve PET/CT Injection Infiltration Rates at Multiple Centers, 47 J. NUCLEAR MED. TECH. 326–331 (2019).

¹⁵ T.Z. Wong, Comment (296) from Terence Wong on FR Doc # 2020-19903. Posted Nov. 3, 2020. <https://beta.regulations.gov/comment/NRC-2020-0141-0300>

Additionally, there is no standard methodology recommended or adopted by professional radiological societies for assessing and documenting extravasations quantitatively. Each licensee would be encumbered with implementing a valid methodology using the technology they have access to, and then justifying these methods to NRC or Agreement State investigators if challenged during investigations.

The significant clinical, professional, medicolegal, financial, and administrative burdens and consequences of PRM-35-22 were discussed previously in this comment submission (see general concern subsection II, “Practice of Medicine Imposition”). Additionally, it should be emphasized during NRC’s considering of PRM-35-22 that nuclear medicine extravasations would be without justification under the existing rationale for medical event reporting as it would not satisfy any of the intended objectives (see subsection I, “NRC’s Medical Event Reporting Rationale Does Not Support This Change in Policy”).

Q: *If the NRC were to require that licensees report certain extravasations as medical events (recorded in NMED), what reporting criteria should be used to provide the NRC data that can be used to identify problems, monitor trends, and ensure that the licensee takes corrective action(s)?*

A: NMED data capturing extravasations would not be useful for identifying problems and trends, as extravasation is generally unpredictable and unavoidable even when best practices are followed, and significant extravasation is extremely rare (see subsection I, “NRC’s Medical Event Reporting Rationale Does Not Support This Change in Policy”). There are no quantifiable reporting criteria that could be useful for NRC in determining and implementing corrective actions.

If NRC determines that further action is needed to capture data on extravasation cases, we recommend using only qualitative assessments by the AU-physician of whether the harm standard of §35.3045(b) has been met instead of requiring novel injection site dosimetry made feasible only through proactive use of the petitioner’s product and services with every relevant nuclear medicine IV administration.

Q: *If the NRC requires reporting of extravasations that meet medical event reporting criteria, should a distinction be made between reporting extravasations of diagnostic and therapeutic radiopharmaceuticals? If so, why? If not, why not?*

A: NRC could clarify that physician-AUs are expected to determine in their best medical judgement if the permanent injury standard of §35.3045(b) for unintended patient intervention has been met. We do not believe subcategorizing nuclear medicine injection extravasations by quantities or use would change most of the inherent problems and unintended consequences of PRM-35-22; however, limiting the change to only therapeutic radiopharmaceuticals, or certain types of therapeutic radiopharmaceuticals, could have the lone benefit of likely reducing the number of compliance products medical licensees would need to purchase from the petitioner’s company (because, again, a licensee would need a unique compliance product for every site and concurrent and sequential nuclear medicine injection to conduct the requisite injection site dosimetry).

While diagnostic extravasation is more common, it would be unlikely if not impossible to meet the §35.3045(b) standard with typical diagnostic nuclear medicine agents. Extravasation of therapeutic radiopharmaceuticals would be more likely to reach the §35.3045(b) harm standard in rare and extreme cases that are essentially unheard of in actual practice. However, for either diagnostic or therapeutic agents, we believe extravasations would be reported as medical events to NRC under §35.3045(b) with the same frequency that they are currently—which is to say, almost never.

There is no unconflicted and trustworthy evidence that a mandate to conduct injection site dosimetry for every relevant administration would be helpful or justifiable within the limitations of NRC’s regulatory authority. NRC should consider the advice of the ACMUI as well as the previously discussed negative effects, burdens, impositions, and consequences of the request in PRM-35-22.

Conclusion

The ACR appreciates the opportunity to provide feedback on PRM-35-22 and NRC’s corresponding request for comments. We believe there are numerous valid reasons to deny the request in PRM-35-22 for a quantifiable dose threshold that would necessitate the use of dedicated compliance technologies to enable novel site injection dosimetry during each relevant IV administration of byproduct material. Most importantly, it would be an intrusive, expensive, resource-intensive, and burdensome imposition into the practice of medicine without justification under NRC’s current policies, including the agency’s long-standing rationale for medical event reporting.

Extravasation is generally unavoidable and unpredictable when best IV access practices and standards are followed, and in the case of byproduct material, is rarely of clinical or radiation safety significance. If further agency action is desired, we believe it is more reasonable and practicable for NRC to classify extravasation as an unintentional “patient intervention” subject to the significantly higher harm standard of §35.3045(b), which requires the physician-AU’s medical judgement to determine whether permanent functional damage to an organ or a physiological system has occurred or will occur. We believe that appropriately limiting the focus of reportable extravasations in this manner would avoid most of the associated burdens, consequences, costs, and inappropriate practice of medicine intrusions implicated by the petitioner’s request in PRM-35-22.

We welcome continued discussion with the NRC on PRM-35-22 and other topics of shared interest. Please contact Gloria Romanelli, JD, ACR Senior Director of Legislative and Regulatory Relations, or Michael Peters, ACR Director of Legislative and Regulatory Affairs, at mpeters@acr.org.

Sincerely,



Howard B. Fleishon, MD, MMM, FACR
Chair, Board of Chancellors
American College of Radiology