

POLICY ISSUE NOTATION VOTE

April 5, 2012

SECY-12-0053

FOR: The Commissioners

FROM: R. W. Borchardt
Executive Director for Operations

SUBJECT: RECOMMENDATIONS ON REGULATORY CHANGES FOR
PERMANENT IMPLANT BRACHYTHERAPY PROGRAMS

PURPOSE:

This paper provides the staff's recommendations for modifying the requirements in Title 10 of the *Code of Federal Regulations* (10 CFR) Part 35, "Medical Use of Byproduct Material," for permanent implant brachytherapy programs. This paper does not address any new commitments or resource implications.

SUMMARY:

The Nuclear Regulatory Commission (NRC) staff is recommending amendments to the regulatory requirements for permanent implant brachytherapy programs that appear in 10 CFR 35.40, "Written Directives," and in 10 CFR 35.3045, "Medical Event Reporting." As directed by the Commission in SRM-M090625B, "Meeting with Advisory Committee on the Medical Uses of Isotopes (ACMUI), 1:30 p.m., Thursday, June 25, 2009," dated July 1, 2009, the staff worked closely with the Advisory Committee on the Medical Uses of Isotopes (ACMUI) and the broader medical and stakeholder community in developing these recommendations. The recommendations include changing from a dose-based criterion for assessing whether a medical event (ME) has occurred, to a hybrid definition using both dose-based and source-strength based criteria, which is in accordance with recommendations by the ACMUI and input received from most stakeholders.

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BACKGROUND:

In SECY-05-0234, dated December 27, 2005, the staff recommended that the Commission approve the staff's plan to revise the ME definition and the associated requirements for written directives (WDs) to be activity-based, instead of dose-based. In SRM-SECY-05-0234, dated February 15, 2006, the Commission directed the staff to proceed directly with the development of a proposed rule to modify both the WD requirements in 10 CFR 35.40(b)(6) and the ME reporting requirements in 10 CFR 35.3045 for permanent implant brachytherapy medical use, to convert from dose-based to activity-based ME criteria. In SRM-SECY-08-0080, dated July 25, 2008, the Commission approved publication of a proposed rule to amend 10 CFR Part 35 sections involving reporting and notification of MEs and also to clarify requirements for permanent implant brachytherapy.

The proposed rule was published in the *Federal Register* on August 6, 2008 (73 FR 45635) for public comment. The vast majority of commenters offered no objection to conversion from dose-based to activity-based ME criteria. During late summer and early fall of 2008, a substantial number of MEs involving permanent implant brachytherapy were reported to the U.S. Nuclear Regulatory Commission (NRC). Based on its evaluation of this information, the staff believed that a number of these MEs would not be categorized as MEs under the proposed rule. This would be inconsistent with the original regulatory intent because the staff had previously been directed to clarify the requirements for reporting of MEs involving permanent implant brachytherapy so that licensees would be able to identify MEs more easily and in a more timely manner. The intent was also not to adversely impact the detection of significant errors as MEs. Additionally, the evaluation of the circumstances and data from the MEs reported in 2008 prompted the staff to reevaluate the regulations related to training requirements and time frames for licensees to assess the dose to the treatment site for permanent implant brachytherapy. To assist in this effort, the NRC requested that the ACMUI reconsider the issue and draft a report to provide recommendations on regulatory changes or improvements to the NRC's processes for permanent implant brachytherapy programs.

The proposed rule language and rationale were modified and in SECY-10-0062, "Reproposed Rule: Medical Use of Byproduct Material – Amendments/Medical Event Definitions," dated May 18, 2010, the staff recommended that a revised proposed rule be published for public comment. In SRM-SECY-10-0062, dated August 10, 2010, the Commission disapproved the staff's recommendation. Instead, the Commission directed the staff to work closely with the ACMUI and the broader medical and stakeholder community to develop event definitions that would protect the interests of patients, allow physicians the flexibility to take actions that they deem medically necessary, while continuing to enable the agency to detect failures in process, procedure, and training, as well as any misapplication of byproduct materials by authorized users (AUs).

Additionally, the SRM directed staff to hold a series of stakeholder workshops to discuss issues associated with the ME definition. These facilitated workshops (with webinar capability) were held in New York, New York, in June 2011 and in Houston, Texas, in August 2011.^{1,2} The

¹ Meeting summaries are available in the NRC's Agencywide Documents Access and Management System (ADAMS) at Accession Numbers ML111930470 and ML112510385, respectively.

nearly unanimous position expressed at both of the meetings was that the ME criterion for the treatment site should be source-strength based (i.e., activity-based), rather than dose-based.

