UNITED STATES
NUCLEAR REGULATORY COMMISSION
OFFICE OF NUCLEAR MATERIAL
SAFETY AND SAFEGUARDS
WASHINGTON, DC 20555

December 23, 2019

NRC INFORMATION NOTICE 2019-11: STRONTIUM-82/RUBIDIUM-82 GENERATOR ELUTION EVENTS AND ISSUES

ADDRESSEES

All U.S. Nuclear Regulatory Commission (NRC) medical-use licensees and NRC master materials licensees. All Agreement State Radiation Control Program Directors and State Liaison Officers.

PURPOSE

The NRC is issuing this information notice (IN) to alert addressees of four strontium (Sr)-82/rubidium (Rb)-82 generator elution events that resulted in patients receiving greater activities of Sr-82 and Sr-85 than those permitted under the concentration criteria in Title 10 of the *Code of Federal Regulations* (10 CFR) 35.204, "Permissible molybdenum-99, strontium-82, and strontium-85 concentrations." The NRC expects that recipients will review the information for applicability to their facilities and consider actions, as appropriate, to avoid similar events. Information contained in this IN does not constitute new NRC requirements; therefore, no specific action or written response is required. 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

In 2011 and 2018-2019, Nevada, Florida, Colorado, and Kentucky licensees reported four separate events involving approximately 90 patients being administered Rb-82 chloride (Cl) for cardiac imaging containing Sr-82 and Sr-85 concentrations exceeding regulatory limits. None of the licensees identified breakthrough of Sr-82 (parent radionuclide) and Sr-85 (production contaminant) in the generator elutions before the administrations. Patients in two of these events exceeded the medical event criteria in 10 CFR 35.3045, "Report and notification of a medical event."

2011 Strontium Breakthrough Events—Caused by Excessive Elutions

The U.S. Department of Homeland Security personnel identified both of the 2011 Nevada and Florida events months later when a patient from each State returned to the United States with detectible radiation levels long after their cardiac scans. The patients were not expected to have detectable levels of radiation at the time of their travel because the half-life of Rb-82 Cl is 76 seconds. The isotopes detected were Sr-82 and Sr-85, with half-lives of 25.3 and 64.8 days, respectively.

ML19281A220

The Nevada Event

In Nevada, the Radiation Control Program (RCP) staff discovered that the licensee did not perform breakthrough tests every day. In addition, the breakthrough test result on the day that the sentinel Nevada patient was scanned did not indicate breakthrough. To determine the extent of the breakthrough problem, the Nevada RCP staff worked with the licensee to contact the local patients who either were administered Rb-82 Cl on the day before or the week after the sentinel patient was injected or were imaged on days when the licensee did not record breakthrough information. By the time the Nevada RCP finished, the number of patients surveyed increased significantly to over 120 patients, all of whom were surveyed for Sr-85 using a portable germanium/lithium isotope detector. The RCP staff calculated that more than 70 patients received more than the permitted Sr-85 concentration criteria of 0.2 microcuries of Sr-85 per millicurie of Rb-82 from two different Sr-82/Rb-82 generators. Over 30 patients were also counted later in a whole-body counter. Even though the whole-body counting was performed 8 to 9 months after the administrations (10 to 11 half-lives later for Sr-82 and 3 to 4 half-lives later for Sr-85), all patients exceeded the Sr-82 breakthrough criteria by 24 to 306 times and the Sr-85 criteria by 2 to 34 times. The sentinel patient received an estimated dose of 4.8 rem, and three other patients received estimated doses of more than the medical event reporting criteria of 5 rem effective dose equivalent.

The Florida Event

In Florida, the Bureau of Radiation Control also inspected the facility of the sentinel Florida patient and other licensees authorized for Sr-82/Rb-82 generators. Review of the quality control records at the Florida site for the 15 days that included the day the sentinel patient was imaged revealed that a value of “0” was entered for each breakthrough measurement. This led to calculated breakthrough values of “0” microcuries for both Sr-82 and Sr-85. As indicated in the whole-body counting data, the Sr values were a total of 40 microcuries of Sr-82 and 73 microcuries of Sr-85. The dose calibrator needed to be manually switched from millicuries to microcuries before measuring the decayed vial. Failure to switch the dose calibrator resulted in readings of “0,” which in turn resulted in the licensee’s failure to identify the Sr-82 and Sr-85 breakthrough. Multiple individuals performed the breakthrough measurements and calculations during this 15-day period, and each performed the test in the same manner.

The sentinel patient and six others who were imaged before and after the sentinel patient were sent for whole-body counting to determine the residual amounts of strontium. The whole-body counting was performed 6 to 8 months after the initial Rb-82 administration (7 to 10 Sr-82 half-lives later and 3 to 4 Sr-85 half-lives later). Each of these patients received 7 to 36 times the permissible activity of Sr-85. Most of the Sr-82 had decayed to background, but three patients had measurable Sr-82 levels that exceeded the permissible activity of Sr-82 by 40 to 115 times. The sentinel patient had an estimated dose of 1.6 rem, and the two patients with the highest doses received estimated doses of 3.1 and 3.8 rem. Therefore, none of these patients’ doses exceeded the medical event criteria.

