November 30, 2020

Sara Lopas and Pamela Noto
Secretary, U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Dear Ms. Lopas and Ms. Noto:

The Organization of Agreement States (OAS) Executive Board (Board) appreciates the opportunity to comment on the Nuclear Regulatory Commission's (NRC) Notice of Request for Comment: "Petition for Rulemaking That Would Require Reporting of Certain Nuclear Medicine Injection Extravasations as Medical Events" (STC-20-066). The Board understands how, in 1980, the NRC chose to exempt extravasations. There was a smaller scope of radioisotopes in use, practice and techniques were still in early development, the consequences were not fully understood, and medical practitioners told the NRC that extravasations were nearly impossible to avoid. Four decades later, it is clear that the rationale for this exemption is no longer appropriate. Overnight, the NRC could make a policy decision to drastically improve the health, safety and clinical outcomes for hundreds of thousands of patients a year. Through accepting this petition for rulemaking, engaging with stakeholders, developing interim enforcement guidance, and providing a generous implementation window we can create a better regulatory framework. A framework that upholds the policies and ideals of the National Materials Program (NMP). Not much can be done for the past; however, the Board hopes that the answers provided below will motivate the NMP to arrive at a solution acceptable for decades to come.

*Injection Quality Monitoring*

1. How frequently does radiopharmaceutical extravasation occur?

   Extravasation rates are reported to occur at various rates. Variance can occur from one institution to another, and even from one technologist to another. Large scale attempts to quantify extravasation rates of radiopharmaceuticals (RP) have yet to take place like they have in other medical sectors (i.e., chemotherapy or CT contrast agents). Studies likely underestimate RP extravasations due to difficulties in identification (i.e., such as injection site not being within the imaging field of view). Six studies conducted between 2006 and 2017 reported extravasation rates between 3% and 23%, cumulatively those six studies showed extravasations in 425 of 2804 patients, or at a rate of 15.2% (Wong, et al., 2019).

   During the October 14, 2020 FDA/NRC workshop, the FDA reported extravasation rates to be between 0.1% and 1.2%; however, this was taken from a manual on CT contrast

media and not specifically for RPs (ACR Committee on Drugs and Contrast Media, 2020). This misclassification demonstrates how easy it is to inaccurately report RP extravasation rates by assigning rates from other injection types. Similar to CT contrast, chemotherapy generally reports a very low extravasation rate. This is in part due to awareness and quality improvement initiatives. If other areas of medicine are able to achieve extravasation rates around 1% or less, then the same should be possible in nuclear medicine.

One study compared Australian RP extravasations to those in the United States and found rates to be 1.0% to 8.8%, respectively. The authors attributed part of this discrepancy to the Australian Radiation Protection and Nuclear Safety Agency's recognition of extravasations as misadministrations, making them subject to reporting requirements and investigations. The reports help reduce rates by enhancing training and education. The study went on to say that it is possible to nearly eliminate extravasations (Currie & Sanchez, 2020). The NMP has a role to bring attention to this matter and ensure facilities work to measure their extravasation rates and to reduce them where practicable.

2. 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.

   In the recent FDA/NRC workshop, there were multiple acute signs and symptoms reported due to RP extravasations. These included pain, erythema, swelling, local blistering, darkening of skin, compartment syndrome, loss of diagnostic or therapeutic efficacy, and finally delayed reactions of either ulceration or fibrosis. The FDA acknowledged that extravasations can be asymptomatic; this is likely a majority of cases and lends itself to the general lack of follow up for patients.

   A well-known systematic review of RP extravasation consequences was published in "The European Journal of Nuclear Medicine and Molecular Imaging" (van der Pol, Vöö, Bucerius, & Mottaghy, 2017). This review is commonly misrepresented to suggest there is little to no harm by extravasations and that only 3 cases out of 3016 posed symptoms or required follow-up after diagnostic extravasations. Instead, the article states that follow-up was only performed in 3 cases, or roughly 0.1% of the time. In every instance that follow-up was performed there were adverse tissue reactions, including radiation ulcers and erythematous patches. Some reactions were noted years after the extravasation. What would have been observed if the other 99.9% of patients were followed? The article goes on to share that 10 therapeutic cases were reported with symptoms; radionecrosis was the most severe effect which occurred in 50% of the reported therapeutic cases.

