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March 20, 2006

DOCKETED 03/30/06

PRM-35-19

Annette L. Vietti-Cook, Secretary
U.S. Nuclear Regulatory Commission
Washington, D.C. 20555-0001

Attention: Rulemakings and Adjudications Staff

Dear Ms. Vietti-Cook:

Pursuant to 10 CFR 2.802, the enclosed petition for rulemaking is submitted to the U.S. Nuclear Regulatory Commission (NRC) to request that a class of physicians, namely medical oncologists/hematologists, be able to qualify as Authorized User physicians for certain unsealed byproduct materials that are currently commercially available and for which written directives are required with 80 hours of classroom and laboratory training, as well as appropriate work experience and written attestation. This would require the addition of a new requirement or modification of an existing training and experience requirement as specified in 10 CFR Part 35. The purpose of this petition is to request the codification of the 80-hour training and experience requirement as appropriate and sufficient for physicians desiring to attain AU status limited to therapeutic administrations of ^{153}Sm-lexidronam (Quadramet®), ^{131}I-tositumomab (Bexxar) and ^{90}Y-ibritumomab tiuxetan (Zevalin), all FDA-approved parenterally-administered therapeutic agents.

Given that medicine is expanding and new agents are coming onto the marketplace, there is currently an unmet regulatory need to address the ability of physicians to qualify for medical use authorization for certain unsealed byproduct materials that are currently commercially available and for which written directives are required. While the addition of § 35.396 was a step in the right direction, it clearly falls short in fully addressing this need.

It is our desire to promote and protect public health and safety and ensure that all patients requiring ^{153}Sm-Quadramet, ^{131}I-Bexxar and ^{90}Y-Zevalin treatments be allowed to receive it. Thank you very much for your consideration and attention to this matter.

4228 Houma Boulevard, Suite 130, Metairie, LA 70006 Phone: 504.883.2960 Fax: 504.883.2967

Sincerely,

William Stein, III, M.D.

PETITION FOR RULEMAKING

We submit this petition for rulemaking pursuant to 10 CFR 2.802. The petitioners request that the NRC amend 10 CFR Part 35, *Medical Use of Byproduct Material*, to add a new requirement, potentially in 10 CFR 35.395, or modify the requirement in 10 CFR 35.396, to define and specify the number of classroom and laboratory training hours appropriate and sufficient for physicians desiring to attain Authorized User status limited to parenteral administrations of ^{153}Sm-lexidronam (Quadramet), ^{131}I-tositumomab (Bexxar), and ^{90}Y-ibritumomab tiuxetan (Zevalin). The proposed new training and experience (T&E) requirement for these agents should reflect those requirements currently in 10 CFR 35.394, *Training for the oral administration of sodium iodide I-131 requiring a written directive in quantities greater than 1.22 Gigabecquerels (33 millicuries)*, and not those currently in 10 CFR 35.396, *Training for the parenteral administration of unsealed byproduct material requiring a written directive.*

^{153}Sm-lexidronam (Quadramet®) is a Food and Drug Administration (FDA) approved agent for commercial use for relief of pain in patients with confirmed osteoblastic metastatic bone lesions and is administered intravenously. The activity is administered on a weight basis according to 1 mCi/kg of patient body weight; an average patient dosage would thus be 70 mCi. The main route of elimination of Quadramet is urinary excretion that is essentially complete within the first 6 hours of administration. Less than 1% of the administered activity remains in the blood 5 hours after administration. The remaining activity, approximately 65.5% ± 15.5% of the administered dosage, will be retained in the skeleton for the physical half-life of ^{153}Sm. ^{153}Sm results in minimal risk of radiation exposure to health care workers, family members, or others with whom the patient may have contact. The patient can be released without any special considerations per NUREG 1556, Vol. 9. Patients can be immediately released if the administered activity of ^{153}Sm is less than 700 mCi, and no instructions are required if the administered activity is less than 140 mCi.