Finally, the SRM directed the staff to provide the Commission with an Integrated Plan (IP), denoting schedule and Agreement States participation, for completing this rulemaking, along with other activities in the medical area. The requested IP was conveyed to the Commission, for information, in March 2011 as Enclosure 1 to SECY-11-0035, "Integrated Plan, Title 10 of the *Code of Federal Regulations* Part 35, „Medical Use of Byproduct Material,’ Activities and Options for Streamlining the Medical Rulemaking Petition and Rulemaking Processes.”

The ACMUI Permanent Implant Brachytherapy Subcommittee (PIBS) issued its report, which was unanimously approved by the ACMUI at its October 20, 2010, meeting (ML103540385). The PIBS report included the caveat that it was to be considered as an interim report that might be revised in the future in response to additional input, such as that expected to be received from stakeholders at the then-upcoming public workshops. The following ACMUI meeting, in April 2011 was devoted to issues associated with the ME definition and was webcast, providing opportunity for public involvement on this issue.³

The ACMUI final report on prostate brachytherapy regulation was provided to the NRC staff following the ACMUI October 18, 2011, teleconference public meeting (ML11292A139). The final report reflected the principal positions expressed and recommendations provided by participants during the NRC public workshops. In particular, the recommendations reflected a change from dose-based ME criteria for the treatment site to source-strength based criteria. The report significantly revised the earlier interim report. For example, the final report no longer included the interim report recommendation to replace the term “treatment site” with different, contemporary nomenclature. The final report also does not include two sets of regulations to separate procedures that result in significant rearrangement of implant locations during the completion of surgical procedures from those procedures that do not generally result in this phenomenon. The final report did include a quantitative metric, the “octant approach,” for determining that a distribution of implanted seeds was irregular enough (i.e., demonstrating “bunching”) to consider the treatment as an ME. The final report also included a dose-related ME criterion for the treatment site.

By letter to the Chairman of the ACMUI dated November 30, 2011,⁴ the American Society for Radiation Oncology (ASTRO) expressed criticism of the ACMUI final report. ASTRO considered the ME definition recommended by the ACMUI to be complex, difficult to regulate, and likely to cause confusion in practice. Consequently, a revised final report⁵ that simplified the ME criteria for the treatment site, removing the “octant approach” and direct reference to absorbed dose, was issued by the PIBS. The revised final report was, with minor modification, approved by the ACMUI during its February 7, 2012, teleconference public meeting and was

² Panelists represented the ACMUI, the Agreement States, licensees (specifically, the Veterans Administration), professional organizations (specifically, the American Society for Radiation Oncology, [ASTRO]), patient rights advocates, and NRC staff.

³ Transcript available at www.nrc.gov.

⁴ ML11341A051, “LTR-11-0639 - Ltr. Laura Thevenot re: Definition of Medical Event.”

⁵ ML12038A279, “Advisory Committee on the Medical Uses of Isotopes (ACMUI) Permanent Implant Brachytherapy Revised Final Report.”

subsequently, in a letter to the Chairman of the ACMUI,⁶ characterized by ASTRO as an improvement.

The “expanded” rulemaking to amend Part 35 began in July 2010 and is currently ongoing. It is anticipated that a regulatory basis for modifying the Part 35 requirements for WDs and reporting MEs involving permanent implant brachytherapy will be completed after receipt of an SRM for this paper, and these modifications will then be ready for inclusion in the ongoing “expanded” Part 35 rulemaking.

DISCUSSION:

The staff used the recommendations in the ACMUI revised final report, along with the substantial input from stakeholders who participated in the facilitated public workshops and in ACMUI public meetings to develop the recommendations in this paper.⁷ Based on the input received from the medical community and other stakeholders on this issue, the staff believes that these recommendations, which include changing from dose-based ME criteria for the treatment site to source-strength based criteria, would protect the interests of patients and allow physicians the flexibility to take actions that they deem medically necessary, while continuing to enable the agency to detect failures in process, procedure, and training, as well as any misapplication of byproduct materials by AUs.

Based on a survey conducted prior to the 2011 public workshops, the Agreement States are generally not supportive of the main objective of the rule revision being proposed, i.e., to change from a dose-based ME criterion to a source-strength ME criterion for the treatment site for permanent implant brachytherapy use. This position of the Organization of Agreement States (OAS) was presented during the two facilitated public workshops and was formally conveyed to NRC in a letter from the OAS Executive Board (Board) dated February 27, 2012.⁸ In its letter, the OAS Board did not oppose the introduction of the proposed source-strength based ME criterion for the treatment site, but recommended that dose-based criteria also be retained, for consistency with ME criteria for other medical uses. This position, however, has been opposed by all other stakeholders from whom NRC has received input, who assert that dose-based ME criteria for the treatment site limit the physician AU’s ability to provide optimum care and could also result in many inappropriately identified MEs.

