LUCERNO DYNAMICS, LLC
140 Towerview Court
Cary, NC 27513
919-371-6800

June 28, 2021

U.S. Nuclear Regulatory Commission
Attn: Rulemaking and Adjudications Staff
Washington, DC 20555-0001

Subject: Petition to Amend 10 C.F.R. § 35.3045

Dear Ms. Noto,

The petition for rulemaking (PRM)-35-22, submitted May 18, 2020, would revise 10 CFR Part 35 Subpart M to require reporting of radiopharmaceutical extravasations that meet existing reporting criteria.

Starting in December 2018 and continuing through the PRM-35-22 process, NRC has received an abundance of peer-reviewed evidence demonstrating that the rationale for the reporting exemption is no longer defensible – **extravasations can be prevented**. A recently published paper in the peer-reviewed journal *Health Physics* demonstrates that significant diagnostic and therapeutic radiopharmaceutical **extravasations can exceed existing reporting limits**.[1] Patients, patient advocates, elected officials, vascular access experts, and the Commission's own regulatory partner support PRM-35-22. Additionally, several physicists, nuclear medicine physicians, cardiologists, radiologists, and nuclear medicine technologists have also supported the petition, contrary to the position of their medical societies. All of these supporters know the exemption is unwarranted. They know that radiopharmaceutical extravasations happen frequently, can irradiate patients with high doses, can negatively affect diagnosis and treatment, and can be easily prevented through basic quality improvement activities.

Parties with a vested interest in maintaining the incorrect status quo have submitted statements to NRC in opposition to the petition. In response to these statements, several scientific and clinical experts with no fiduciary interest in the petition have identified inaccuracies, unsupported statements, and gross misrepresentations of evidence and literature by these parties.[2] A peer-reviewed paper published today, The Scientific and Clinical Case for Reviewing Diagnostic Radiopharmaceutical Extravasation Long-Standing Assumptions, also shows these opposition statements to be inaccurate.

The patient advocate on the NRC Advisory Committee on the Medical Uses of Isotopes (ACMUI) Subcommittee on Extravasation officially expressed a dissenting opinion in the October 2019 ACMUI report. She disagreed with the ACMUI recommendation to maintain the exemption and to consider extravasations the result of "passive patient intervention." She wrote that instances of extravasations above the current NRC reporting limit *"should be reported just as any other misadministration of such magnitude would be reported as [medical events]."* The "*current specific exclusion of extravasation is inconsistent with other regulation and unwarranted*."[3]

[1] Osborne D, Kiser JW, Knowland J, Townsend D, Fisher DR. Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements. Health Phys. 2021.
[2] Letter from Daniel Fass, MD; Darrell R. Fisher, PhD; Daniel Sullivan, MD; David Townsend, PhD; Jocelyn Grecia Hill; and Marjan Boerma, PhD. March 15, 2021, available at: https://www.regulations.gov/comment/NRC-2020-0141-0488.
[3] NRC ACMUI Subcommittee on Extravasation. *Final Report.* October 23, 2019.

LUCERNO DYNAMICS, LLC
140 Towerview Court
Cary, NC 27513
919-371-6800

We understand NRC medical staff is independently evaluating extravasations in response to the October 2019 ACMUI report, and these findings will help inform NRC's decision on PRM-35-22. While NRCs review should be thorough, time is of the essence. Every day hundreds of patients are significantly extravasated in the United States, resulting in irradiation above the current medical event reporting limit. This current limit represents an absorbed tissue dose 500 times higher than the tissue dose that results from properly administered radiopharmaceuticals. NRC has consistently maintained that medical events exceeding this limit suggest a potential problem in the handling of byproduct material.

Examples of patient cases exceeding the current reporting limits have been submitted as part of PRM-35-22 and in supplemental communications. However, the indefensible inconsistency created by the extravasation reporting exemption is clearly illustrated in the comparison of three cases below.

Case	A	B	C
Location	Vanderbilt	Fox Chase Cancer Center*	Sanford Medical Center
Isotope	Lutetium-177	Lutetium-177	Fluorine-18
Medical Intent	Therapeutic	Therapeutic	Diagnostic
Event Description	**Leak on patient**	**Extravasation in patient**	**Extravasation in patient**
Extravasated Activity	Not reported	85-206 mCi	10 mCi
Skin Dose	**7 Gy** to peri-labial skin	**18 Gy** to 10 cm^2 of arm skin	**3.3 Gy** to 10 cm^2 of arm skin
Tissue Dose	**Not calculated**	**161 Gy** to 11.5 cm^3 of tissue	**6.5 Gy** to 5 cm^3 of tissue
Clinical Follow-up	Skin injury	No Clinical Follow-up	No Clinical Follow-up
Reporting Status	Reported	Retracted†	Retracted
Source	2019 Event Notification	Public Presentation	Retracted Event Notification

***** Fox Chase public presentation and our analysis are attached.
† Pennsylvania notification of event retracted per public presentation.

