UNITED STATES
NUCLEAR REGULATORY COMMISSION
OFFICE OF NUCLEAR REACTOR REGULATION
OFFICE OF NUCLEAR MATERIAL SAFETY AND SAFEGUARDS
WASHINGTON, DC 20555-0001

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NRC INFORMATION NOTICE 2024-04: RECENT MEDICAL EVENTS INVOLVING ADMINISTRATION OF THERAPEUTIC RADIOPHARMACEUTICALS

ADDRESSEES

All U.S. Nuclear Regulatory Commission (NRC) medical-use licensees and master materials licensees that are authorized for medical use under Title 10 of the *Code of Federal Regulations* (10 CFR) 35.300, "Unsealed Byproduct Material—Written Directive Required." All Agreement State Radiation Control Program Directors and State Liaison Officers.

PURPOSE

The NRC is issuing this information notice (IN) to inform licensees of recent reported medical events that involved the administration of therapeutic radiopharmaceuticals. The NRC expects that recipients will review the information for applicability to their facilities and consider actions, as appropriate, to avoid similar medical events. INs may not impose new requirements, and nothing in this IN should be interpreted to require specific action. The NRC is providing this IN to the Agreement States for their information and for distribution to their medical licensees, as appropriate.

DESCRIPTION OF CIRCUMSTANCES

Licensees are required to report medical events that meet the criteria defined in 10 CFR 35.3045, "Report and notification of a medical event," except those that result from patient intervention. While a medical event rarely means that a patient has been harmed, it is important to minimize the number of events, as they have the potential to cause harm and may indicate a potential problem with how a medical facility administers radioactive materials. The purpose of reporting medical events is to identify their causes in order to correct them, prevent their recurrence, and allow the NRC to notify other licensees so they can avoid similar incidents. Both the NRC staff and the Advisory Committee on the Medical Uses of Isotopes (ACMUI) regularly review medical event reports to identify generic issues or concerns and to recognize any inadequacies or the unreliability of specific equipment or procedures. The NRC staff and the ACMUI present their findings at biannual ACMUI meetings. The presentations from recent years are posted on the NRC Medical Uses Licensee Toolkit webpage at https://www.nrc.gov/materials/miau/med-use-toolkit.html.

Over the past few years, the number of radiopharmaceuticals approved by the U.S. Food and Drug Administration (FDA) and undergoing clinical trials has increased. With this additional usage, the NRC staff has identified an increase in reports of medical events involving therapeutic radiopharmaceuticals, with 29 events occurring from fiscal years 2021 through 2023. Many of these reports involve new therapeutic radiopharmaceutical procedures. The root

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causes of these reports include, 1) failure to confirm the written directive (i.e., prescribed) activity before delivering the dosage, 2) incorrect setup or administration procedures, and 3) failure to train staff involved in the handling and administration of the radiopharmaceuticals before first usage.

Eight of the reported medical events were associated with failure to confirm the written directive (i.e., prescribed) activity before delivering the dosage. Two of the new therapeutic radiopharmaceuticals recently approved by the FDA, Lutathera® (lutetium Lu-177 dotatate) and Pluvicto® (lutetium Lu-177 vipivotide tetraxetan), have standard dosage protocols of 7.4 gigabecquerels (GBq) (200 millicuries (mCi)). However, their package inserts recommend reducing the prescribed activity to 3.7 GBq (100 mCi) based on the patient's kidney function from laboratory results. Examples of these events are provided below.

- Many events involved patients being given the full standard dosage of 7.4 GBq (200 mCi) when the authorized user (AU) prescribed a reduced dosage on the written directive based on the patient's laboratory results.
- One event occurred when a patient was scheduled to receive 3.47 megabecquerels (MBq) (27.1 microcurie (µCi) of Xofigo® (radium (Ra)-223 dichloride); however, the patient presented with low blood pressure on the day of treatment, and the licensee cancelled the procedure. When returning 1 month later, the patient received the dosage from the original vial, which had decayed, resulting in an underdosage of 0.63 MBq (17.0 µCi).
- Another event involved switched radiopharmaceuticals for two patients receiving treatment on the same day. One patient was to receive 7.4 GBq (200 mCi) of Pluvicto® but received the other patient's dosage of 7.4 GBq (200 mCi) of Lutathera®. The patient who was to receive Lutathera® received the other patient's dosage of Pluvicto®. To avoid reoccurrence, this licensee implemented corrective actions by scheduling treatments with these radiopharmaceuticals on different days.

Newer radiopharmaceuticals protocols are more complex and may include multiple steps within and outside the department which administers the radiopharmaceutical. Furthermore, there are more drug interactions that may change the biokinetics of the radiopharmaceuticals, which can impact the dose to the treatment site or other organs and tissues. While not all incidents involving scheduling or drug interference are reportable under NRC regulations, two recent incidents met the NRC criteria for reporting under 10 CFR 35.3045. These examples are provided below.

- One incident involved a Lutathera® administration where the patient informed the AU that they received an octreotide injection the day before the treatment. Per the prescribing information for Lutathera, short-acting octreotides should be discontinued at least 24 hours before each dose. Therefore, the AU immediately stopped the administration, which led to the patient receiving a lesser dose than that prescribed in the written directive.
- In another incident, a nuclear medicine technologist realized approximately 20 minutes after a Lutathera administration began that the patient was not being administered the amino acid infusion because the infusion line was still clamped. Per the prescribing information for Lutathera, an amino acid solution is administered before, during, and after the Lutathera administration to decrease the radiation dose to the kidneys. The technologist started the amino acid infusion at that time, but the licensee calculated that

the kidneys received an estimated dose of 740 centisieverts (cSv) (rem) instead of the intended 490 cSv (rem).

