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Submitter Information

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Submitter's Representative: M Saiful Huq, PhD, President
Organization: American Association of Physicists in Medicine

General Comment

See attached AAPM Comment Letter.

Attachments

AAPM NRC Extravasation Final

AMERICAN ASSOCIATION of PHYSICISTS IN MEDICINE

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November 30, 2020

Annette L. Vietti-Cook
U.S. Nuclear Regulatory Commission
Office of the Secretary
Washington, DC 20555-0001

VIA: http://www.regulations.gov/

RE: Petition for Rulemaking: "Reporting Nuclear Medicine Injection Extravasations as Medical Events" [Docket No. PRM–35–22; NRC–2020–0141]

Dear Ms. Vietti-Cook:

The American Association of Physicists in Medicine (AAPM)[1], is pleased to submit comments to the Nuclear Regulatory Commission (NRC) regarding the petition for rulemaking entitled, "Reporting Nuclear Medicine Injection Extravasations as Medical Events."

Background

The NRC seeks public comments on Lucerno Dynamics, LLC's (Lucerno) petition for rulemaking, which requests the NRC to revise its regulations to require reporting of certain nuclear medicine injection extravasations as medical events. Extravasation is the leakage or infiltration of injected fluid into the extravascular tissue around the injection site.

Lucerno's petition seeks rulemaking to require the reporting of extravasations that exceed the 0.5 Sv dose equivalent to tissue as medical events. In support of its request, Lucerno asserts that "ample evidence has been published that nuclear medicine extravasations are, in fact, avoidable and are capable of causing

[1] AAPM is the premier organization in medical physics, both in the U.S. and abroad. Medical physics is a scientific and professional discipline that uses physics principles to address a wide range of biological and medical needs. The mission of AAPM is to advance medicine through excellence in the science, education and professional practice of medical physics. Currently, AAPM represents over 9,000 medical physicists.

Medical physicists contribute to the effectiveness of medical imaging by ensuring the safe and effective use of radiant energy (e.g., optical, ionizing, ultrasonic, or radiofrequency) to obtain detailed information about the form and function of the human body. Medical physicists continue to play a leading role in the development of novel imaging technologies, as well as in guiding the optimization of existing imaging modalities. In addition, medical physicists contribute to development of new therapeutic technologies in radiation oncology, as well as in other disciplines, such as in thermal ablation or high intensity focused ultrasound. Clinically, medical physicists work side by side with radiation oncologists to design treatment plans and monitor equipment and procedures to ensure that cancer patients receive the prescribed dose of radiation at the correct location.

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 NRC, which currently does not classify radiopharmaceutical extravasations as medical events, is examining the issues raised by Lucerno to determine whether to proceed with rulemaking to include extravasations in its medical event reporting schema. If it does decide to do so, the NRC will address reporting criteria, including whether a different reporting threshold should be applied, and whether a distinction should be made between diagnostic and therapeutic extravasations.

The NRC has been working on this issue for some time in collaboration with its Advisory Committee on the Medical Uses of Isotopes (ACMUI). In April 2019, Lucerno, an external stakeholder engaged in device manufacturing, made a presentation at an ACMUI meeting to describe a new device that can monitor injection sites during and after radiopharmaceutical injections. Lucerno expressed its view that its device may help in lowering extravasation rates, and it advocated for the NRC to revise its medical event reporting requirements to include extravasations.

The ACMUI has been reluctant to recommend that extravasations be included in medical event reporting, citing the numerous factors that may result in extravasation, including the anatomy of the patient, and patient activity. In September 2019, the ACMUI concluded that there is no evidence to support reclassifying extravasation as a medical event, and it made recommendations that extravasations be considered a type of "passive" patient intervention and that extravasations be reportable as medical events only when they lead to unintended permanent functional damage. As reported at the March 2020 ACMUI meeting, the advisory committee continues its work on review of the regulatory definition of "patient intervention," and how that definition would be modified to incorporate extravasations.

Comments

AAPM has reviewed Lucerno's petition and the relevant literature. AAPM disagrees with the assertion that extravasation of diagnostic radiopharmaceuticals may have a meaningful impact on the quality of diagnostic images, and AAPM believes that extravasations of therapeutic injections of radiopharmaceuticals are best managed on an institutional level at the discretion of the authorized user and do not require changes to NRC regulations.

