Summary of Proposed Changes to the Medical Event Abnormal Occurrence Criteria

Background

Consistent with the staff requirements memorandum (SRM) to SECY-19-0088, the staff convened a working group and developed limited proposed revisions the medical events Abnormal Occurrence (AO) criteria. The proposed revisions include two considerations. The first, like the current criteria, is a dose-based threshold criterion. The new proposed second criterion would be medical-consequence-based. NRC staff is proposing that both the dose-based and medical-consequence-based criteria must be met for a medical event to be an AO.

Discussion

Dose-based Criterion III.C.1

As discussed in SECY-19-0088, the current AO criteria may capture events that are not significant from a public health or safety standpoint. Applying the FY 2018 revised criteria to the medical events from 2010 to 2017 that were identified as AOs showed no change to which events would have been identified as AOs. The NRC staff is proposing to retain Criterion III.C.1 as a dose-based threshold criterion with additional proposed revisions. Under the NRC staff's 2-step proposal, the dose-based threshold criterion would be used as a screening tool to identify those medical events that need to be further reviewed for public health or safety significance under the medical-consequence based criterion.

The NRC staff is also proposing new revisions to the dose-based criterion to include:

1) adding medical events that are being reported under both 35.3045 and specific license conditions;

2) reflecting developments in new medical radiation treatments that could result in expected doses to a major portion of the bone marrow, or lens of the eye, or to the gonads in excess of the current AO criteria;

3) addressing activity-based medical events to explicitly conform with current regulatory requirements; and

4) removing written directives as a necessary requirement for an AO.

The current licensing guidance for 10 CFR 35.1000 medical uses of yttrium (Y)-90 microspheres and radioactive seed localization include specific medical event reporting criteria due to the unique characteristics of these products. The Y-90 guidance informs the licensee that if an administration of Y-90 microspheres cannot be completed because of "stasis,[1]" the event is not a medical event and the authorized user can indicate the reason for failure as stasis and record the delivered activity. This change in the criteria for a medical event resulted from the NRC's recognition that the unique characteristics of one manufacturer's Y-90 microsphere involving larger microspheres routinely filling the capillary bed before the administrations could be completed. The radioactive seed localization procedure is a diagnostic procedure requiring the

[1] "Stasis" is a physical condition when the microspheres fill the intended capillary bed before the complete prescribed activity can be delivered.

seed to be removed with the tissue sample. Because it is a diagnostic procedure, it does not require a written directive. If the seed is not removed, it could under certain situations result in a reportable medical event. Future emerging technologies may also need either new exemptions from or new criterion for medical reporting requirements other than those in 10 CFR 35.3045.

The current dose-based criterion considers doses that differ from the expected doses based on a written directive. However, radiopharmaceutical administrations are for prescribed dosages (activities or ranges of activities) and not doses. Some radiopharmaceuticals do not need written directives because they may have directives from the authorized user for procedures performed under 10 CFR 35.100 and 35.200.[2] Also, in 2019 NRC revised the requirements for permanent brachytherapy to define medical events for this medical use is in terms of activities and not doses. Therefore, proposed revisions were needed to include doses that would have resulted from delivery of the prescribed dose, prescribed dosage or prescribed activity. Also, the staff is proposing to remove the term "written directive" from the criterion to capture administrations that did not have a written directive because they were intended to be low dose procedures but resulted in doses exceeding Criterion III.C.1.

One of the current dose-based criteria is that the dose is equal to or greater than 1 Gy (100 rad) to a major portion of the bone marrow or to the lens of the eye; or equal to or greater than 2.5 Gy (250 rad) to the gonads. This does not recognize that there are new radiopharmaceuticals, medical devices, and medical uses that intentionally deliver doses near these sites that could exceed these dose limits. The proposed revision would provide that the unintended dose must be greater or equal to the specified doses for these sites.

Discussion of the Medical-Consequence-Based Criterion III.C.2

Advances in the medical use of byproduct material result in the use of novel radionuclides, new administration procedures, new medical devices, and new treatment targets. These advances complicate the evaluation of whether particular medical events have public health and safety significance and make the use of a single dose criterion ineffectual. For this reason, the proposed revised Criterion III.C describes how NRC will determine medical events of significant public health or safety based upon both dose screening using Criterion III.C.1 and the medical consequence in Criterion III.C.2.