Each of these cases in the table above resulted in tissue exposure or irradiation that significantly exceeded the reporting limit. Yet, because of the exemption, only the radiopharmaceutical leak ***on a patient*** (Case A) was a reportable medical event. Significant radiopharmaceutical extravasations ***in patients*** (Cases B and C, as well as those provided with PRM-35-22) were not reported because of the existing exemption policy.

As serious as the extravasation was in Case B, more concerning is the fact that the radiation safety officer (RSO) demonstrated the same misunderstanding of regulations and scientific principles highlighted in the previously cited Dr. Fass Letter. This RSO assumed all 206 mCi of Lutathera had been extravasated yet did not determine the absorbed dose to the patient's arm tissue and stated during a public presentation that nothing could be learned by reporting this case. NRC should provide regulatory guidance so that practitioners who do not understand the risk from extravasations will protect patients.

Significant extravasations can clearly exceed the current medical event reporting criteria and harm patients, yet they continue to go unreported. Though this patient protection issue has been brought before the medical staff numerous times (December 2008 and May 2009 ACMUI meetings, as well as multiple communications from Lucerno since December 2018), the issue is not being resolved with the immediacy warranted. NRC should follow the guidance of the U.S. Congress to *"complete its evaluation of the inconsistent approach to medical event reporting expeditiously*."[4]

[4] Energy and Water Development and Related Agencies Appropriations Bill, 2021. Enacted through P.L. 116-260.

LUCERNO DYNAMICS, LLC
140 Towerview Court
Cary, NC 27513
919-371-6800

Hundreds of patients are experiencing significant extravasations every day in the United States. NRC should accept the Organization of Agreement States (OAS) conclusion that the 1980 exemption is "no longer appropriate." By following the OAS suggestion to approve the petition and move to rulemaking immediately, "*NRC could make a policy decision to drastically improve the health, safety, and clinical outcomes for hundreds of thousands of patients a year*."[5]

Sincerely,

Ronald K. Lattanze

Digitally signed by Ronald K. Lattanze
DN: cn=Ronald K. Lattanze, o=Lucerno Dynamics, LLC, ou, email=rlattanze@lucernodynamics.com, c=US
Date: 2021.06.28 15:48:36 -04'00'

Ronald K. Lattanze

Cc: Chairman Christopher T. Hanson
Commissioner Jeff Baran
Commissioner David A. Wright
Kevin Williams, Director, Division of Materials Safety, Security, State & Tribal Programs
David Crowley, Chairman, Organization of Agreement States

Attachments:
1. Fox Chase Cancer Center presentation (separate file)
2. Fox Chase Cancer Center Lutathera extravasation analysis

[5] Public comment by Organization of Agreement States to PRM-35-22. November 30, 2020.

Analysis of Fox Chase Cancer Center's "Lutathera® (Lu-177) Extravasation Event" Presentation

Josh Knowland*

On June 9, 2021, the Delaware Valley Society for Radiation Safety, a local chapter of the Health Physics Society, held the 2021 Robert Forrest Memorial Medical Health Physics Symposium. Kendall Berry, the Radiation Safety Officer at Fox Chase Cancer Center (Philadelphia PA) and a member of the Health Physics Society's Board of Directors, reported on a case of extravasation during infusion of Lutathera® (Lutetium-177 Dotatate, Advanced Accelerator Applications, Millburn NJ USA).

The presentation may be the first of its kind in terms of identifying and assessing an extravasation of Lutathera, but it could be improved in several areas. The objective of this work was to analyze the Fox Chase presentation, identify areas for improvement, and discuss their decision to not report this extravasation as a medical event.