   The van der Pol article highlights 34 interventions following diagnostic or therapeutic extravasations; these would not be necessary if there was no risk of harm. A common action for addressing all extravasations is informing the patient (Barré, et al., 2013) (van der Pol, Vöö , Bucerius, & Mottaghy, 2017). This important patient safety step is not required in the United States (as it is with other medical events) due to the NRC providing a blanket exemption to extravasations.

Tissue damage due to irradiation is well established and understood. The nuclear medicine community agrees that beyond 1 Gy of dose, deterministic effects are possible (Siegel, 2001). Localized radiation symptoms from extravasations, whether from diagnostic or therapeutic applications, presented similarly and arose systematically. Predominantly this is seen as alopecia around 3 Gy, erythema at 4-8 Gy, dry or wet flaking of the skin from 8-25 Gy, and eventually necrosis is seen beyond 25 Gy (capable with therapies) (Barré, et al., 2013). The petition for rulemaking (PRM-35-22) offered several case studies demonstrating that localized tissue doses, even from diagnostic agents, can exceed 3-5 Gy.

Therapeutic uses of Y-90 and I-131 have demonstrated skin burns, erythema, desquamation, and possible need for surgical intervention (Barré, et al., 2013) (van der Pol, Vöö , Bucerius, & Mottaghy, 2017). Going beyond deterministic effects, there is also a risk with radiation damage to cause stochastic effects such as secondary cancers. In one known event where Ra-223 was extravasated into a patient's hand, the patient developed a focal cutaneous squamous cell carcinoma within a few months of receiving treatment; authors suggest this is a likely side effect that goes severely underreported (Benjegerdes, 2017) (Bonta, Halkar, & Alazraki, 2011) (Williams, Palmer, Parker, & Joyce, 2006).

In addition to localized physical effects, there can also be potentially severe clinical consequences by extravasations. Nuclear medicine relies on the biophysical interactions of the RP within the body. Extravasating the dose interferes with the intended redistribution of the RP throughout the patient's anatomy. For diagnostic purposes this can lead to false-positives, negatives, incorrect staging for disease, and ultimately leading to the wrong course of treatment for the patient. With therapeutics, the full doses will not be received by the intended treatment location, reducing the effectiveness of the treatment, and ultimately causing significant radiation burden to unintended tissues (Barré, et al., 2013).

Finally, in the 2019 abnormal occurrences report from the NRC to Congress, there was an event reported of I-131 MIBG spilled onto a patient (United States Nuclear Regulatory Commission, 2019). Though not an extravasation, it shows the tremendous dose consequence (estimated between 500-1200 Gy to the skin, more than 1000x the reportable dose criteria) when a RP is not delivered as intended. The NRC concluded this event to be a medical event and abnormal occurrence; however, if it was extravasated or "spilled" into the patient's arm rather than onto their skin then it would be exempt from reporting per the 1980 policy.

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

   Many professional standards call for monitoring of extravasations and for them to be included with the report to the ordering physicians (Barré, et al., 2013) (Intersocietal Accreditation Commission, 2016) (Strauss, et al., 2008) (Boellaard, Delgado-Bolton, Oyen, & al., 2015) (Tilkemeier, Cooke, Grossman, McCallister, & Ward, 2009). As stated earlier, if not identified to physicians then inaccurate decisions for patient care may result. Licensees with a strong safety culture and medical practice are likely to track and implement programs to report and reduce extravasations internally. As a regulator, we

enact regulation not for model licensees, but to set a minimum level of acceptable criteria that applies to all licensees.

Some monitoring can be achieved with careful observation during the injection, for instance higher volume injections may physically present themselves or show resistance when extravasated. Unfortunately, RP are commonly low volume injections. Other ways to monitor include the use of radiation detection equipment or imaging 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?

   Absolutely; if we examine other medical procedures such as chemotherapy or CT contrast agents then there is demonstrated evidence for the effectiveness of quality improvement initiatives. Rates for extravasations in these areas have been driven down into the tenths of a percent; this is attributed to large scale quality improvement efforts by clinicians. Ultimately, nuclear medicine can achieve the same injection performance through similar efforts. A 2019 article published in "The Journal of Nuclear Medicine Technology" showed that multiple centers were able to significantly reduce their extravasation rates by monitoring their injections and applying quality improvement strategies (Wong, et al., 2019).

   Other countries attribute lower extravasation rates to classifying extravasations as misadministrations and paying attention to injection standards. Facilities examine their practices, refine their training and education, improve medical technique, adjust their choice of delivery devices and share their experiences.

