Summary of Retrospective Review of Medical Events

Background:

All medical use licensees are required (under the provisions of Title 10 of the *Code of Federal Regulations* (10 CFR) 35.3045), "Report and notification of medical events," (or equivalent Agreement State requirements) to report medical events because these events can indicate a potential problem in the medical use of radioactive materials. The reports allow the NRC to follow up on events, identify deficiencies in the safe use of radioactive material, ensure that corrective actions are taken to prevent recurrence, and determine if other licensees might be experiencing the same or similar challenges. Therefore, a medical event may indicate a potential problem in a medical facility's use of radioactive materials, but it neither necessarily results in harm to the person receiving the administration (i.e., the patient, human research subject, or other person) nor is it significant from a public health or safety perspective.

The reported medical events are further reviewed against the abnormal occurrence (AO) criteria to determine which medical events are significant from a public health or safety perspective. This retrospective review covers the period that includes both the current (post-2017) AO criteria and the pre-2017 AO criteria. The changes made in 2017 to the AO criteria refined the higher dose criterion in an attempt to improve the AO criteria's objective of identifying events of significant public health and safety. The NRC staff concluded in SECY-19-0088, that the AO criteria established in 2017 (42 FR 45097) still included both events that were and were not significant to public health and safety. The conclusion was based upon the information included in the AO reports for the previous five years.

This retrospective review expands the period of time from five to ten years and is based only on those medical events that were reported to NRC from 2010 to 2020 that were also determined to be AOs. This retrospective review analyzes the quantitative data (radiation doses, the date the event occurred, the date it was reported to NRC, and the date it was reported to congress as an AO) and qualitative data (description of the event, the cause, and the effect on the patient) in the AO reports. Both NRC and Agreement State medical use licensees are required to provide both quantitative and qualitative information under the provisions of 10 CFR 35.3045(c) or equivalent Agreement State requirements.

The intent of the retrospective review is to provide a quantitative or qualitative basis to address critical concerns arising before, during, and after the development of the newly proposed AO criteria. A summary of proposed changes to the medical event abnormal occurrence criteria is provided in Enclosure 3. Enclosures 3 and 4 are interrelated and cross references between the two are provided.

Table: Overview Summary of the Retrospective Review

The table below provides an overview of the medical events reported to the NRC by fiscal year (FY) and the number of those medical events reported to Congress as Abnormal Occurrence (AO) events. For each year, the table notes those medical events that would be reportable to Congress under the pre-FY 2018 AO criteria, the current criteria (revised in 2017), and the proposed medical-consequence criteria.

FY[1]	Medical Events reported to NRC in FY[1]	Medical events[2] meeting pre-FY 2018 AO criteria[1]	Medical events[2] meeting current AO criteria	Medical events[2] with a high likelihood of meeting the proposed medical-consequence AO criteria	Medical events[2] – indeterminate for proposed medical-consequence AO criteria
Column 1	Column 2	Column 3	Column 4	Column 5	Column 6
2010	49	18	18	1	1
2011	58	14	14	5	2
2012	48	15	15	4	0
2013	43	7	7	3	2
2014	46	11	11	3	2
2015	57	13	13	5	2
2016	50	8	8	2	1
2017	43	10	10	0	0
2018	48		8	2	1
2019	56		7	1	1
2020	48		8	3	0
Total	546		119	29	12

[1] Medical Events were reported in the year listed; they were included in either that year's AO report or a subsequent year's report depending on the time it took to evaluate the event.

[2] Based on changes to 10 CFR 35.1000 guidance and regulatory requirements, the definition of a reportable medical event has changed over the years. If a reported medical event met the medical event criteria in the year it was reported to NRC, it was not reevaluated for the purposes of the retrospective review.

Discussion:

The table provides an overview of the NRC staff's retrospective analysis of medical events by the FY identified in Column 1. The number of medical events reported to NRC in the FY are in Column 2. Column 3 shows the number of these medical events from 2010 to 2017 that were later determined to be AOs under the criteria at that time.