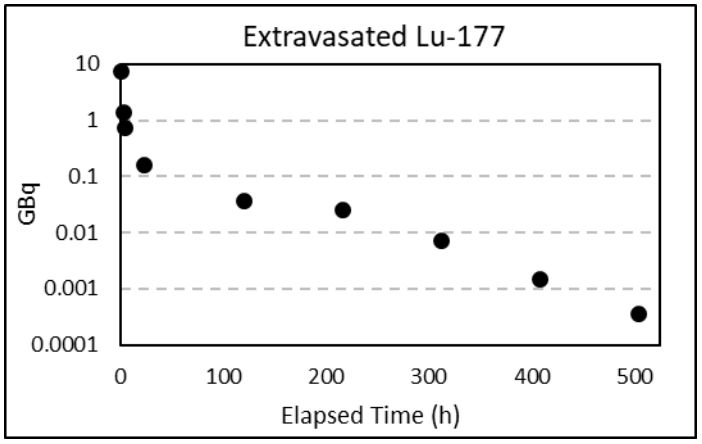

Figure 1. Presented values for extravasated activity.

Presentation Synopsis

On November 12, 2020, a patient was infused with 7.66 GBq Lu-177 along with 150 mL of saline. The infusion process was performed through peripheral IV and lasted 30 minutes.

Following the infusion, the patient complained of pain at the IV site and a raised "bump" was present. The medical team suspected extravasation and began mitigations (compression, elevation, and application of heat) within 90 minutes.

The team performed skin-contact dose-rate measurements and whole-body gamma camera imaging. For several days, dose-rate measurements and imaging were repeated to estimate the rate of biological clearance of the extravasate.

Within 24 h of the event, Pennsylvania radiation protection officials were notified that this event may have met the medical event reporting threshold. The presenter indicated that even though they know that extravasations are federally exempted from medical event reporting (*1*), they have a good relationship with the regulators and wanted to be open and honest about the event. The team estimated the extravasated radioactivity over time (**Figure 1**) using skin-contact measurements from a Model 451P ionization chamber (Fluke Biomedical, Cleveland, OH). The measurements were calibrated against a vial containing 0.12 GBq Lu-177. Based on dosimetry methods proposed by Bonta et al. (*2*), the team then calculated skin absorbed dose over time (**Figure 2**).

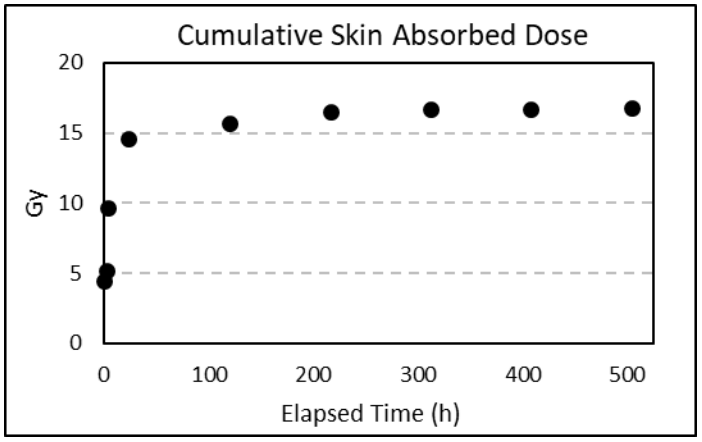

Figure 2. Presented values for skin dose. The assumed area and mass for the critical target (basal cells) was not addressed.

The presentation included a conversion of skin absorbed dose into units of effective dose by dividing the calculated value by 100 (*3*). The resulting effective dose, 0.16 Sv, was then used as justification to retract the previously submitted medical event notification. Two audience attendees questioned whether this conversion was appropriate for cases of extravasation and suggested that absorbed dose or dose equivalent should be used instead. When the presentation slides were electronically distributed to attendees following the presentation, the slides had been edited to remove the effective dose conversion and only included the skin absorbed dose of 17 Gy.

* Josh Knowland is an engineer with over 14 years of experience designing technology to improve the safety and effectiveness of diagnostic and therapeutic medical radiation. He is currently the VP of Product Development at Lucerno Dynamics.

The presenter indicated that the patient passed away not long after this incident (unrelated to the extravasation), so no information was available concerning adverse skin or tissue effects.

Following the extravasation event, the Fox Chase medical team developed a process for promptly identifying extravasations so that mitigations may be started as soon as possible. They referred to a database of typical skin-contact dose-rates obtained from non-extravasated Lutathera infusions.

Review and Analysis

The dosimetric portion of the presentation demonstrated a misunderstanding of basic dosimetry principles and their consequences for regulatory compliance. The Fox Chase calculated skin absorbed dose was 17 Gy, representing more than thirty-two times the medical event reporting threshold[†]. In addition to skin dose, a significant volume of arm tissue was infiltrated with Lutathera. But the Fox Chase presentation failed to recognize earlier publications showing that dose to infiltrated tissue can be significantly higher than to the skin (*4,5*).