Also in its letter, the OAS Board recommended that for the proposed dose-based ME criteria for normal tissue structures, the dose thresholds for ME reporting be established by the AU for each treatment being provided, rather than through regulation. This is essentially what the ACMUI recommended and proposed as the ME reporting criterion for normal tissue structures located within the treatment site, for which the AU specifies the expected/intended absorbed dose in the pre-implant-approved dose distribution and for which the threshold for reporting an ME is a pre-set percentage of this expected/intended absorbed dose (see Enclosure). For normal tissue structures located adjacent to the treatment site, the proposed dose-based criterion for ME reporting would be indirectly established by the AU through prescribing an

⁶ ML12044A358, “Ltr frm American Society for Radiation Oncology (ASTRO) to Dr. Leon Malmud dtd 02/13/12 RE: Reconsideration of Advisory Committee on the Medical Uses of Isotopes (ACMUI) Permanent Implant Brachytherapy Subcommittee Recommendations.”

⁷ Note that the staff recommendations for modifying the WD requirements and ME criteria, which follow, reflect the widely-based stakeholder position that MEs should only reflect circumstances in which there is actual or potential harm to patients being treated.

⁸ ML12072A330, “OAS Board Position on Pre-Decisional Draft of Recommendations on Regulatory Changes for Permanent Implant Brachytherapy Programs.”

intended absorbed dose to the treatment site. The threshold for reporting an ME would be a pre-set percentage of this intended absorbed dose (see Enclosure). No other stakeholders, from which NRC received input on this issue, had objections to the pre-set percentage approach nor the values recommended.

A recommendation from ASTRO, incorporated into the ACMUI revised final report but not incorporated into staff's recommended ME criteria, involves possible "bunching" of implanted radioactive seeds in the treatment site, instead of being distributed as the AU had planned before the start of the procedure. ASTRO recommended that the AU affirm in writing on the WD, after the implant is completed, that the distribution of the sources within the treatment site was as intended per the pre-implant WD.¹ The staff believes that appropriate regulation for patient protection from undeclared or unrecognized "bunching" exists through two current requirements, and the AU affirmation would be unnecessary.⁹

Specifically, 10 CFR 35.40(b)(6) requires completion of the written directive after the implantation. This affords the AU an opportunity to acknowledge any seed "bunching" that may have been done intentionally or that may have been unavoidable¹⁰. In either case, the physician now has the opportunity to initiate follow up medical remediation, if deemed appropriate.

Additionally, 10 CFR 35.41, "Procedures for Administrations Requiring a Written Directive," requires licensees to develop, implement, and maintain written procedures to provide high confidence that, among other things, each administration is in accordance with the written directive and, if applicable, with the treatment plan. To accomplish this objective, these written procedures must include conducting post-implant assessment of each implant procedure. "Bunching" that is not declared and explained in the completed WD¹⁰ would become apparent through this assessment, and follow up medical remediation could be considered.

Moreover, as noted above, this paper includes a recommended ME criterion involving absorbed doses to normal tissue structures. In order to evaluate the doses to normal tissues and structures, or at least to assess whether variances from expected results (including absorbed doses) are significant, imaging to determine the positions/locations of the implanted sources would be essential. "Bunching" that is not declared and explained in the WD would become apparent, and follow up medical remediation could be considered. Therefore, the staff believes that an ME criterion for the treatment site that is based on the ASTRO recommendation for an AU attestation as to the acceptability of the distribution of sources within the treatment site is unnecessary for patient protection from unintentional and unrecognized seed "bunching."

The regulatory basis to be developed for rulemaking will be based on the staff recommendations contained in this paper, as directed by the Commission. A Commission meeting is being scheduled to hear and discuss these staff recommendations, as well as medical community views of these recommendations. Consequently, the staff recommends that this notation vote paper be released for public review prior to the Commission meeting.

RECOMMENDATIONS:

⁹ See the minority report in the ACMUI revised final recommendations at ML12019A196.

¹⁰ As specified in the WD a) by design for preservation of normal tissue or, b) for intentional dose escalation to a particular region or c) for cases in which patient anatomy or technical limitations preclude physically reaching certain areas.

The staff recommends that the Commission approve the following recommendations for modifying the regulatory requirements that appear in 10 CFR 35.3045 for permanent implant brachytherapy ME reporting, as discussed in the Enclosure.