In 2017, the NRC approved new medical use AO criteria for use beginning in FY 2018. Specifically, the dose-based threshold was changed from a simple 10 gray (Gy) (1,000 rad) dose-based threshold to a dose that exceeds, by 10 Gy (1,000 rad), the expected dose to any other organ or tissue from the administration in the written directive (except for doses to the bone marrow, gonads, or lens of the eye which have a more conservative dose threshold that ranges from 1 - 2.5 Gy (100 - 250 rad)). All the medical events that were determined by the NRC to be AOs were reviewed to determine if they would meet the current 2018 AO criteria and those that met the criteria are included in Column 4. The table shows that although the criteria changed in FY 2018, all the AOs determined to be AOs under the pre-FY 2018 criteria also met the FY 2018 criteria confirming that the previous dose-based change to the AO criteria had no impact on AO reporting.

NRC staff compared the data in Column 2 with that in Column 4 and concluded that the current dose-based AO criteria was able to screen out medical events without dose significance. During this period there were 427 medical events (approximately 78 percent of the events) that NRC determined were neither dose-significant nor of public health and safety significance because they did not meet the dose-based AO criteria. There were also 119 events (approximately 22 percent of events) that meet the AO criteria but as concluded in SECY-19-0088 and this review are dose-significant but may or may not be of public health or safety significance.

The NRC staff was able to affirm in this portion of the retrospective review that a dose-based AO criterion is effective in eliminating most but not all medical events that are not of public health or safety significance from the AO report to Congress. Therefore, the NRC staff concluded a dose-based-criterion should be retained as an effective preliminary screening tool.

Retrospective Review of Specific AO Text

As discussed in SECY-19-0088, the qualitative information in the AO reports can be used by the NRC to identify the significance of medical events from a patient public health or safety perspective. This is because the NRC medical event reporting requirements in 10 CFR 35.3045(c) require licensees to identify “the effect, if any, on the individual(s) that received the administration” that resulted in a reported medical event. The Agreement State licensees have equivalent requirements.

Review Based on Proposed Medical Consequence Criteria

This part of the retrospective review addressed several concerns: (1) could the NRC identify medical events that meet the proposed “medical consequence-based” AO criteria? and (2) could the determination be made from information licensees were already required to provide by regulation or would NRC need to impose future regulatory requirements?

Once the NRC staff developed its proposed medical consequence AO criterion described in Enclosure 3, the 119 AO reports identified in Column 4 were again reviewed to determine if they would qualify as AOs under the proposed revised criterion. The coding of an event in one of the three categories described above (i.e., not meeting, high likelihood of meeting, or undetermined) is based on the NRC staff’s assessment of whether radiation-induced injury occurred based on the information available.

The 78 AO reports[1] coded as "not meeting the proposed criteria" ranged from general statements that the medical event would not have "an adverse" or "a significant medical" effect on the patient to more detailed descriptions such as "faint erythema over the lumpectomy site and no evidence of erythema where the source had been in contact with the skin. Later ulcerations developed and healed without further complication."

If an event indicated radiation-induced injury without an indication of naturally healing and thus a higher possibility of meeting the proposed AO criteria, it was coded as "high likelihood of meeting the new criteria." Examples of the information in the 29 AO reports, in Column 5, with this coding included:

- "this elevated dose may result in an increased risk of atrophy to the left lobe of the liver"
- "after consultation with international and domestic experts, the patient was administered the radio-protective agent amifostine. The licensee concluded that the event may result in unintended, permanent functional damage and some form of future medical intervention was likely needed"
- "the patient also experienced rectal wall thickening, urethral stricture, and ulceration of the anterior rectal wall, as confirmed by a colonoscopy"
- "the patient was admitted because of severe anemia and suspected gastrointestinal bleeding, … endoscopy revealed a duodenum lesion and an ulcer that had developed seemingly because of microspheres migrating to the stomach (wrong treatment site)"
- "potential short-term effects include progression of these skin reactions and possible urinary and rectal irritation. Long term effects may include thickening of the skin and the mucosa, development of scar tissue and urinary track and rectal issues."

These events indicate radiation-induced injury. Under the proposed revised criteria, similar events would be coded with greater certainty as meeting or not meeting the new criteria because additional information related to potential permanent impairment would be provided.

The 12 AO reports, in Column 6, coded as "undetermined" either lacked information on the effect on the patient or included information that did not permit a definitive determination. These reports also included a range of statements. Many of these event descriptions contained statements that the patient will continue to be monitored or that there was a non-quantified possibility of transient or permanent medical effects. Examples of these statements include: "unable to perform a dose assessment of the affected tissue due to the radiation oncologist's inadequate post procedure seed implant records," "no unintended medical effects have been identified … the patient will continue to be medically monitored," "possible transient numbness to the right side of the patient's face," and "potential generation of a duodenal ulcer caused by the radiation …the licensee is treating the patient to minimize radiation damage to the duodenum and will continue to monitor the patient's condition." In the future, the NRC staff would need to seek further clarification for such events to determine whether they meet the AO criteria.