^{131}I-Bexxar is a Food and Drug Administration (FDA) approved agent for commercial use for the treatment of non-Hodgkin's lymphoma and is administered intravenously. The administered activities have ranged from 33 - 161 mCi, with an average of approximately 84 mCi; activity dosages that are generally less than those used for oral Na^{131}I treatment of thyroid cancer. Actual dose measurements in family members of released Bexxar patients have indicated that no individual is likely to receive a dose in excess of the 500 mrem limit. Interestingly, a patient receiving 30 mCi of orally administered ^{131}I for hyperthyroidism can potentially expose individuals to a larger radiation dose than a typical patient receiving ^{131}I-Bexxar due to the much longer retention of ^{131}I in the body in the former case. Further, the radionuclide, ^{131}I, is firmly attached to the protein antibody in the Bexxar regimen and therefore represents a much lower contamination hazard than that associated with oral ^{131}I administrations.

^{90}Y-Zevalin is a Food and Drug Administration (FDA) approved agent for commercial use for the treatment of non-Hodgkin's lymphoma and is administered intravenously. The activity is administered on a weight basis according to 0.4 mCi/kg (or 0.3 mCi/kg in the case of mild thrombocytopenia) of patient body weight up to a maximum patient dosage of 32 mCi. ^{90}Y results in minimal risk of radiation exposure to health care workers, family members, or others with whom the patient may have contact. The patient can be released without any special considerations per NUREG 1556, Vol. 9.

All the above activity administrations, which require written directives, are from a radiation safety perspective no more and generally less hazardous than oral ^{131}I administrations. The T&E requirements for ANY physician wishing to treat their patients with ^{153}Sm-Quadramet, ^{131}I-Bexxar and ^{90}Y-Zevalin should, therefore, not exceed those for an endocrinologist treating thyroid disorders with oral Na^{131}I, i.e., T&E requirements for a physician to attain AU status for these parenteral administrations should be similar to those applicable to the alternate pathway for oral Na^{131}I-only requiring a WD in quantities of $\leq$ 33 mCi (§ 35.392) or > 33 mCi (§ 35.394). In both these latter cases, the alternate T&E pathway requires 80 hours of classroom and laboratory training as well as appropriate work experience and written attestation, and is specifically intended to enable ANY physician to obtain AU status under this limited authorization. The T&E requirement addressing parenteral administrations pursuant to 10 CFR 35.396, *Training for the parenteral administration of unsealed byproduct material requiring a written directive,* is overly restrictive and unduly burdensome for these agents as it requires board certification in radiation oncology.

There is no question that training and experience requirements should be appropriately rigorous for those types of uses of byproduct material for which potential hazards are greater. Currently, 10 CFR Part 35 permits physicians to be able to use byproduct materials for which a WD is required based on one of three T&E requirements pertaining to the following: 1) use of oral Na^{131}I and ALL parenteral administrations; 2) use of only oral Na^{131}I; and 3) use of ALL parenteral administrations. The minimum number of hours of classroom and laboratory training applicable to the "alternate pathway" for these administrations are

1. 200 hours: § 35.390 (oral Na^{131}I and ALL parenteral administrations);
2. 80 hours: §§ 35.392 and 35.394 (oral Na^{131}I only);
3. 80 hours: § 35.396 (ALL parenteral administrations, but only applicable to board-certified radiation oncologists).

We have reviewed the commission paper prepared by NRC staff, SECY-05-0020, *Final Rule: Medical Use of Byproduct Material – Recognition of Specialty Boards*, and all its attachments, dated January 19, 2005. As stated by NRC staff in Attachment 2, the increased hours required for § 35.390 physicians is justified because these physicians are authorized to elute generators and prepare radioactive drugs, as well as administer a wide variety of radionuclides for which WD's are required; thus, the associated radiation risks of use could be greater. More knowledge is therefore required in the topic areas of radiation physics and instrumentation, radiation protection, mathematics pertaining to use

and measurement of radioactivity, chemistry of byproduct material for medical use, and radiation biology to ensure the safe use of ALL byproduct material, orally AND parenterally administered, for which WD's are required. NRC staff justifys these increased hours, for the most part, on the basis of the wide variety of radionuclides that might be used and because of the greater quantities of byproduct material that might be involved.