Deterministic Vs. Stochastic Medical-Consequences Criterion

All medical uses of radiation carry a probability of stochastic or deterministic effects. Stochastic effects may not appear for years or decades and can occur from any administrations of radiation from radiopharmaceuticals and medical devices. Deterministic effects manifest promptly, but still may not appear as immediate radiation-induced injury. Such effects, while sometimes occurring with some delay, nevertheless provide a reasonably timely basis for assessing events of potential public health and safety significance. Therefore, the proposed new Criterion III.C.2 is not based on stochastic medical consequences, but on deterministic effects.

Other Federal Regulatory Agencies Approaches to Medical-Consequence Criterion

[2] 10 CFR 35.100, "Use of unsealed byproduct material for uptake, dilution, and excretion studies for which a written directive is not required" and 10 CFR 35.200, "Use of unsealed byproduct material for imaging and localization studies for which a written directive is not required."

The NRC staff reviewed the practices of other federal regulatory agencies to determine how they addressed medical health and safety significance. The NRC staff reviewed the U.S. Food and Drug Administration (FDA) adverse event definitions for drugs[3], biologics[4], and medical devices[5] and the Department of Health and Human Services' (HHS) November 27, 2017, publication "Common Terminology Criteria for Adverse Events" Version 5.0. All FDA adverse or reportable events included the common factor that the drug, biologic or device adverse event has or may have caused or contributed to a death or serious injury.[6] The HHS publication provides guidance for defining adverse events for almost every part of the body. The document uses five grades to describe the severity of an adverse event. Grade 5 is death, Grade 4 is life-threatening (immediate risk of death), and Grade 3 was not immediately life-threatening, but medical or surgical intervention was needed to prevent severe or medically significant consequences. Grade 2 is moderate, minimal, local or non-invasive and Grade 1 is asymptomatic or mild symptoms. The NRC staff asserts that events that cause death or life-threatening consequences have *serious* public health or safety significance. Adjusting the AO criteria to include the qualitative threshold of "impairment of a body function or damage to a body structure," as described in the HHS definition of a Grade 3 "severe adverse event," adequately captures the subset of medical events that staff recommends classifying as having public health or safety significance. As further discussed in Enclosure 4 this qualitative threshold may be effective in capturing public health or safety significance within the larger set of medical events that meet the dose-based AO criteria.

Determining Medical Consequences from Medical Event Reports

Both NRC and Agreement State licensees are required under 10 CFR 35.3045, "Report and notification of a medical event," or equivalent Agreement State regulation to provide a written report that describes the event, why the event occurred, and the effect (if any) on the individual receiving the administration. As discussed in more depth in Enclosure 4 (the retrospective review), the staff analyzed the description of medical events determined to be AOs from 2010 - 2020 and the adverse health effects on the patients that were reported by licensees (such a radiation induced injury) and concluded that licensees were providing the kind of information that could be used to reach conclusions on "impairment of a body function or damage to a body structure" and occurrence of "medical or surgical intervention." The NRC and the Agreement States perform inspections as a result of reported medical events and give a higher priority to those events that have or are expected to have medical consequences.

Further, the medical events that result in high enough doses to trigger adverse effects based on the staff's proposed qualitative threshold would reflect deterministic effects that are likely to be immediately observable or could be identified later either by chart reviews or when the patient complains of pain or other complication to another physician. As shown in the retrospective review in Enclosure 4, only 12/586 medical events reported from 2010 – 2020, or 2 %, were indeterminate and would need additional licensee follow-up by the NRC or Agreement State staff to determine whether the events meet the staff's recommended changes to the AO criteria. As discussed in more detail in the retrospective review, licensees dealing with patient or other physician identified radiation induced injuries were able to describe the injury, the medical and

[3] Title 21 Code of Federal Regulations (21 CFR) Part 314.80, "Postmarketing reporting of adverse drug experiences."

[4] 21 CFR 600.80 — Postmarketing reporting of adverse experiences (a) Definitions.

[5] 21 CFR 803.3 — How does FDA define the terms used in this part?

