

SUNSI Review Complete
Template=ADM-013
E-RIDS=ADM-03

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Comment (14)
Publication Date:
4/21/2023
Citation: 88 FR 24495

As of: 8/1/23, 11:05 AM
Received: July 30, 2023
Status: Pending_Post
Tracking No. lkp-qoam-8mzq
Comments Due: August 20, 2023
Submission Type: Web

PUBLIC SUBMISSION

Docket: NRC-2023-0086

Draft Regulatory Guide: Release of Patients Administered Radioactive Material

Comment On: NRC-2023-0086-0001

Draft Regulatory Guide: Release of Patients Administered Radioactive Material; Extension of Comment Period

Document: NRC-2023-0086-DRAFT-0015

Comment on FR Doc # 2023-08418

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General Comment

See attached file(s)

Attachments

Lantheus Letter to NRC - DG 8061



July 28, 2023

Office of Administration
ATTN: Program Management, Announcements and Editing Staff
Mail Stop: TWFN-7-A60M
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

RE: DOCKET ID NRC-2023-0086, DRAFT REGULATORY GUIDE (DG), DG-8061, RELEASE OF PATIENTS ADMINISTERED RADIOACTIVE MATERIAL," FEDERAL REGISTER VOL. 88, NO. 77; APRIL 21, 2023

Lantheus hereby provides the NRC with its comments on Draft Regulatory Guide (DG) DG-8061, "Release of Patients Administered Radioactive Material," which is proposed Revision 2 to Regulatory Guide (RG) 8.39 of the same name. Lantheus is a global leader in the development, manufacture, and commercialization of innovative diagnostic medical imaging agents and radiopharmaceuticals that provide tremendous benefits to patients by improving both the diagnosis and treatment of disease. Radiopharmaceuticals have increased overall survival rates and improved patient quality of life in a number of disease states. In addition, new radiopharmaceuticals now in clinical trials will extend these patient benefits across broader classes of disease.

The NRC's longstanding guidance regarding the criteria for releasing patients following radiopharmaceutical administration has enabled predictability in the medical community and aided the development and use of radiopharmaceuticals. The current guidance in Regulatory Guide 8.39, Revision 1, allows medical providers to release patients if the dosage administered is not greater than the activity listed in Table 1. These thresholds were developed using the conservative and scientifically justified assumption of an occupancy factor (i.e., the fraction of time a person is assumed present at a certain distance from a source of radiation) of 0.25. Providers are comfortable administering radiopharmaceuticals under these longstanding guidelines because they provide practical, predictable, bright-line thresholds for patient release.

The proposed guidance in DG-8061 represents a significant departure from this longstanding guidance because it significantly lowers the activity thresholds in Table 1. This change results from the proposal to use an assumed (but entirely unrealistic) occupancy factor of 1.0. However, there is no scientific basis to justify this occupancy factor. In practical effect, the proposed guidance in DG-8061 will likely cause many healthcare providers to turn away from offering critical and innovative treatments to patients. Healthcare providers may do so because the complexity and cost to comply with the revised patient release requirements will simply be too high. Thus, any incremental benefit from the draft guidance will be far outweighed by the harm to public health caused by restricting, unnecessarily, patients' access to care. Therefore, the NRC should retain the 0.25 occupancy factor assumption to calculate values in Table 1 and Table 2, consistent with criteria permitted by 10 CFR 35.2075, and described in the current Regulatory Guide 8.39 (Revision 1).

The Benefits of Radiopharmaceuticals

Patients benefit greatly from radiopharmaceuticals, which are used to improve both the diagnosis and treatment of disease. Some recent examples include the FDA approval of F-18 prostate-specific membrane antigen (PSMA) agents for imaging prostate cancer, Lu-177 DOTATATE for treating neuroendocrine tumors, and Lu-177 PSMA for treating prostate cancer. Many more radiopharmaceuticals are in development, with clinical trials underway for treatment of conditions including acute myeloid leukemia, glioblastoma, multiple myeloma, non-small-cell lung cancer, and pancreatic cancer. This combination of products both approved and in development shows the promise of radiopharmaceuticals to improve the lives of patients, offering longer survival and better quality of life. Unfortunately, the restrictive and complex patient release criteria proposed in DG-8061 would curtail access to these treatments.