Because of these two events, the U.S. Food and Drug Administration (FDA) issued a Drug Safety Communication, and the manufacturer voluntarily recalled its generators. The manufacturer determined that the root cause for the generator failures was overuse of individual generators. The two facilities with breakthrough events had the highest patient throughput of all the generator users. Before these events, there was no indication in the generator labeling that the generators could fail if the total eluent was too high. The manufacturer revised its FDA-accepted labeling to restrict the total eluent volume, increased the frequency for

performing the breakthrough measurements if the required daily pre-patient breakthrough value exceeded 10 percent of the breakthrough value, developed and distributed standardized breakthrough calculation sheets, and retrained all customer personnel responsible for the breakthrough test on how to perform the test correctly.

2018–2019 Strontium Breakthrough Events—Wrong Eluent

The two newer events in Colorado (2018) and Kentucky (2019) involved the wrong eluent. Both licensees were using the new standardized breakthrough calculation forms that were designed to identify breakthrough events before patient administrations. However, both failed to identify the breakthrough before administering Sr-82 and Sr-85 in excess of the criteria in 10 CFR 35.204 because their completed forms indicated there was no breakthrough.

The Colorado Event

In Colorado, eight patients were administered Sr-82 and Sr-85 in excess of the criteria in 10 CFR 35.204. The event was identified 3 days after a bag of Ringer's lactate intravenous (IV) fluid was inadvertently used as the eluent. The licensee verified the duration of the event by surveying patients treated the day before the Ringer's lactate was used as well as patients treated during the 3 days after its use. The licensee found that only the patients treated the day before the Ringer's lactate was used had radiation readings indistinguishable from background. Later, the root cause of the generator failure was determined to be the use of Ringer's lactate on day one as the eluent. Sterile saline was used on days 2 and 3, but the generator was already compromised and releasing Sr-82 and Sr-85 in the eluate.

The licensee performed the breakthrough tests on each of the 3 days that patients were later found to have excess strontium in their administrations. The test on each of these 3 days was performed by a different experienced individual who completed the manufacturer's breakthrough training 3 to 7 years before the event. A review of the quality control records for the breakthrough test showed that the recorded data for the decayed vial were consistently between 0.01 and 0.02 for each day, subsequent calculations were performed appropriately, and the data were reasonable when compared with previous entries. Therefore, the licensee concluded that no breakthrough occurred for each of the 3 patient treatment days. On the third day, the routine area survey of the hot lab, performed after all patient treatments were completed, indicated unexpected readings above background. The next day, the licensee discovered that the higher-than-expected area survey results resulted from above-background readings from the quality control vials used to determine breakthrough. The breakthrough vial measurement on the fourth day was elevated, and the generator was taken out of service.

Once the strontium breakthrough was identified, the licensee used the quality control vials to estimate the maximum breakthrough for the appropriate day and estimate the dose to each patient from the Sr-82 and Sr-85 in their Rb-82 Cl administrations. The estimated activity levels administered to each patient ranged from 1,000 to 2,000 microcuries of Sr-82 and 700 to 1,300 microcuries of Sr-85. The eight patients received doses that ranged from 27 to 53 rem effective dose equivalent. These doses were 5 to 10 times greater than the medical event criteria in 10 CFR 35.3045.

The staff of the Colorado Department of Public Health and the Environment determined that the licensee knew how to perform the breakthrough tests but that inconsistencies existed among individuals at the facility about how to handle the dose calibrator readings. For example, one individual always entered a value of 0.2 because of fluctuations in the reading, one individual

"zeroed out" the dose calibrator when getting "erroneous readings," and another said the particular dose calibrator could not be "zeroed out." Another individual said that because the numbers displayed by the dose calibrator were within the expected values that the units being displayed were "not observed" and recorded in microcuries when the values were really in millicuries. This was confirmed for the data recorded on the quality control sheet on the day of the inspection, which were too low by a factor of 1,000. This shows that even experienced individuals are capable of taking actions that result in the failure to recognize the occurrence of breakthrough.

The Kentucky Event

In Kentucky, four patients were imaged on a single day. The licensee noted that the eluate volumes were decreasing slightly for each patient but the activity was the same and reported this to the manufacturer. The next day, the routine quality control procedures indicated Sr-82 breakthrough of 18.6 microcuries instead of the expected value of less than a microcurie. The manufacturer asked the licensee to check the IV fluid bag used for the elution, and the licensee discovered that Ringer's lactate instead of sterile saline had been used the preceding day. The generator was taken out of service.

If 18.6 microcuries had been administered to a patient, the patient would have received a dose of 0.44 rem. Therefore, none of the four patients was estimated to have received an effective dose equivalent that exceeded the medical event criteria in 10 CFR 35.3045. The licensee determined the hospital distributor accidently stocked the Ringer's lactate in the cardiology department.

One of the four patients was still in the hospital the next day and was surveyed with a Geiger-Mueller detector in the vicinity of the sternum and spine. The radiation levels were indistinguishable from background.

