

August 31, 2022

The Honorable Christopher T. Hanson
Chairman, U.S. Nuclear Regulatory Commission
One White Flint North
11555 Rockville Pike
Rockville, MD 20852-2738

Dear Chairman Hanson:

The American College of Radiology (ACR)—a professional association representing more than 41,000 diagnostic radiologists, interventional radiologists, radiation oncologists, nuclear medicine physicians and medical physicists—appreciates the opportunity to share clarifications and stakeholder concerns regarding the petition for rulemaking filed in 2020 by Ronald K. Lattanze on behalf of Lucerno Dynamics, LLC (PRM-35-22) currently under Nuclear Regulatory Commission (NRC) review. In PRM-35-22, the petitioning device company requested “dose-based” reporting of certain nuclear medicine (NM) agent extravasations as Medical Events under 10 CFR 35.3045. The petitioner sells a proprietary system which includes class I, premarket notification-exempt “FDA-listed” medical devices (legally marketed without FDA’s review and approval or clearance) that detect levels of radiation below topical probes near injection sites, as well as software-as-a-service for novel quantifications using data from the probes.

The ACR has serious concerns with the practicability and resultant patient access issues, anxiety, inconvenience, and costs associated with PRM-35-22. Therefore, ACR strongly opposes a dose-based methodology for extravasation Medical Event reportability determinations. Notwithstanding the extensive lobbying and public relations campaign behind the petition, any NRC requirement necessitating use of the petitioner’s proposed methodology for approximately 20 million NM procedures annually would appear to benefit only the petitioning device company at the direct and continuing expense of patients, health care providers, and regulators. As detailed below, these added burdens would not create discernible value for patients, providers, or regulatory bodies.

Extravasation/Infiltration

In a corresponding request for public comment (85 FR 57148), NRC defined *extravasation* as “the infiltration of injected fluid into the tissue surrounding a vein or artery.” As defined, extravasation is a nonroutine potential of any intravenous (IV) administration. It occurs in every health care institution with any type of drug or other fluid. Health care providers routinely seek to minimize infiltration potential through standard IV practices that are medically appropriate for the relative risk of the drug or material being administered. Patient-specific characteristics, such as weight, age, medical conditions, movement, blood vessel fragility, and other variables, significantly influence occurrence. Extravasation does not demonstrate operator carelessness, substandard operator technique, inadequate institutional quality assurance, an unsuccessful medical procedure, or patient harm.

There is a carefully crafted misperception surrounding PRM-35-22 that NM agents are intrinsically more dangerous when infiltrated than nonradioactive IV medications or fluids due to the presence of the radionuclide.

However, extravasation is almost exclusively an injury concern with inherently caustic solutions such as certain chemotherapeutic compounds that severely damage tissue upon contact, as well as with large fluid volume leakages. By contrast, most NM agent injections involve very small volumes of solutions with inert chemical properties. Extravasations with such NM agents typically resolve spontaneously within minutes through reabsorption into the venous or lymphatic systems. Due to the body's rapid reabsorption in combination with the intrinsic bonding properties of unsealed NM agents, infiltration rarely results in any additional radiation safety concern or problem for the subsequent imaging or therapy procedure. In any outlier case in which imaging is below diagnostic quality due to insufficient uptake, the study would simply be repeated as it would be for any other reason (e.g., patient movement during imaging).

IV Practice of Medicine

Standard risk-based injection quality and safety practices and clinical decision-making broadly apply to injections of NM agents. Low-risk NM agents are commonly administered via peripheral venous access and rapid injection. Higher risk surgically installed central venous access procedures, such as subclavian vein lines and indwelling ports, reduce infiltration occurrence compared to peripheral access. However, central lines are not medically appropriate for all drugs, fluid volumes, patients, and clinical circumstances due to the additional risk of carotid artery puncture, subclavian artery puncture, pneumothorax, hematoma formation, hemothorax, and other severe adverse events.

Medical decision-making intrinsically considers the risks and benefits of IV access procedures and drugs in addition to patient-specific variables and other clinical considerations. For example, it would be viewed as medically inappropriate in most cases to surgically insert a tunneled central venous catheter typically used with caustic chemotherapeutic solutions to administer a unit dose of Tc-99m or other diagnostic NM agent. The tunneled central line would greatly reduce the extravasation potential of the Tc-99m administration, but at the expense of significant health risks and other consequences for the patient that far outweigh any reasonable extravasation concern with such an agent.

Quality Assurance

Diagnostic and therapeutic radionuclide programs have existing quality assurance (QA) as mandated by institutional, jurisdictional, and accreditation requirements. QA programs for these procedures are carried out prior to infusions and include provider education and practice in handling and administration of the radioactive agents, appropriate strategies to reduce extravasation potential, management of extravasations, and selection of appropriate vascular access devices, among other elements. If, during medical practice, an extravasation does occur, it is managed and reported as required by relevant policies and procedures. In the rare event of significant harm, the incident could rise to the level of a sentinel event, which could trigger a root-cause analysis determination. Any NRC compliance necessity to determine extravasation reportability under §35.3045 based on a clinically irrelevant dose estimation as the reporting threshold suggested by the petitioner would not add value to existing QA.

Doctor-Patient Communications

Patients are routinely apprised of pertinent information about their care services, including limitations and challenges encountered during NM imaging and therapy procedures. For example, the [*ACR Practice Parameter for Communication of Diagnostic Imaging Findings*](#) describes clinical communications, including dedicated subsections in radiology reports, capturing adverse events or "any factors that may compromise the sensitivity and specificity of the examination." Standard medical practice dictates that rendering physicians document any significant technical impacts on accuracy of findings.