[6] The FDA drug and biologic adverse event requirements also included criteria that are not appropriate for NRC purposes (e.g., overdose, drug abuse, drug withdrawal).

surgical intervention delivered to the patient, and the effect on the patient shortly after being informed of the injury. Further, evaluation of a medical event to determine if it meets the high likelihood criteria will help the NRC determine if an event meets the proposed criteria in a timely manner. There is usually time to identify the effect, for the physicians to understand the consequences, and for licensees and regulators to add clarifying information from an inspection into the AO report.

The AO Determination

Because the proposed criteria are based on medical consequences, the NRC staff would need to determine responsibility for assessing whether a medical event "results in (or has a probability or resulting in) a radiation induced injury causing permanent impairment of a body function or permanent damage to a body structure" or in a "radiation induced injury without medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure." The NRC staff concluded that licensees are responsible under 10 CFR 35.3035(c) to identify "the effect, if any, on the individual(s) that received the administration" that resulted in a reported medical event, it would be the NRC's responsibility to determine if such an event is an AO based on the information provided by the licensee, inspections, physicians (referring, licensee, or independent physicians), other health care professionals (including medical physicists and radiation biologists), and other resources (e.g., subject matter experts, future guidance, consultation with the Advisory Committee on Medical Uses of Isotopes (ACMUI)). The NRC staff recognizes that evaluating certain cases could be difficult, and could depend on expert input and professional judgment, as well as effective NRC/Agreement State coordination. Upon request, similar support to the Agreement States may be provided by an NRC contract physician or health care professional. The staff is not proposing any changes to the medical event reporting criteria in 10 CFR 35.3035.

Proposed Changes to the AO Criteria

Based on the staff's assessment, the following are the proposed changes Sections III.C.1 and III.C.2:

Section III.C. - Events Involving the Medical Use of Radioactive Materials in Patients or Human Research Subjects[7]

1. A medical event, as defined in § 35.3045 or in conditions of a license[8], which results in an unintended dose ~~that~~:

    (a) That is equal to or greater than 1 gray (Gy) (100 rad) to a major portion of the bone marrow or to the lens of the eye; or equal to or greater than 2.5 Gy (250 rad) to the gonads; or

    (b) To any other organ or tissue from the administration that exceeds, by 10 Gy (1,000 rad), the ~~expected~~ dose or dose that would have resulted from delivery of the prescribed dose, prescribed dosage

[7] Criteria III.A.2, III.A.3, and III.A.4 also apply to medical licensees. (*This will actually be Footnote 16 in the final criteria if approved.*)

[8] "In conditions of a license" means either the specific 35.1000 medical criterion can be written out in a license condition or included as a commitment in a document referenced in the "tie down" license condition. (*This will actually be Footnote 17 in the final criteria if approved.*)

or prescribed activity ~~to any other organ or tissue from the administration defined in the written directive~~;

and

2. A medical event, as defined in § 35.3045 or in conditions of a license[8] ~~which involves~~ that results or has high likelihood of resulting in:

   (a) ~~A dose or dosage that is at least 50 percent greater than that prescribed~~Radiation-induced injury causing permanent impairment of bodily function or permanent damage to a body structure[9], or

   (b) Radiation-induced injury that needs medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure.[9]

   ~~A prescribed dose or dosage that:~~

   ~~(i) Uses the wrong radiopharmaceutical or unsealed byproduct material; or~~

   ~~(ii) Is delivered by the wrong route of administration; or~~

   ~~(iii) Is delivered to the wrong treatment site; or~~

   ~~(iv) Is delivered by the wrong treatment mode; or~~

   ~~(v) Is from a leaking source or sources; or~~

   ~~(vi) Is delivered to the wrong individual or human research subject.~~

Proposed Changes to Section III.C.1

1. The current criteria in Section III.C.1 indicate the AO must be a "medical event, as defined in § 35.3045, which results …" However, several medical uses[10] regulated under 10 CFR 35.1000, "Other Medical Uses of Byproduct Material or Radiation from Byproduct Material," include medical event criteria based upon the unique characteristics of that medical use. While regulated under a different provision, these medical event criteria often mirror those in other subparts of 10 CFR Part 35. If there are medical event criteria in the license (generally also reflected in the licensing guidance for that particular medical use), such events may be eligible for AO reporting, as appropriate. These different medical event criteria can only become an NRC or Agreement State requirement when included in the license. Therefore, the text, "or in the license (based on specific 10 CFR 35.1000 licensing guidance)," was added to the Criteria III.C.1 and III.C.2.