- Define separate ME criteria exclusively for permanent implant brachytherapy utilizing radioactive seeds, for all treatment sites.
- For the treatment site, an ME will have occurred¹¹ if 20 percent or more of the implanted seeds are located outside of the intended implant location.
- For normal-tissue structures, an ME will have occurred¹¹ if: a) for neighboring structures (such as the bladder or rectum in prostate implants as an example), the dose to at least 5 contiguous cm³ exceeds 150 percent of the absorbed dose prescribed to the treatment site; or b) for intra-target normal structures (such as the urethra in prostate implants as an example), the absorbed dose to at least 5 contiguous cm³ exceeds 150 percent of *that structure's* expected absorbed dose based on the approved pre-implant dose distribution. These dose determinations are to be made within a time frame to be determined by the AU consistent with prevailing medical practice, but not to exceed 60 days unless accompanied by written justification.
- An ME will have occurred if a treatment is administered: a) using the wrong radionuclide; b) using the wrong activity or source strength (+/-20%) as specified in the WD; c) with delivery to the wrong patient; d) with seeds implanted directly into the wrong site or body part, i.e. into other (distant from the treatment site) locations; e) with delivery using the wrong modality; or f) using leaking sources.

The staff notes that the current WD requirements for brachytherapy in 10 CFR 35.40(b)(6) would require only minor modification to conform with the recommended modifications to 10 CFR 35.3045, listed above, for permanent implant brachytherapy. These modifications, as discussed in the Enclosure, are summarized as follows:

- Define separate WD criteria exclusively for permanent implant brachytherapy utilizing radioactive seeds, for all treatment sites.
- Delete “total dose” as an option for completion of the WD, leaving the other option, “total source strength and exposure time,” as the required entry field (along with entry fields for radionuclide, treatment site, and number of sources).
- Replace “before completion of the procedure” with “before the patient is released from the AU’s control and leaves the post-procedure recovery area.” (As recommended by the ACMUI in its final and revised final reports¹², to remove uncertainty that has been encountered in interpretation of the existing requirement.)

¹¹ With exceptions for seed migration, edema and other patient-related factors, or source displacement following placement, as long as the criterion is not violated.

¹² ML11292A139 and ML12038A279, respectively.

COORDINATION:

The Office of the General Counsel has reviewed this paper, and has no legal objection.

In accordance with Policy & Procedure 2-5, "FSME Procedure for Interacting with the Advisory Committee on the Medical Uses of Isotopes during Development of Major Medical Policy Issues," the staff has engaged the ACMUI on the recommendations in this paper for modifying the Part 35 requirements for WDs and reporting MEs involving permanent implant brachytherapy. The ACMUI had an opportunity to review this paper, and its views are reflected in this paper.

/RA Michael F. Weber for/

R. W. Borchardt
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for Operations

Enclosure:

[Recommended Changes, Permanent Implant
Brachytherapy Regulatory Program](#)

Staff's Recommendations for Modifying the Requirements in Title 10 of the Code of Federal Regulations (10 CFR) Part 35, "Medical Use of Byproduct Material," for Permanent Implant Brachytherapy Programs

The staff is proposing certain recommendations for modifying the requirements in 10 CFR Part 35 for permanent implant brachytherapy programs. As directed by the Commission in SRM M090625B, these recommendations were formulated in close cooperation with the Advisory Committee on the Medical Uses of Isotopes (ACMUI), as well as with substantial input from stakeholders.

The recommendations, with comments and explanations, are as follows.

A. The staff's recommendations for modifying the regulatory requirements that appear in 10 CFR 35.3045 for permanent implant brachytherapy medical event (ME) reporting are:

1. *Define separate ME criteria exclusively for permanent implant brachytherapy utilizing radioactive seeds, for all treatment sites.*

The ME criteria recommended in this paper for permanent implant brachytherapy use are primarily source-strength based, while the ME criteria currently appearing in 10 CFR 35.3045, "Report and Notification of a Medical Event," for all use modalities are primarily dose based. Accordingly, separate ME criteria are recommended.

Also, the recommended ME criteria are intended for permanent implant brachytherapy use involving radioactive seeds, but not for use of radioactive microspheres, which are currently regulated under 10 CFR 35.1000, "Other Medical Uses of Byproduct Material or Radiation from Byproduct Material."

2. *For the treatment site, an ME has occurred¹ if 20 percent or more of the implanted seeds are located outside of the intended implant location.*

Source strength/positioning is the measurable metric/surrogate for dose, as related to harm/potential harm. Twenty percent is the variance limit (from physician intention) that was approved by the Commission, on the recommendation of the ACMUI, for all medical uses of byproduct material.²

¹ With exceptions for seed migration, edema and other patient-related factors, or source displacement following placement, as long as the criterion is not violated.