5. 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?

   Yes, requiring monitoring of injections would be in alignment with other NRC regulations that ensure accurate delivery of doses, as prescribed by a physician. As stated, there can be radiological and clinical consequences to patients who have been extravasated. Fortunately, it is possible to reduce these errors through quality improvement practices; however, that effort is delayed until facilities are required to track their injection performance. The NRC needs to reject the 1980 policy and no longer accept that extravasations are inconsequential and unavoidable. This will result in better quality of care to potentially hundreds of thousands of patients each year.

*Medical Event Classification and Reporting Criteria*

1. 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?

The first few benefits are related to the patient and the care that they will receive. Raising awareness and tracking lessons learned will improve the quality of nuclear medicine across the NMP. When things do go wrong, patients would now be informed of what happened and told what to look out for down the road. This way if adverse reactions do present, they can come back to the licensee for reporting and follow-up care.

Next, by disregarding the 1980 exemption, the NRC would take a regulatory action more aligned with other medical regulations and the Medical Policy Statement (MPS). For instance, why bother with dose calibrators and verifying dosages, if you are not concerned with half the injection ending up in the wrong tissue? The current medical event rule uses 50 rem as a performance based dose threshold for any other medical event, radiation dose is the same no matter if from a brachytherapy source or from a diagnostic RP. It does not follow that the dose from one source is any less important than from another; thus, both events should be equally significant to track for licensees and regulators. The MPS states that the NRC has a role in regulating the safety of patients, at least as much as assuring the treatment is delivered accurately and in accordance with the physician's directions. No physician would give directions to intentionally extravasate a patient.

Another benefit the NRC should consider is compatibility to agreement state positions. In March 2020, the Board polled the agreement states to understand their interpretation of the medical event rule. The survey request explained the NRC's exemption, but even so, 75% (24 of 32) of agreement state respondents would expect a nuclear medicine extravasation exceeding 50 rem to unintentionally impacted tissue to be reported as a medical event. Agreement state programs do not need to recognize the NRC's 1980 policy; however, it compromises the state's decision by having the federal authority issue an exemption. By accepting this petition for rulemaking, agreement states can engage with the NRC and other stakeholders to establish a rule that can be implemented consistently across the NMP.

The Board acknowledges that there will be a burden associated with monitoring and reporting extravasations as medical events. For some facilities this may already be happening and it will add minimal expense or time, others may have a heavier lift. The NMP will work to minimize these burdens and aim to reduce the RP extravasation rates to be as low as reasonably achievable. Improvement cannot be found through inaction.

2. 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)?

   Reporting criteria should remain consistent with current medical event regulations for therapies, no question. That said, to acknowledge the burden discussed above and the fact that almost every licensee will experience diagnostic extravasations, the NMP should consider different reporting approaches or timelines. More discussion is provided in the next answer.

3. 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?

   First, to reinforce the Board's earlier stated position, if 50 rem is the dose threshold for what is considered a medical event then any medical procedure causing that level of dose deposition to an unintended tissue should be subject to the rule. It should not matter the origin of that radiation; it was not ordered by a physician and it ended up in the wrong anatomical location.

   Second, the Board recognizes that there can be potentially hundreds of thousands of diagnostic extravasations every year. This would immediately dwarf any other type of reportable event; as such, the NMP needs to develop an appropriate method for licensees to monitor, record, analyze and report on extravasations. Perhaps for each extravasated patient a licensee would record the important details, suspected causes, and any lessons learned. Over a set period of time the licensee would track event frequency and note if they are trending up or down with their extravasation rates. Rather than report every time 50 rem is exceed for a diagnostic extravasation, they are bundled together, and it would be the frequency of extravasations at a facility that become reportable. This is where a new reporting criteria could be useful, one that emphasizes negative shifts in a licensee's performance rather than each and every diagnostic event. Licensees should improve their extravasation rates fairly rapidly if they start taking note of how and when it is happening.

   At present time, therapeutic RP extravasations happen infrequently enough that they should follow standard medical event response procedures.

The Board requests that the NRC accept the petition for rulemaking on extravasations. Until the rule can be finalized, the NMP will need to raise awareness, engage with stakeholders, and develop interim guidance. The Board is confident that through the rulemaking process we will arrive at the best solution for future regulation, and ensure that patients get the highest quality care. We look forward to working with the NRC on this issue. Please let us know if we can answer any additional questions or provide clarification to our responses.

Sincerely,

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