---

[9] NRC will use dose and medical consequence information from the licensee, inspections, physicians (referring, licensee, or consultant physicians), other professionals (e.g., medical physicist, radiation biologist), and other resources to make its AO determination. (*This will actually be Footnote 18 in the final criteria if approved.*)

[10] For example Y-90 microspheres and radioactive seed localization medical uses.

2. The current Criterion III.C.1(a) has simple dose thresholds for the following three body parts: a major portion of the bone marrow, the lens of the eye, and the gonads. This criterion does not recognize the development of new medical radiation treatments that may target these body parts or nearby areas that could be expected to deliver "intended" doses at or exceeding these dose criteria. The proposed criterion clarifies that the dose has to be an "unintended dose" to these locations that is equal to or exceeds the specified doses.

3. Criteria III.C.1(a) and (b) are both unintended dose-based criteria. By adding "unintended" in III.C.1 the term "expected" is removed from Criterion III.C.1(b).

4. The current Criterion III.C.1(b) referred only to the expected dose "defined in the written directive." Some medical administrations resulting in medical events do not require written directives.[11] Removal of the phrase "defined in the written directive" clarifies that a written directive is not needed for a medical event to be considered an AO. As discussed in change 3 above, the use of "unintended" in III.C.1 retains the concept of deviation from the expected dose.

5. The current criterion only considered the expected dose and did not explicitly include doses resulting from administrations based on dosages and activity instructions.[12] Because criterion III.C.1 is still dose-based (the unintended dose is measured in Gy or rad), the criterion would be revised to read "dose or dose that would have resulted from delivery of the prescribed dose, prescribed dosage, or prescribed activity."

Proposed Changes to Section III.C.2

1. The expanded definition of a medical event would be revised to include criteria specific to 10 CFR 35.1000 medical use authorizations consistent with Criterion III.C.1.

2. The current Criterion III.C.2 unnecessarily repeats regulatory medical event criteria and was deleted for this reason. NRC will continue to include the appropriate medical event criteria in future reports of particular abnormal occurrences.

3. The new proposed Criterion III.C.2 introduces a medical-consequence standard to capture medical events of public health and safety significance.

4. The proposed revised criterion would be based on deterministic radiation-induced injury, but some injuries will not manifest themselves immediately. To ensure NRC AO reports capture those events with public health and safety significance to Congress in a timely manner, the phrase "high likelihood" was included in the criterion to indicate the expected occurrence of the medical induced injury or the need for medical or surgical intervention needed to mitigate its occurrence.

5. Some radiation induced injuries will naturally heal, and the NRC generally does not consider these to be of public health and safety significance. The location, dose, time of onset, and the description of the radiation injury are key to determining if the injury will heal naturally, require medical or surgical intervention, or is beyond medical or surgical

[11] For example, some radiopharmaceutical administrations and radioactive sed localization medical uses do not require written directives.

[12] For example, radiopharmaceutical medical uses are prescribed in dosages and permanent implant brachytherapy medical uses are prescribed in units of activity.

intervention. This is why NRC would add the condition that the radiation induced injury causes permanent impairment of bodily function or permanent damage to a body structure.

6. Consistent with the revised focus on dose as well as injury, to capture those radiation induced injuries that would have caused permanent impairment of a bodily function or permanent damage to a body structure absent medical or surgical intervention, Criterion III.C.2(b) would be added.

7. The final determination of whether Criteria III.C.2(a) or (b) is met is made by the NRC. The NRC has the responsibility to determine when medical events are AOs. The footnote clarifies that the NRC will make this determination based on dose and medical consequence information provided by the licensee, inspections, physicians (referring, licensee, or independent physicians), other health care professionals (including medical physicist and radiation biologists), and other resources (e.g., subject matter experts, future guidance, consultation with the ACMUI).