² See SRM-SECY-05-0234, available on the NRC public web site, at www.nrc.gov.

3. *For normal-tissue structures, an ME has occurred³ if: a) For neighboring structures (such as the bladder or rectum in prostate implants as an example), the dose to at least 5 contiguous cm³ exceeds 150 percent of the absorbed dose prescribed to the treatment site; or b) For intra-target normal structures (such as the urethra in prostate implants as an example), the absorbed dose to at least 5 contiguous cm³ exceeds 150 percent of that structure's expected absorbed dose based on the approved pre-implant dose distribution. These dose determinations are to be made within a time frame to be determined by the authorized user consistent with prevailing medical practice, but not to exceed 60 days unless accompanied by written justification.*

Because of this dose-based ME criterion for organs and tissues other than the treatment site, there is an implicit operational requirement for post-implant imaging, as strongly recommended during the public workshops and as practiced in most clinical facilities.

4. *An ME has occurred if a treatment is executed: a) using the wrong radionuclide; b) using the wrong activity or source strength (+/- 20%) as specified in the WD; c) with delivery to the wrong patient; d) with seeds implanted directly into the wrong site or body part, i.e., into other (distant from the treatment site) locations;³ e) with delivery using the wrong modality; or f) using leaking sources.*

For this criterion, +/- 20% is used for the ME threshold for source strength variance because +/- 10% is considered too close to the actual variance associated with this quantity in clinically acceptable implant procedures.

Criterion A.4.d., for other (distant from the treatment site) locations, directly reflects an ACMUI recommendation but appears more restrictive on acceptable practice than the current regulation, as the proposed criterion is based on direct deposition only, without a minimum required dose for ME declaration. However, the localized dose associated with any misplaced seed far exceeds the 0.5 Sievert (50 rem) dose threshold in the current regulation.

Note that if seeds are directly deposited into the urinary bladder, because prompt removal typically follows, rather than permanent residency at the implantation site, exceeding criterion A.3.a. (dose to neighboring tissue structures) would be the basis for an ME, rather than criterion A.4.d. (direct delivery to the wrong site).

B. The staff notes that the WD requirements for brachytherapy that currently appear in 10 CFR 35.40(b)(6) would require only minor modification for compatible applicability with the recommended modifications to 10 CFR 35.3045, listed above, for permanent implant brachytherapy. These modifications with comment and explanation are summarized as follows.

1. *Have separate WD criteria exclusively for permanent implant brachytherapy utilizing radioactive seeds, for all treatment sites.*
2. *Delete "total dose" as an option for completion of the WD, leaving the other option, "total source strength and exposure time," as the required entry field (along with entry fields for radionuclide, treatment site, and number of sources).*

³ With exceptions for seed migration, edema and other patient-related factors, or source displacement following placement.

3. *Replace “before completion of the procedure” with “before the patient is released from the AU’s control and leaves the post-procedure recovery area.”*

The wording of this recommendation reflects the ACMUI position that “released from the AU’s control” equates to “released from the post-procedure recovery area.”⁴

This recommendation is offered to remove uncertainty that has been encountered in interpretation of the existing requirement.

C. Additional Comments and Explanations

1. Consistent with ACMUI recommendations, all of the proposed ME criteria reflect circumstances in which there is actual or potential harm to patients being treated.
2. The ACMUI final recommendations in its October 2011 report are collectively more prescriptive than those in its interim (2010) report. The ACMUI revised final recommendations for MEs (2012) are based on the 2011 source-strength positioning ME criterion recommendation of American Society for Radiation Oncology (ASTRO)⁵ but include some dose-based components for tissues other than the treatment site.
3. The ACMUI revised final recommendations for MEs (2012) are a modification of the ASTRO recommendations (2011). Although the ACMUI considers its revised final recommendations to be a more workable version of the ASTRO recommendations,⁶ unlike the ASTRO recommendations, the ACMUI ME criteria include explicit consideration of doses received by normal tissues and organs. This approach clearly would introduce additional licensee obligations if the ACMUI, rather than the ASTRO recommendations, were adopted as regulatory requirements. However, the staff believes that these additional criteria are warranted, in that they address the need to identify and report high doses to normal tissue.

⁴ See page 71 of the transcript for the 10/18/11 ACMUI teleconference, in ADAMS at ML11318A333.

⁵ ASTRO ACMUI Meeting Testimony on Permanent Implant Brachytherapy available in ADAMS at ML111010724.

⁶ See page 71 of the transcript for the 10/18/11 ACMUI teleconference.