NRC's Medical Event mechanism is independent of clinical communications. Exclusion from Medical Event reporting does not mean extravasation is "hidden" or "kept secret." The 24-hour notification described under §35.3045(e) is for informing relevant parties of a Medical Event report made to NRC, and not for conveying health care information.

NRC Medical Events

§35.3045(a) exists to collect reports of erroneous uses of byproduct material from which analyses can be performed, bestowing actionable data to regulators, federal advisors, and other medical licensees to prevent similar problems at other licensed facilities. Medical Events with unsealed byproduct material under §35.3045(a)(1) include wrong patient, wrong drug, and wrong route of administration (for example, erroneously administering an IV solution orally). These are not intended to include phenomena that can occur without cause due to licensee error, such as shunting, seed migration, patient intervention, and unsealed material extravasation.

Additionally, §35.3045(b) enables NRC collection of significant injuries caused by non-error "patient interventions." §35.3045(b) Medical Events involve qualitative medical assessments by the authorized user (AU) for reportability determinations. §35.3045(b) Medical Events are exceedingly rare and have a significantly high harm threshold for reporting because they are outside the reasonable control of licensees.

Importantly, Medical Events—whether §35.3045(a) errors or §35.3045(b) non-errors—are analyzed on a case-by-case basis by NRC staff and the NRC Advisory Committee on the Medical Uses of Isotopes (ACMUI). There must be attributable cause, discernible effects, and actionable lessons for meaningful value to be obtained from the agency's evaluations. The NRC's Nuclear Material Events Database is not a clinical data registry for comparative quality analyses.

Other federal regulatory agencies with jurisdiction over health care do not require PRM-35-22-equivalent reporting of nonradioactive IV fluid extravasations, even for caustic chemotherapeutic compounds. The PRM-35-22 approach would require prioritization of, and adoption of new monitoring protocols exclusive to, radiological materials under NRC's authority without regard to risk or significance.

Dose-Based Reporting Problems

There is no medically standard methodology for measuring and quantifying transient dose to surrounding tissue from infiltrated fluid. In real-world practice, most NM care providers would instead image the injection site for confirmation and medical assessment if they believed any outlier extravasation case to be of consequence.

In PRM-35-22, the petitioning medical device company requested elimination of NRC's enforcement policy toward extravasation and sought implementation of a "dose-based" Medical Event reportability determination process for extravasation. The PRM identified an arbitrary value below the threshold for somatic biological effects as the reporting trigger, presumably because of its reference in §35.3045 for purposes unrelated to extravasation. As clarified by the NRC ACMUI in its [September 2021 report](#), *"this 0.5 Sv dose threshold was not intended [by NRC] to be applied to very small volumes of tissue, such as that surrounding an extravasation, which do not result in patient harm."*

The injection site-focused Medical Event reportability determination methodology implied by PRM-35-22 is effectively an assumption or estimate—not a definitive quantification of what is happening in the patient's body

The Honorable Christopher T. Hanson

August 31, 2022

Page 4

at the time of the subsequent NM imaging or therapy. This methodology would detect dose remaining in the blood vessel from venous stasis (i.e., slow blood flow). It would not provide information about causes or effects of assumed extravasation cases, nor demonstrate diagnostic quality or uptake at the imaging or treatment site following reabsorption. As a pragmatic consideration, any small amount of extravasate, either by volume or radiation activity, will begin to decline instantly through absorption, diffusion, and radioactive decay. There currently exists no standardized or meaningful guideline(s) to determine time of measurement, frequency of measurement, or even the size of the area to be measured. As a result of these issues, PRM-35-22 implementation would produce an overwhelming influx of inconsequential, nonstandard, and unusable Medical Event data that provides no discernible regulatory, patient, or provider value.

ACR Recommendations

The current NRC enforcement policy for extravasation and Medical Events continues to be generally appropriate and understandable from a clinical perspective. Maintaining it would be the most practical option, and one we believe to be in the best interest of patients, providers, and regulatory agencies.

Any extreme outlier case that resulted in injury from radiation should obviously be reportable to NRC for analysis. If the agency believes it must change its current enforcement policy and/or regulatory language to do so, the most appropriate and meaningful determination process would be a “harm-based” reportability determination method. There are two possible options for implementing such an approach, both of which involve an obvious need for medical intervention and AU assessment, and neither require special knowledge on the part of the patient:

- Enable reporting of any extravasation meeting the criteria of the existing §35.3045(b). Depending on the NRC Office of the General Counsel’s view, this approach could be expeditiously implementable via enforcement policy revision referencing existing CFR language, as initially recommended by the NRC ACMUI prior to the filing of PRM-35-22.
- Enable reporting of any radiation-attributable extravasation injury meeting the Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 for medical intervention. This would be a clinically understandable, National Institutes of Health-promulgated, nationally accepted metric leveraging the radiation expertise of AUs. This approach would be a more actionable and medically meaningful standardized way of implementing and enforcing the most recent NRC ACMUI recommendation from its September 2021 report.

Thank you for your time and consideration of these clarifications and recommendations. For questions about this topic, please contact Gloria Romanelli, JD, ACR Senior Director of Government Relations, at gromanelli@acr.org; or Michael Peters, ACR Senior Government Affairs Director, Regulatory Policy, at mpeters@acr.org.

Sincerely,



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Chair, Board of Chancellors
American College of Radiology