The Existing Guidance Uses Conservative Assumptions That Adequately Protect Public Health and Safety

As mentioned above, existing guidance in Regulatory Guide 8.39 gives clear criteria for releasing patients administered radiopharmaceuticals based on the dose administered to them. Regulatory Guide 8.39 allows patients to be released if the dose administered to the patient does not exceed the activities listed in Table 1, Column 1 for the listed radionuclides. In calculating these thresholds, the NRC assumed an occupancy factor of 0.25 at 1 meter for physical half-lives that are greater than 1 day. The NRC characterized this (in its own words) as a “conservative assumption.” These published thresholds give health care providers the clear guidance needed to comfortably administer radiopharmaceuticals because they provide certainty and predictability that a patient will be releasable based on the planned dose.

The Draft Guidance Proposes an Arbitrary and Overly Conservative Occupancy Factor

The proposed draft guidance does not improve upon the framework used in Regulatory Guide 8.39. To the contrary, the draft guidance drastically lowers the activity thresholds for patient release in Table 1 by assuming an occupancy of 100 percent instead of the current occupancy factor of 0.25. However, the NRC identifies no scientific basis to justify quadrupling the occupancy factor.

First, the NRC’s Office of Research (RES) conducted a review of published literature regarding external dose to family members from patients released following administration of radiopharmaceuticals. That review determined that “[n]early all of the recorded doses to the family members were below the NRC dose limit of 5 mSv (0.5 rem)”¹, with a maximum recorded dose of 8.5 mSv (850 mrem). For context, a single Computed Tomography (CT) imaging exam is equivalent to approximately 600-1540 mrem². These real-world dose levels

¹ SECY-18-0015, Encl. 1, “Summary of Patient Release After Radioiodine Therapy Research Review” at 2 (Jan. 29, 2018) (ML17279B142).

² <https://www.acr.org/-/media/ACR/Files/Radiology-Safety/Radiation-Safety/Dose-Reference-Card.pdf>

do not indicate harm to the general public, and therefore neither necessitate nor justify the assumption of a 100% occupancy factor nor the drastic changes to the patient release criteria that result therefrom.

Second, Lantheus agrees with the Advisory Committee on the Medical Use of Isotopes' (ACMUI) assessment that, "[a]n occupancy factor of 1.0 is *unrealistic and cannot be justified* by routine application, even for radionuclides with a physical half-life less than one day."³ The ACMUI is an independent advisory panel of health care professionals from various disciplines who provide expert technical analysis to support NRC decision-making. The ACMUI noted that this unrealistic and unjustified occupancy factor results in "extremely conservative" activity thresholds in Table 1. Furthermore, the ACMUI noted that a 100 percent occupancy factor is inconsistent with the NRC's own codified occupancy factor of 0.25 in 10 CFR 35.2075(a), which pertains to recordkeeping requirements for radiopharmaceutical administrations. On July 10, 2023, the NRC rejected these observations from its own independent advisory panel.⁴

One cited basis for the NRC's rejection of the ACMUI's recommendation is that SECY-18-0015 observed that the current thresholds may underestimate exposure to bystanders "in some situations." Even so, the NRC did not provide any explanation as to how this vague, anecdotal, and generally unremarkable observation somehow could justify an occupancy factor of 1.0. The NRC considered neither the frequency nor the consequences of those limited "situations," and did not consider whether those (unidentified) probability-weighted consequences outweighed the substantial harm to public health and safety that would result from the proposal, as discussed further below. Moreover, a separate observation in SECY-18-0015 notes that, "[i]n the few instances where the dose to another individual exceeded [the applicable threshold]," it was attributable to the patient "not observing ALARA [as low as is reasonably achievable] principles and patient instructions." Thus, the solution proposed in DG-8061 (i.e., the quadrupling of the occupancy factor) appears to be disconnected from the root cause of the speculative underestimation.