Figure 3 shows analysis of the biological (decay-corrected) clearance of the Lutathera extravasation, which was found to fit a bi-exponential function using linear least-squares regression analysis (**Eq. 1**).

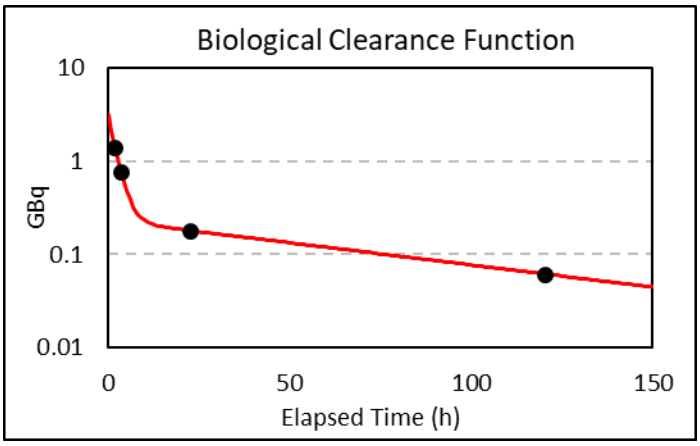

Figure 3. Bi-exponential fitting to the Fox Chase data.

$$A(t) = A_{early} * 2^{\left(\frac{-t}{T_{early}}\right)} + A_{late} * 2^{\left(\frac{-t}{T_{late}}\right)} \qquad \textit{Eq. 1}$$

The parameters of the function indicated an early half-time of 1.45 h and a long-term retention half-time of 63.4 h. This function was consistent with patient images obtained at early and late timepoints.

Considering the physical half-life of Lu-177 (160.8 h) and the biological clearance function, the effective time-activity function (**Eq. 2**) was determined for dosimetry calculation. This function indicated that initial activity in the arm tissue was 3.17 GBq.

$$A(t) = A_{early} * 2^{\left(\frac{-t}{T_{early}}\right)} + A_{late} * 2^{\left(\frac{-t}{T_{late}}\right)} * 2^{\left(\frac{-t}{T_{1/2}}\right)}$$

$$A(t) = 2.94 * 2^{\left(\frac{-t}{1.45}\right)} + 0.23 * 2^{\left(\frac{-t}{63.4}\right)} * 2^{\left(\frac{-t}{160.8}\right)}$$

$$A(0) = 3.17\ GBq \qquad \textit{Eq. 2}$$

Integration of **Eq. 2** resulted in the time-integrated activity within the source tissue, or cumulated activity, of 21.4 GBq·h (**Eq. 3**).

$$Cumulated\ Activity \cong \sum_{i=0}^{n-1} A(t_i) * \Delta t$$

$$\cong 21.4\ GBq \cdot h \qquad \textit{Eq. 3}$$

Using the presented patient images, geometry, volume, and mass (assuming a tissue density of 1 g/cm^3) for the infiltrated region of arm tissue were calculated by referencing to a known average head size for adult US males (*6*). The estimate for the volume of infiltrated tissue was 11.5 cm^3.

Using the methods of Osborne et. al. (*4*), absorbed doses to both infiltrated arm tissue and the sensitive basal cell layer of overlying skin were calculated. The chosen skin surface area of 10 cm^2 is consistent with regulatory guidance[‡]. For infiltrated arm tissue, self-dose was calculated using the *Spheres* module of the internal dosimetry software IDAC Dose (*7*). **Figure 4** depicts the position and geometry of tissue and skin used for these calculations.

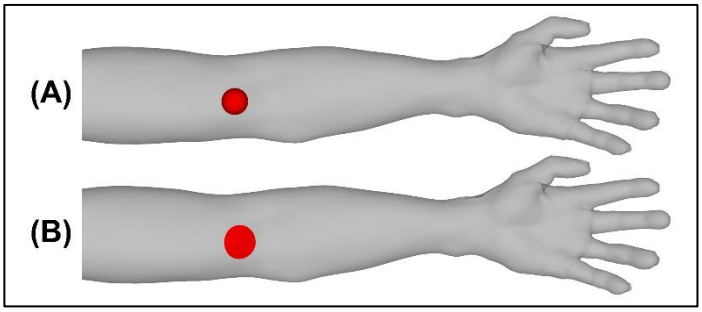

Figure 4. Representations of the tissue volume (A) and skin area (B) used for absorbed dose calculations.