NRC's reasoning and rationale for 10 CFR 35.396 is not known. The revised 10 CFR Part 35, *Medical Use of Byproduct Material*, became effective on October 24, 2002. Because of "issues" with the T&E requirements, the revised rule retained the then current T&E requirements for a 2-year transition period until October 25, 2004. The NRC then extended the transition period for an additional year to October 24, 2005. It was during this final year that § 35.396 was first established and published in the Federal Register on March 30, 2005 (70 FR 16335) as part of the Final Rule pertaining to T&E requirements. No comment period was offered before this new requirement appeared in the Final Rule.

In the case of a proposed ^{153}Sm-Quadramet, ^{131}I-Bexxar and ^{90}Y-Zevalin physician, similar to an oral Na^{131}I-only AU physician, these radioactive drugs do not have to be prepared using generators and reagent kits. The radiopharmaceuticals are generally prepared at a commercial radiopharmacy and then supplied to medical facilities as a unit dosage (a dosage that is generally much less than that employed with oral Na^{131}I for the treatment of thyroid cancer). The risks for patient care personnel as well as for the public after patient release are equal to or much less than those associated with oral ^{131}I administrations. The possibility of emesis may complicate radiation safety considerations in patients receiving oral administrations. Parenteral administration essentially removes this potential source of radioactive contamination and exposure. While it is true that these three agents represent a variety of radionuclides, they are generally administered in quantities much less than that required for the treatment of thyroid cancer with oral Na^{131}I; thus, none of these agents or all of them collectively pose a potential risk that is any greater than oral Na^{131}I. Use of these agents should therefore be a medical issue rather than a radiation safety issue.

We believe that physicians seeking to attain AU status for the limited authorization of parenteral administrations of ^{153}Sm-Quadramet, ^{131}I-Bexxar and ^{90}Y-Zevalin requiring a WD should be subjected to an alternate T&E pathway consisting of 80 hours of classroom and laboratory training, plus supervised work experience and a written attestation as a necessary and sufficient requirement, similar to the current requirement for oral Na^{131}I administrations pursuant to 10 CFR 35.394. We believe that the Final Rule has unintentionally excluded such a requirement. (We note, without comment, that only 24 hours of didactic training is required for the ophthalmic use of Sr-90 pursuant to § 35.491 despite the occurrence of 757 misadministrations by 8 different licensees between 1990 and 2000 according to NRC Information Notice 02-017, *Medical Use of Sr-90 Eye Applicators*, dated April 5, 2002).

Moreover, unlike §§ 35.392 and 35.394, NRC has not contemplated codification of individual agents as they become commercially available for medical use. Given that

medicine is expanding and new agents are coming onto the marketplace, there is currently an unmet regulatory need to address the ability of physicians to qualify for medical use authorization for certain unsealed byproduct materials that are currently commercially available and for which written directives are required. Pursuant to 10 CFR 35.390(b)(1)(ii)(G)(3) and (4) and 10 CFR 35.396(d)(2)(vi), only two generic types of parenteral administrations, for which written directives are required, have been considered:

1. Parenteral administrations of any beta emitter or photon-emitting radionuclide with a photon energy less than 150 keV; and/or
2. Parenteral administrations of any other radionuclide.

The current T&E requirements involving ALL parenteral administrations do not adequately consider the training necessary to attain AU status for the recently FDA-approved ^{153}Sm-Quadramet, ^{131}I-Bexxar and ^{90}Y-Zevalin. These agents should be subjected to training requirements pursuant to their potential radiation safety risks, as is the case for oral administrations of $Na^{131}I$, rather than be lumped into a collective group of agents, as is the current practice. This would allow NRC to evaluate each agent individually and create a mechanism whereby these agents, as well as future agents, can be handled appropriately. It may be that other more hazardous parenterally-administered agents, if they become commercially available, would require the increased training currently specified in §§ 35.390 and 35.396.

The current rule is, therefore, unduly burdensome and deficient in this regard. Without regulatory relief, an entire class of physicians would be unfairly discouraged from providing these FDA-approved and commercially available treatments resulting in an adverse impact on their ability to practice medicine. As they would be required to become board-certified radiation oncologists, pursuant to 10 CFR 35.396, or obtain 700 hours of training (to include a minimum of 200 hours of classroom and laboratory training) pursuant to 10 CFR 35.390, without justification of the need for board-certification in radiation oncology or the additional training hours to further ensure the safe use or minimize the associated radiation risks of use of ^{153}Sm-Quadramet, ^{131}I-Bexxar and ^{90}Y-Zevalin.