The retrospective review affirmed that some of the AO reports specifically included information on radiation induced injury, if the injury healed without intervention, if medical or surgical intervention was needed, and the possibility of permanent injury or loss of bodily function. The review affirmed only a small number of medical events (12 events) were indeterminant and would require NRC staff follow-up (1-2 per year) with the licensee for clarification, and that the NRC would not need to impose any future regulatory requirements on licensees to gather the

[1] The total reports in Column 4 minus the sum of the total reports in Column 5 and Column 6.

required information. Further, the review affirmed that in the 29 AO reports with a high probability of meeting the proposed medical use AO criteria, the effects were consistent with significant public health or safety events.

Review based on when events occurred and when they were reported to NRC and Congress

The NRC staff performed an additional review of the quantitative information in the AO reports to determine if the medical consequence criteria would significantly delay NRC's AO determination and ability to report to Congress in a timely manner. This review focused on the date the event occurred, the date NRC received the medical event reported, and the date the event was reported to Congress as an AO and also looked at the description of the event. The 29 medical AO reports that included statements interpreted as indicating a high likelihood of meeting the proposed medical consequence criteria were reviewed. The description of these events showed that they were from a wide variety of medical uses[2] and they fell into two groups: patient-identified and licensee-identified. Patients self-identified 11 of the events either because they experienced immediate pain during the administration or called attention to wet clothing from a leaking catheter that within days caused a radiation burn, or reported visible radiation induced burns or non-healing wounds later, or reported symptoms that resulted in medical and surgical treatment for internal injuries determined to be caused by radiation from radioactive sources. Those events that occurred within a month of the administration were followed up by the licensee. In the events identified by other physicians, there was usually a delay in both recognizing that radiation caused the injury and in reporting the injury to the licensee. This resulted in delays in reporting previous unrecognized medical events. Licensees self-identified the remaining 18 events. Some were identified on the day of the administration either during or just after the administration. Some were identified within a few days or weeks during routine post treatment scans and chart reviews. One was identified much later when transferring information from one system to another.

Licensees dealing with patient- or other-physician-identified injury were able to describe the injury, the medical and surgical intervention delivered to the patient, and the effect on the patient shortly after being informed of the injury and reporting the medical event. Inspections were performed by the regulators to confirm the extent of condition associated with the medical events. Licensees self-identifying medical events were generally able to recognize the likelihood of injury from the site receiving the unintended dose, the dose delivered to that site, and monitoring the patient. Delayed onset of the injury was usually within weeks but sometimes occurred months later. These observations from the retrospective review affirmed the value of the four aspects of the medical consequence criteria (i.e., radiation induced injury, high likelihood of radiation induced injury, permanent injury, and intervention to prevent permanent injury). Also, the evaluation of a medical event to determine if it meets the high likelihood criteria will help licensees determine in a timely manner if an event meets the proposed criteria. Therefore, NRC is expected to receive the medical event reports, make the AO determination, and reports to Congress in a reasonable time frame.

[2] The medical uses included radiation administrations from radiopharmaceuticals, permanent and temporary implant brachytherapy sources, high dose rate remote afterloaders, gamma stereotactic radiosurgery units, and yttrium-90 microspheres.

Conclusion:

The retrospective review involved several re-assessments of the quantitative and qualitative information included in the AO reports. The reviews affirmed that NRC has access to the information needed to determine if a medical event meets the refined dose criterion and the medical consequence criterion described in the development of the new proposed AO criteria. The refined dose criterion is beneficial as a screening tool to identify and dismiss those events that are neither significant from a dose nor public health or safety perspective because they did not meet the dose-based AO criteria. The medical consequence criterion enables the NRC to distinguish between medical events that are only dose-significant and those that are also significant from a public health or safety perspective. Since licensees are already required to provide the medical event reports that include the dose-based and medical consequence information necessary for the NRC to make its AO determination, there would be no need to impose any further regulatory requirements or other additional burden on NRC or Agreement State licensees. Further, past reporting patterns indicate that once the medical event is identified and reported to NRC, both the patient- and licensee-identified radiation induced injury (or high likelihood of radiation induced injury) events can be evaluated by NRC and reported to Congress as AOs in a reasonable time frame.