The root cause of both these events was found to be inadequate training of staff, including those outside the nuclear medicine department, on the various steps of a Lutathera administration, and lack of confirmation from the nuclear medicine staff that the protocol was being followed before starting the radiopharmaceutical administration.

Other medical events have been associated with inadequate equipment setup.

- In one event, a nurse removed an occluding clamp and opened the roller clamp on a flush bag at the beginning of an iodine (I)-131 Iomab-B-treatment. This led to a leak in an infusion system tube and resulted in the patient receiving only 53 percent of the prescribed dose.
- One event involved an incorrect cap placed on the unused port of a three-way stopcock during a Ra-223 Xofigo administration. The incorrect cap was designed to maintain sterility of the port connection but allowed flow out of the unused port. The correct cap should have prevented flow. The incorrect cap caused leakage during administration that resulted in the patient receiving only 3 percent of the prescribed dose.
- In one event, the treatment apparatus that the licensee normally used for Lu-177 Pluvicto® treatment was unavailable, so the licensee used another apparatus for two patient infusions. During the infusions, the licensee noticed leaks from the vials into the shielding container. The licensee believed the leaks happened because the replacement apparatus pressurized the vials for administration, unlike the apparatus the manufacturer recommends. This incident led to the underdose of two patients, with 60 and 64 percent of the prescribed doses being received.
- Three events associated with infusion tubing led to patients receiving less than 80 percent of the prescribed dose due to leakage although no setup issues were noted in those reports. One report involved a leak in an infusion tube; the licensee stated that other tubing in the same lot also had leakage. In another example, a patient reported their hand felt wet during a Lu-177 Lutathera administration, and the licensee discovered a leak at the connection between the syringe pump and patient's IV site. The licensee believed the connection was not secure and had become partially undone during the injection. This event resulted in the patient receiving only 70–75 percent of the prescribed dose.

Additional underdose medical events were associated with lack of adherence to procedures. These events are summarized below.

- Two events were associated with an inadequate volume of saline used to flush tubing. This event led to patients receiving 69 and 39 percent of their prescribed doses due to increased residual activity in the tubing.
- One event was associated with I-131 sodium iodine thyroid ablation therapy. The prescribed activity was divided into two capsules, but the patient only took one. In this event, the administration staff failed to notice that one of the capsules remained in the original vial such that the patient received 20 percent of their prescribed dose.

Licensees reported failure to follow procedures as a root cause in all these events, and one of the corrective actions was to ensure adequate training of the administration staff to ensure all aspects of the procedure would be followed in the future.

DISCUSSION

This IN is intended to provide licensees with a heightened awareness of recent medical events involving therapeutic radiopharmaceuticals. In accordance with 10 CFR 35.41, “Procedures for administrations requiring a written directive,” licensees are required to develop, implement, and maintain written procedures to provide high confidence that each administration is in accordance with the written directive for any therapeutic radiopharmaceutical administration. When licensees are considering adding new treatment protocols to their clinic, they should update the procedures to ensure that the new therapeutic radiopharmaceuticals can be administered in accordance with the written directive. Licensees are encouraged to consider the medical events experience provided here in the development of these procedures.

Many of the medical events show the importance of validating the written directive information immediately before administration. The use of time outs, as recommended in IN 2019-07, “Methods to Prevent Medical Events,” dated August 26, 2019 (ML19240A450), to review the process, procedure, and material being administered can be an effective method to prevent these incidents. It is especially important to verify that the correct radiopharmaceutical is being administered to the patient. For example two of the newly FDA-approved radiopharmaceuticals have a standard dosage of 7.4 GBq (200 mCi) of Lu-177, but are used to treat different indications. In addition, these events show the importance of checking the prescribed activity on the written directive, as both of these pharmaceuticals have a standard dose that the AU may change based on the medical needs of the patient.

Finally, these medical events illustrate the importance of training staff on new procedures and setup before treating the first patients. Licensees should consider which staff members may be involved in the procedures to ensure they have the necessary training. Mock runs before treating the first patient may minimize the risk of medical events associated with inadequate setup. To prevent incidents involving a failure to adhere to administration protocols, licensees could consider providing training for all staff involved in these procedures, including protocol and administration staff. In addition, the nuclear medicine staff should confirm protocols are being followed before the administration of the radiopharmaceutical. Licensees are encouraged to communicate with their peers in the industry or with manufacturers to identify additional best practices to minimize the potential for medical events, especially when they begin using a new radiopharmaceutical, equipment, or protocol.

PAPERWORK REDUCTION ACT STATEMENT

This IN does not contain new or amended information collection requirements that are subject to the Paperwork Reduction Act of 1995 (44 U.S.C. 10 CFR 3501 et seq.). Existing requirements were approved by the Office of Management and Budget (OMB) under approval control number 3150-0010.

PUBLIC PROTECTION NOTIFICATION

The NRC may not conduct or sponsor, and a person is not required to respond to, a collection of information unless the document requesting or requiring the collection displays a currently valid OMB control number.

CONTACTS

This IN requires no specific action or written response. Please direct any questions about this matter to the technical contact listed below or to the appropriate regional office.

/RA/

Russell Felts, Director
Division of Reactor Oversight
Office of Nuclear Reactor Regulation

/RA/

Kevin Williams, Director
Division of Materials Safety, Security, State, and Tribal Programs
Office of Nuclear Material Safety and Safeguards

Technical Contact: Katie Tapp, NMSS
E-mail: Katherine.Tapp@nrc.gov

Note: NRC generic communications may be found on the NRC public website, http://www.nrc.gov, under NRC Library/Document Collections.

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DATE	8/9/24					

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