In order to conclude that board-certification in radiation oncology or the additional training hours are required for the safe use of parenteral administrations of ^{153}Sm-Quadramet, ^{131}I-Bexxar and ^{90}Y-Zevalin, the NRC would have to assert that each of these agents represents a greater radiation safety hazard than oral $Na^{131}I$. This is more a practice of medicine issue than a radiation safety issue. We believe that NRC would be intruding into the practice of medicine if it did not conclude that physicians, and more specifically medical oncologists/hematologists, who have received 80 hours of classroom and laboratory training, as well as appropriate work experience and written attestation, could be granted AU status for these therapies. A prohibition would likely restrict the ability of medical oncologists/hematologists, who are the primary care providers for cancer patients, to administer these agents and thus limit patient access to treatments for life threatening diseases. Therefore, we request that 80-hour T&E for physicians, as

required under the alternate pathway for oral $Na^{131}I$ administrations, be recognized by the NRC as adequate and sufficient to ensure the radiation safety of workers and the general public, pursuant to its Medical Use Policy Statement. This will allow properly trained medical oncologists/hematologists and their patients access to these FDA-approved therapeutic agents.

This would be consistent with prior NRC thinking. Specifically, NRC has stated, both in SECY-05-0020 and in 67 FR 20249 (Part II, General Issues, Section E, issued April 24, 2002), that the T&E for AU's under § 35.300 was revised to focus on radiation safety and that 80 hours of classroom and laboratory training for physicians authorized to administer oral $Na^{131}I$, pursuant to §§ 35.392 and 35.394 is sufficient for radiation safety purposes, since these physicians do not prepare radioactive drugs using generators and reagent kits. The additional training pursuant to §§ 35.390 and/or 35.396 was justified by NRC because these physicians are preparing radioactive drugs and handling unsealed source material in quantities that "can cause deterministic effects" or whose associated radiation risks of use "could" be greater. Physicians desiring to administer ^{153}Sm-Quadramet, ^{131}I-Bexxar and ^{90}Y-Zevalin do not need to prepare radioactive drugs and none of these agents are associated with activity administrations and/or radiation risks greater than orally-administered $Na^{131}I$ for the treatment of thyroid cancer.

In conclusion, we request that NRC recognize that 80 hours of classroom and laboratory training, supervised work experience, and a written attestation for physicians is adequate and sufficient to attain AU status for parenteral administrations of ^{153}Sm-Quadramet, ^{131}I-Bexxar and ^{90}Y-Zevalin, all requiring written directives. We offer three options:

1. A specific requirement should be added to 10 CFR Part 35, potentially in 10 CFR 35.395, entitled *Training for the parenteral administration of samarium-153 lexidronam, iodine-131 tositumomab and yttrium-90 ibritumomab tiuxetan requiring a written directive.* The language would be essentially equivalent to that currently in 10 CFR 35.394 for oral administrations of $Na^{131}I$, particularly with regard to the alternate T&E pathway to attain AU status. An important required language change would involve dosage administrations, as specified in § 35.394(c)(2)(vi), to require administering dosages to patients or human research subjects, that includes at least 3 cases involving each of these parenteral administrations.

2. A separate requirement for each of these three agents should be added; this is certainly in keeping with the already codified stand-alone T&E requirements for the oral administration of $Na^{131}I$, particularly with respect to parenteral administrations of ^{131}I. This allows NRC to evaluate each agent individually and create a mechanism whereby these agents, as well as future agents, can be handled appropriately from a radiation safety perspective.

3. As an alternative to a new requirement(s), 10 CFR 35.396, which pertains to parenteral administrations, should be modified to allow the 80-hour classroom and laboratory training, as well as appropriate work experience and written

attestation, to apply to the "alternate" pathway for ANY physician (not just board-certified radiation oncologists).This could easily be accomplished by removing § 35.396(c) and changing sections (d)(1), d(2) and d(3) to (c)(1), (c)(2), (c)(3) with no required language changes. The Commission may not agree with this proposed rule change if other more hazardous parenterally-administered agents become available, necessitating the increased training currently specified in this requirement.