On May 18, 2020, Lucerno Dynamics, LLC ("Lucerno") filed a petition for rulemaking with the Nuclear Regulatory Commission (NRC) to amend 10 C.F.R. § 35.2 and 10 C.F.R. § 35.3045 to require the reporting of extravasations that exceed the 0.5 Sv dose equivalent to tissue as medical events. In their petition Lucerno cites the NRC's final ruling in May, 1980, which exempted extravasations from medical event reporting with the understanding that extravasations are virtually impossible to avoid. Lucerno further states that "ample evidence has been published that nuclear medicine extravasations are, in fact, avoidable and are capable of causing considerable harm to the patients," and conclude by requesting that the NRC revisit the policy established in 1980 and require the reporting of certain extravasations as medical events.

The Society of Nuclear Medicine and Molecular Imaging (SNMMI), the American Society of Nuclear Cardiology (ASNC), and the American College of Nuclear Medicine (ACNM) have reviewed Lucerno's petition and the relevant literature, and our position is as follows.

The NRC's policy regarding extravasations established in May 1980 does not require additional rulemaking

Although the NRC considered the question of radiopharmaceutical extravasations in 1980, the Commission has also revisited this issue several times since then. In August, 2000, the NRC issued a revised Medical Use Policy Statement to focus its regulatory emphasis on those medical procedures that pose the highest, potentially significant, risks.[1] In April, 2002, 10 CFR §35 was revised to be more risk-informed and performance-based, consistent with the revised Medical Use Policy Statement. Specifically, the term, "Misadministration," was changed to "Medical Event," and the reporting criteria were revised to include different types of deviations from the radiopharmaceutical administration that was prescribed (i.e., wrong activity, wrong radioactive drug, wrong route of administration, wrong patient, wrong mode of treatment, wrong treatment site, or implantation of leaking sealed source). The definition of a Medical Event also includes dose-threshold criteria: an effective dose equivalent exceeding 0.05 Sv (5 rem), an organ or tissue dose equivalent exceeding 0.5 Sv (50 rem), or a shallow (skin) dose equivalent exceeding 0.5 Sv (50 rem).[2] There was also an exclusion from the Medical Event reporting requirement for an event that results from "patient intervention."[3]

[1] The policy statement outlined the intent of the NRC to regulate the medical use of radioisotopes based on the following four guiding principles:

1. The NRC will continue to regulate the medical use of radioisotopes as necessary to provide for the radiation safety of workers and the general public.
2. NRC will not intrude into the medical judgements affecting patients, except as necessary to provide for the radiation safety of workers and the general public.
3. 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 direction.
4. NRC, in developing a specific regulatory approach, will consider industry and professional standards that define acceptable approaches of achieving radiation safety.

[2] 10 CFR §35.3045(a)

[3] "Patient intervention" is defined 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" (10 CFR §35.2)

However, a licensee must 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.[4] This statement encompasses the societies view that although therapeutic extravasations should be 100% reportable medical events, diagnostic extravasations should not.

SNMMI agrees with the current NRC position that extravasations are a practice-of-medicine issue and therefore not subject to NRC regulation

This issue of extravasations has been addressed by the NRC's Advisory Committee on the Medical Uses of Isotopes (ACMUI) several times in recent years. In 2017, the ACMUI Patient Intervention Subcommittee examined unintentional treatment outcomes with Y-90 microsphere therapy and introduced the concept of "passive" rather than "active" patient intervention.[5] It stated, "Unintentional treatment outcome due to anatomic or physiologic anomaly and/or imaging uncertainty falls into the category "the Art of Medical Practice" provided that the standards of medical practice are met. Reporting such unpredictable and unavoidable patient-specific medical events will not help to prevent such events in the future, and therefore cannot be regulated."[6]

Most recently, in 2019 ACMUI Subcommittee on Extravasation reviewed the 1980 NRC decision to exclude extravasations from being considered a misadministration (medical event).[7] The Subcommittee agreed with the 1980 assessment that extravasations frequently occur in otherwise normal intravenous or intra-arterial injections and are virtually impossible to avoid. They concluded that extravasations are a practice-of-medicine issue and thus beyond the scope, appropriately, of NRC regulatory oversight. The Subcommittee reconfirmed that the exclusion of extravasation from medical-event reporting was appropriate for both diagnostic and therapeutic procedures. However, one of its recommendations was for extravasations to be considered a type of passive "patient intervention" and that extravasations that lead to "unintended permanent functional damage" be reportable as a Medical Event under 10 CFR §35.3045(b). This is not inconsistent with the NRC's policy from 1980 and therefore such policy is still current. The literature confirms this. A systematic review performed by van der Pol, et al. concluded that, although extravasation of diagnostic radiopharmaceuticals is not uncommon, of more than 3,000 reported cases of extravasation of diagnostic radiopharmaceuticals, only 3 cases (<0.1%) resulted in patient symptoms that required follow-up.[8] More specifically, none of the reported cases of extravasation of ^{99m}Tc-, ^{123}I-, ^{18}F-, and ^{68}Ga-labelled tracers required intervention; the only cases where patient symptoms were reported were for the less-often-used tracers ^{201}Tl and ^{131}I- iodocholesterol. In summary, there is no clinical data that supports Lucerno Dynamic's claim that extravasation of diagnostic radiopharmaceuticals is a patient safety issue.

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[4] 10 CFR §35.3045(b)

[5] "Passive" patient intervention type was intended to address situations where there was a stasis of arterial flow or shunting of microspheres through aberrant vessels, resulting in a medical event for the Y-90 microsphere therapy. ACMUI, Subcommittee on Patient Intervention, Draft Report, Part II, April 27, 2017.

[6] *Id.*

[7] ACMUI, Subcommittee on Extravasation, Final Report, October 23, 2019

[8] van der Pol, J., Vöö1, S., Bucerius, J., and Mottaghy, F. "Consequences of radiopharmaceutical extravasation and therapeutic interventions: a systematic review." Eur J Nucl Med Mol Imaging (2017) 44:1234–1243.

This systematic review also noted that extravasation of therapeutic radiopharmaceuticals is a more significant event that can potentially induce severe soft-tissue reactions and possibly require surgical intervention.[9] In this context, it is important to point out that extravasation of chemotherapeutic agents is an on-going safety concern in medical oncology and that there are well-established procedures for management of extravasated chemotherapeutic agents, similar to those in place for extravasated radiotherapeutic agents.

In summary, we believe that extravasations are best managed on an institutional level at the discretion of the authorized user and do not require additional NRC regulation. Furthermore, the Society recognizes the effect that extravasation of diagnostic radiopharmaceuticals may have on the quality of diagnostic images, particularly on quantitative studies, and is actively addressing this as the quality-control issue that it is, rather than a patient-safety issue.

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[9] *Id.* at 1234.