AAPM provides the following comments:

1. Definition of quantitative imaging in nuclear medicine

We define quantitative imaging as the measurement of radiotracer concentration and the ability to know (or estimate) the bias and variance of the measurements, such as 18F-FDG in positron emission tomography (PET) imaging. The units can be measured as a radioactivity concentration, such as Bq/c, or in relative uptake units of standardized uptake values (SUVs), which attempt to normalize for the injected amount of radiotracer and patient size. These are the two largest sources of uncontrollable variability (Kinahan and Fletcher, *Semin Ultrasound CT MR*. pp.496–505, 2010; Adams et al. *Amer J Roentgenology*. pp. 310–320, Aug. 2010).

2. What is known about the bias and variance of measurements of radiotracer concentration in nuclear medicine.

The most well-understood form of quantitative imaging in nuclear medicine is PET imaging of 18F-FDG. The recently published result of the RSNA QIBA group state "... the maximum SUV (SUVmax) is measurable from FDG PET/CT with a within-subject coefficient of variation of 10%–12%". (Kinahan et al. *Radiology*, pp.647-657, 2020). Beyond this there is little else known. This lack of knowledge includes the bias or precision of values from a single PET image, as opposed to the differences in test-retest images, or for measures other than SUVmax, or for other radiotracers, or for single photon emission computed tomography (SPECT) imaging.

3. Quantitative imaging is not used in clinical nuclear medicine.

The primary use in nuclear medicine imaging is diagnostic imaging with radiotracers, such as 18F-FDG imaged with PET, which is the bulk of the supporting materials provided in Appendix 1 of the petition from Lucerno. It is well-established that quantitative values, specifically standardized uptake values (SUVs) from PET images should not be used for diagnostic purposes. As the late Ed Coleman, universally recognized as a leader in clinical PET imaging, wrote: "From 1996 to 2001 we have performed more than 13,000 clinical PET scans at our institution. The number of clinical PET scans that we have performed quantitatively is *zero*." [emphasis added by Dr Coleman] (*Eur J Nucl Med Mol Imaging*. pp.135–138, 2002).

Since the time of this writing, relative uptake values, i.e. comparing tumor uptake of 18F-FDG to that of the blood-pool or liver have been proposed. For example, the Deauville criteria uses a five-point scale based on visual analysis of FDG PET imaging of the site of initial (pre-treatment) lymphoma as follows:

Score	Definition
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Moderately increased uptake compared to the liver
5	Markedly increased uptake compared to the liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

The Deauville criteria are essentially for the basis of later or more comprehensive criteria, but none are based on quantitative imaging. As stated by the Food and Drug Administration (FDA) (“Clinical Trial Imaging Endpoint Process Standards Guidance for Industry,” FDA, Mar. 2018) quantitative imaging has no impact on clinical practice:

> In medical practice, images of human anatomy and/or physiology typically are acquired and interpreted, often with limited or no formal quantification, by a single facility’s imaging professional staff. The images typically achieve the medical practice’s diagnostic purposes even though the acquisition, display, and interpretation methods may vary somewhat among imaging facilities and imaging professionals. This variability may have little or no impact on the ability to provide a diagnosis in medical practice, yet in a clinical trial, imaging process variability may result in increased

variability in endpoint measurements and may compromise the ability of the trial to achieve its objectives.

In summary, the only combination of imaging modality and radiotracer that might have the potential to be used in a quantitative manner is 18F-FDG PET imaging. However, there is no current clinical role for quantitative imaging in nuclear medicine.

4. The statement that extravasation invalidates or degrades clinical 18F-FDG PET or other nuclear imaging methods is misleading.

The petition states that "In an extravasation, some radiopharmaceutical remains in the tissue around the injection site and some leaks back into circulation during the uptake period." This is true. However, the subsequent assertion "Extravasations negatively affect imaging in two ways that combined, reduce the image contrast and sensitivity" is misleading. While it is true that trapped and/or slowly released radiotracer may reduce the number of detected photons and/or decrease contrast, these effects are dwarfed by other effects, including patient size and scanning protocol and the type of scanner (Kinahan and Fletcher, *Semin Ultrasound CT MR*. pp.496–505, 2010; Adams et al. *Amer J Roentgenology*. pp. 310–320, Aug. 2010). These confounding effects are even more of an overriding factor in SPECT imaging. The biggest potential challenge of extravasation is the production of image artifacts, as illustrated in the supporting materials provided in Appendix 1 of the petition from Lucerno. Nonetheless, these images while suboptimal in some cases are all clearly useful diagnostically.