The other basis cited by the NRC for rejecting the ACMUI's recommendation is that providers can choose to use patient-specific or measurement-based release methods, develop their own alternative release criteria, or simply "hold the patient for a period of time." This observation likewise provides no justifiable scientific, technical, or regulatory basis for selecting an occupancy factor of 1.0. And, from a practical perspective, these options fail to provide the certainty and predictability associated with the current thresholds in RG 8.39. The NRC has not considered the potential harmful effects of removing that certainty and predictability in the broader healthcare context, as explained below.

³ Advisory Committee on the Medical Use of Isotopes, Final Report on Revision 2 to Regulatory Guide 8.39, "Release of Patients Administered Radioactive Materials" at 2 (Jan. 21, 2022) (ML22021B300).

⁴ Memorandum from C. Einberg to D. Metter, "Responses to the [ACMUI]'s Recommendations on Draft Proposed Revision 2 to Regulatory Guide 8.39, "Release of Patients Administered Radioactive Materials" at 2-3 (July 10, 2023) (ML23178A090).

Using an Arbitrary and Overly Conservative Occupancy Factor Could Curtail the Availability of Radiopharmaceutical Treatments, Causing Negative Impacts on Patients, with No Tangible Improvements to Public Health and Safety

Slashing the activity thresholds in this manner could cause providers to stop administering radiopharmaceuticals—with real, negative impacts on patients. If the proposed revisions to Table 1 are implemented, many providers may simply choose to treat the revised activity thresholds as firm limits—particularly in smaller facilities, which represent the predominant treatment locations for widely-used therapies. If a product’s recommended dose is above the Table 1 values, those providers will be less likely to make that product available to patients.

Administering a dose above Table 1 values presents an unappealing set of options to the provider. The provider can either (1) take on the cost, complexity and regulatory risk of using second-tier methods, or (2) admit the patients for in-patient care for a lengthy time (potentially several days) at high cost, which is unlikely to be reimbursed by insurance. These requirements are particularly burdensome for community hospitals, which lack the resources of large academic institutions, but ultimately provide the majority of care for cancer patients. If radiopharmaceutical therapy treatments are limited to large academic “centers of excellence,” travel requirements will dramatically limit patient access, as has been demonstrated by real-world experience with therapies that are limited to such centers.

From a patient standpoint, inpatient admission is a significant burden—both personally and financially. Patients who are currently administered many therapeutic isotopes, such as Lu-177 PSMA, can be discharged the same day and pose no significant risk to family, friends, or the general public. Under the proposed DG-8061 guidelines, these same patients could have to stay in the hospital for approximately one week, creating disruptions to both their personal and family lives as well as missing extended time at work. Thus, even assuming treatment availability and insurance coverage for inpatient care, these increased burdens may disincentivize patients from electing to pursue these treatments in the first place. In creating these hurdles for both the provider and the patient, the arbitrary and overly conservative occupancy factor proposed in DG-8061 could significantly reduce access to life-saving radiopharmaceutical therapies.

Ultimately, the burdens of using an occupancy factor of 1.0 far outweigh the benefits. The extraordinary and unjustified conservatism proposed by DG-8061 does not provide meaningful benefit to the public to outweigh the loss of benefit to patients. While any beneficial effect on public health and safety that may result from this overly conservative approach are marginal and theoretical, patients would face a realistic possibility of being deprived of treatments that extend survival and improve quality of life.

The Importance of Patient Discharge Instructions

Overall, the most effective means of keeping exposure ALARA is through improving communication with patients regarding adherence to discharge instructions. As noted above, the NRC Staff concluded that, “[i]n the few instances where the dose to another individual exceeded [the applicable threshold],” it was attributable to the patient “not observing ALARA principles and patient instructions.” Lantheus supports and appreciates the addition of a new section in DG-8061 addressing the content of patient instructions and believes these provisions will enhance public health and safety without the detrimental effects that would result from using an occupancy factor of 1.0.

Conclusion

Lantheus recommends that the NRC maintain the 0.25 occupancy factor and bring the values in Table 1 and Table 2 in line with the current version (Revision 1) of Regulatory Guide 8.39. This will preserve patient access to beneficial treatments while maintaining the health and safety of the general public.

Respectfully submitted,

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