[†] 10 C.F.R. § 35.3045 - Report and notification of a medical event.

[‡] 10 C.F.R. § 20.1201(c) - Occupational dose limits for adults

Using these methods, absorbed doses were found to be 0.88 Gy per unit GBq·h for basal layer skin and 7.53 Gy per GBq·h for infiltrated arm tissue. Knowing the initial infiltration activity, **Eq. 4** and **Eq. 5** were used to calculate the absorbed dose to skin and infiltrated tissue.

$$Skin\ Dose = 21.4\ GBq\ hr * 0.88\ Gy/\ GBq \cdot hr = 18.8\ Gy \quad \textit{Eq. 4}$$

$$Tissue\ Dose = 21.4\ GBq\ hr * 7.53\ Gy/\ GBq \cdot hr = 161\ Gy \quad \textit{Eq. 5}$$

Conclusion

Based on the presented activity measurements, calculated doses were 18.8 Gy to 10 cm^2 of skin and 161 Gy to 11.5 cm^3 of underlying tissue. These results are based on reasonable assumptions using the available data and are not worst-case scenarios.

The calculated skin dose compares well to the value reported by Fox Chase. However, the more important dose is that to infiltrated tissue (161 Gy), which was not reported by Fox Chase.

Regarding the Fox Chase team's use of the Model 451P ionization chamber for determination of extravasated activity, the reader should be cautioned. This meter is specified for detection of beta radiation above 1 MeV, which is well above the beta emissions for Lu-177 (maximum 0.498 MeV, average 0.149 MeV). The method that the Fox Chase team described should provide reasonable relative measurements, but this meter would not be appropriate for measuring skin dose directly as the beta emissions that are responsible for most of the absorbed dose could not be detected.

These results indicated the importance of extravasation characterization, dosimetry, and follow-up. Not only should institutional procedures be put into place concerning extravasation response and mitigation, but the underlying causes should be determined. Through root-cause analysis and dissemination of pertinent findings, these types of events can be avoided. Regulatory reporting of serious extravasation events is one mechanism to aid in this process.

Fox Chase calculated effective dose to the skin and used it as the basis for non-reporting. The problem with using effective dose as a surrogate to risk is that it is not applicable to therapy, short term deterministic effects, or medical exposures (*8*). Effective dose is a forward-thinking concept for risk of cancer many years into the future. Furthermore, it is always a whole-body dose calculation and should not be applied partially, for instance to areas of skin.

Although they have since edited their presentation, it was clear that the Fox Chase team decided to retract their initial medical event notification based on an inappropriate conversion to effective dose. Through the Organization of Agreement States, most states in the US share regulatory oversight and enforcement responsibilities with the Nuclear Regulatory Commission (NRC). Because the NRC's extravasation reporting exemption is based on an internal policy—not Federal regulation—these states may still expect serious extravasations to be reported as medical events. Although the Fox Chase team may have now realized that effective dose should not be used for extravasation dosimetry, it is unknown whether they have reinstated their initial medical event notification. They should do so and should begin building a *public* database of events, their significance, and ways to improve the infusion process for Lutathera.

References

1. Federal Register. Vol 45: United States Federal Government; 1980:31701-31705.
2. Bonta DV, Halkar RK, Alazraki N. Extravasation of a therapeutic dose of 131I-metaiodobenzylguanidine: prevention, dosimetry, and mitigation. *J Nucl Med.* 2011;52:1418-1422.
3. ICRP publication 103: The 2007 Recommendations of the International Commission on Radiological Protection. *Ann ICRP.* 2007;37:1-332.
4. Osborne D, Kiser JW, Knowland J, Townsend D, Fisher DR. Patient-specific Extravasation Dosimetry Using Uptake Probe Measurements. *Health Phys.* 2021.
5. Tsorxe IY, Hayes RB. *Dose Estimation for Extravasation of 177-Lu, 99m-Tc, and 18-F*: North Carolina Policy Collaboratory; 2021.
6. Young JW. Head and Face Anthropometry of Adult US Civilians. In: Transportation UDo, ed: Civil Aeromedical Institute, Federal Aviation Administration; 1993.
7. Andersson M, Johansson L, Eckerman K, Mattsson S. IDAC-Dose 2.1, an internal dosimetry program for diagnostic nuclear medicine based on the ICRP adult reference voxel phantoms. *EJNMMI Res.* 2017;7:88.
8. Fisher DR, Fahey FH. Appropriate Use of Effective Dose in Radiation Protection and Risk Assessment. *Health Phys.* 2017;113:102-109.