DISCUSSION

Medical-use generators, such as those used to produce Rb-82 Cl, are produced and eluted using mechanical and chemical processes, and all generators can fail but rarely do. The manufacturer did not anticipate that licensees would image the number of patients seen at the Nevada and Florida sites and did not warn the FDA or the licensees about the high probability of breakthrough after exceeding a total eluent volume. The manufacturers did warn the licensees about the need to use additive-free sterile sodium chloride.

Because generators rarely fail, licensees may be used to seeing only negative results from the breakthrough test every day and may expect to continue to see negative results in the future. It is easy to conclude that the test is unnecessary and could be skipped. These four Rb-82 events show that the breakthrough test is important and must be performed each day (under the provisions of 10 CFR 35.204) and the data must be correctly collected and analyzed to prevent the administration of the parent radionuclide Sr-82 and the contaminant Sr-85.

Performing the test every day, performing it correctly, and properly analyzing the results are important in preventing Rb-82 Cl with excess Sr-82 and Sr-85 from being administered to patients. In the cases described, approximately 90 patients were identified after the fact as being administered excess Sr-82 and Sr-85. In addition to receiving additional unintended total radiation doses, these patients also received higher doses to unintended organs. The organ receiving the largest unintended dose is the red marrow.

Eluting generators on a daily basis may become so routine that details and departures from the normal in setting up the generator for the elution can be missed. In the more recent Colorado and Kentucky events, the licensee expected to see sterile saline in the same location every day and did not question whether the bag being picked up was sterile saline. In both events, the IV fluid picked up was unfortunately not sterile saline but Ringer's lactate. There was an FDA recognized shortage of sterile saline and some suppliers were substituting Ringer's lactate for sterile saline. The Ringer's lactate, which contains other chemicals and elements in addition to the saline, might have been an acceptable substitution for other clinical uses. However, one of the Ringer's lactate additives, calcium, interchanges with the strontium molecules on the generator column, causing the Sr-82 and Sr-85 to be washed into the eluate along with the Rb-82. The FDA-approved package inserts for both current manufacturers of the Sr-82/Rb-82 generators included a warning about using only sterile saline without additives. After these events, the FDA and the manufacturers have moved the warning about using additive-free sterile saline to the top of the package insert and have placed it in the "boxed announcement."

During an Rb-82 Cl procedure, the patient is usually imaged twice (the resting image and the stress image). Although a patient could be administered a dosage of 50 millicuries of Rb-82 per image, most patients receive less than 100 millicuries of Rb-82 for both images. According to the package insert, a dosage of 100 millicuries would result in a total dose of 177 millirem averaged for both the resting and stress tests (or using a different method of calculation, a dosage of 100 millicuries would result in an effective dose equivalent of 474 millirem for the stress test). If the Sr-82 and Sr-85 are at the breakthrough limit (2 and 20 microcuries, respectively) for this 100-millicurie total dosage, the effective dose is an additional 46 and 80 millirem, respectively. The total dose to the red marrow from the Rb-82 would be 119 millirem (averaged for both the resting and stress tests) and approximately an additional 200 millirem from Sr-82 and Sr-85 at the breakthrough limits. These estimates are significantly less than the 5 to 50 rem whole-body estimates and the 21 to 200 rem dose estimates to the red marrow for the 11 patients that exceeded the medical event reporting criteria.

An additional consideration in the licensees' inability to identify excess administration of Sr-82 and Sr-85 is the inherent quality of positron emission tomography (PET) images. Rb-82 Cl is a PET radiopharmaceutical, and the PET camera is designed to detect only the gamma rays from the positron emissions and not the other gamma rays from the Sr-82 and Sr-85. This means that PET images will not show image degradation because of the presence of non-PET radionuclides, such as Sr-82 or Sr-85. Furthermore, the time delay between the administration and the imaging (a few minutes) is too short for the Rb-82 produced by small amounts of administered Sr-82 to affect the image in unexpected sites.

In two of the four cases, the licensees attempted, after the fact, to determine whether a breakthrough event had occurred. One licensee was able to successfully identify that a breakthrough event had occurred by detecting readings above background and determining that the radiation was coming from the breakthrough vials that would normally be indistinguishable from background. Radiation surveys of the breakthrough vials may identify breakthrough events when they are not detected by the breakthrough measurements. However, remeasuring the breakthrough vials in the dose calibrator may not be effective in quantifying the breakthrough levels if the individual makes the same reading or transcription error he or she made the day before.

Another licensee unsuccessfully used a Geiger-Mueller probe to try to detect Sr-82 and Sr-85 in the red marrow of a patient a day after the administration. A much more sensitive radiation detection device than the Geiger counter would be needed to detect the microcurie quantities of

Sr-82 and Sr-85 distributed through the red marrow of the patient. The U.S. Department of Homeland Security and the State of Nevada used sensitive devices to identify and quantify the Sr-85.

CONTACT

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

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

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ADAMS Accession No.: ML19281A218 (Package) *concurred via email

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