5. The statement that extravasation is common is misleading.

The petition states that "Studies suggest that an average of 15% (range between 2-23%) of nuclear medicine intravenous injections may result in an extravasation." A review of one of the publications cited to support this statement (Silva-Rodríguez, et al, *Medical Physics*, May 2014) shows that from a study of 1,367 consecutive patients receiving 18F-FDG PET imaging, only 3 or 4 patients (depending on classification method) had an extravasation of 10% or more of the total injected dose, i.e. less than 0.3%. Lucerno's assumed average extravasation rate of 15% is inaccurate and not supported by the majority of the referred literature. The rate of extravasation involving 10% or more of the dose is less than 1%.

6. The examples provided do not support the request to require the reporting of extravasations that exceed 500 mSv of dose equivalent to tissue.

The bulk of the supporting materials provided in Appendix 1 of the petition from Lucerno are from 18F-FDG imaging. A nominal injected amount of radioactivity in 18F-FDG imaging is 370 MBq, which has an effective dose of 7 mSv (nominal). This is two orders of magnitude (i.e. 100x) less than the proposed threshold of 500mSv.

7. Extravasations of therapeutic levels of radiopharmaceuticals should continue to be treated as a practice-of-medicine issue.

The Advisory Committee on the Medical Use of Isotopes (ACMUI) Subcommittee on Extravasations provided a report dated October 23, 2019 with a charge to "Re-evaluate and provide recommendations on the NRC decision on infiltrations and extravasations published in the Federal Register, Volume 45, No. 95, on May 14, 1980." (https://www.nrc.gov/docs/ML1931/ML19316E067.pdf).

This committee was formed, in part, to review a presentation that was made by Lucerno regarding a technology, which may help identify extravasations. The goal for the use of this product is to reduce the frequency of extravasations. Data was presented relative to this product's use for PET isotope injections and the effect on Standardized Uptake Value (SUV) of tumors or organs when extravasation occurs.

Among the recommendations of the committee were:

- "Extravasation is a practice of medicine issue and not an item that needs to be regulated by the NRC."
- Extravasation should be characterized as a type of "patient intervention" so that only extravasations resulting in patient harm are reported as medical events.

AAPM agrees with these recommendations. While extravasations do occasionally occur, either from a technical inadequacy or a challenging patient anatomy, it does not necessarily represent an "error" on the part of the licensee, which is part of the required criteria for a medical event. Performing an injection is a "practice of medicine" issue and not something that should be regulated by the NRC.

8. Determining if the radiation dose attributable to an extravasation exceeds the proposed threshold of 0.5 Sv would be difficult and is an inappropriate threshold.

The use of dosimetric values to gauge misadministration is inappropriate. Currently, no FDA-approved radiopharmaceutical is administered based on dosimetry, rather than on fixed activity or weight-based activity calculations. It is therefore unrealistic to relate misadministration to prescribed or targeted absorbed dose or absorbed dose to organs at risk, when no such values are calculated. Variability in pharmacokinetics precludes absorbed dose prescription with accuracy and precision equivalent to those in external beam or brachytherapy. The radiation treatment is systemic and thresholds for equivalent dose on the order of 0.5 Sv could repeatedly be exceeded whether there was extravasation or not. As a systemic therapy, the criteria for misadministration should follow other systemic therapies as is currently done by treating such events as a practice of medicine issue, and not an item that needs to be regulated by the NRC. This was also discussed in the previous paragraph.

Briefly stated, it would be very difficult to accurately determine the radiation dose to the surrounding tissue from an extravasation with all of the unknown variables (tissue volume, clearance rate) and the required technology and software required to image or measure the extravasated activity. This would place an unnecessary or impractical burden on the licensees. The threshold dose of 0.5 Sv does not represent any level of patient harm. Accordingly, it should not be required to be reported.

Conclusion

In summary:

- AAPM disagrees with the assertion that extravasation of diagnostic radiopharmaceuticals may have a meaningful impact on the quality of diagnostic images.

- Furthermore, AAPM believes that extravasations of therapeutic injections of radiopharmaceuticals are best managed on an institutional level at the discretion of the authorized user and do not require changes to NRC regulations.

AAPM hopes that the NRC will address AAPM's concerns with the petition for rulemaking when determining its path forward. Thank you for the opportunity to comment on this petition for rulemaking. If you have any questions or require additional information, please contact Richard J. Martin, JD, AAPM's Government Relations Program Manager, at richard@aapm.org .

Sincerely,

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