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General Comment

See attached file(s)

Attachments

Comments to NRC re T&E1

Comments Re: Training and Experience Requirements for
Different Categories of Radiopharmaceuticals
Docket ID NRC–2018–0230

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A brief history relevant to the Training and Experience (T&E) issue

Prior to NRC's revision of Part 35 (pre-2002), only 80 hours of T&E (actually only 80 hours of classroom and laboratory training plus an unspecified number of clinical experience hours) were required for the alternate pathway to attain AU status for therapeutic use pursuant to 35.930 (only I-131 use was considered). At the same time, diagnostic use pursuant to 35.920 required 700 hours.

During the revision NRC modified Part 35 based on a risk-informed performance-based approach. 35.930 was replaced with 35.390 requiring 700 hours for the alternate pathway. Pursuant to 35.392 and 35.394 only 80 hours of training were and are still required for oral $Na^{131}I$ use. In essence, NRC tailored T&E requirements for the specific use of oral $Na^{131}I$ – the alternate pathway to attain AU status for all other therapeutics required 700 hours. The 80 hours was maintained by NRC due to effective persuasion by endocrinologists over 15 years ago – but today, ANY physician desiring the limited authorization to use $Na^{131}I$ can attain AU status with only 80 hours of training, which the NRC believes is adequate and sufficient.

Then in 2006, a petition was submitted to NRC requesting the 700 hours be reduced to 80 hours for medical oncologists and hematologists to use Quadramet, Bexxar and Zevalin, arguing that these agents were no more hazardous, and even less, than oral $Na^{131}I$. This petition was denied by NRC noting that I-131 is considered (by them) to be less of a radiation safety issue than any of these 3 agents. NRC also believed that "further" tailoring of T&E requirements ("further" because NRC had already established tailored requirements for oral $Na^{131}I$ use), would increase the complexity of regulatory oversight with no benefit to anyone.

As stated by the NRC in its denial of this petition in the Federal Register on October 24, 2007 (72 FR 60285): "The current approach to training and experience for the medical use of unsealed byproduct material accommodates the introduction of new radiopharmaceuticals without requiring additional rulemaking, with its associated costs to the Agreement States. Attempting to tailor the training and experience requirements to specific uses of unsealed byproduct material and to the amount of flexibility that a user may wish to have would significantly increase the complexity of the regulatory oversight. The NRC does not believe that such added complexity would be of benefit to patients, the Agreement States, licensees, current and prospective authorized users, or the medical specialty boards."

Tailoring T&E requirements to specific agents and uses may indeed increase the complexity of regulatory oversight, but this should only be a minor concern if an enormous benefit to patients were realized as would likely occur if usage of any demonstrably safe radiopharmaceutical was regulated with an appropriately tailored reduced T&E requirement. This would represent a risk-informed approach, increasing physician and patient access to important treatments without adversely affecting public health and safety.

It is necessary for NRC to establish further tailored T&E requirements for certain therapeutic radiopharmaceuticals commensurate with their associated radiation risk

Currently pursuant to 10 CFR 35.390, physicians must be either certified by a medical specialty board whose certification process is recognized by the NRC or an Agreement State or completed 700 hours of training and experience (T&E) under an alternate pathway to attain authorized user (AU) status for any radionuclide therapy (except only oral $Na^{131}I$ where only 80 hours is required pursuant to 10 CFR 35.392 or 35.394). Using a one-size-fits-all regulatory approach is not beneficial to all - it is overly burdensome and limits patient access to vital radionuclide therapy treatments that may involve a minimal radiation safety hazard. Increased regulatory complexity should be of minor concern if significant beneficial effects can be realized. All therapeutic radiopharmaceuticals do not pose the same risk so it follows that their use should not be subjected to, and limited by, identical T&E requirements. This contradicts the risk-informed approach adopted by NRC.

NRC should establish additional tailored T&E requirements ("additional" since NRC has already established tailored requirements for oral $Na^{131}I$ use) since not all radiopharmaceuticals pose the same risk. Important considerations to ascertain sufficient T&E for a given radiopharmaceutical to ensure adequate and appropriate radiation protection for patients and workers include: emissions profile, how supplied, intended administered activity level, route of administration, half-life, impurity/radiocontaminant levels, route of elimination from the body, waste disposal, patient release issues (potential dose rate to others, contamination), etc.

Currently, physicians are not free to select agents for limited use authorization regardless of their safety profile as they must attain AU status for all agents pursuant to 35.390. Of course this is no true for limited use authorization of $Na^{131}I$ since a physician would undoubtedly choose the alternate pathway pursuant to 35.392 or 35.394 since much fewer hours are required. The pathways for attaining AU status pursuant o 35.390 are not reasonable since physicians desiring limited AU status are required to have the same T&E as physicians seeking full AU status for all agents under 35.300. This becomes a practice of medicine issue for use of those agents associated with limited radiation safety concerns.

For example, since the launch of Xofigo in 2013 over 100,000 doses have been delivered and administered to patients at more than 1,000 sites located across the United States.

During this time there have been no significant radiation-related issues. Based on these historical data and the safety considerations listed above, Xofigo poses limited radiation safety concerns. If a physician is seeking limited authorization without any additional flexibility for use of this relatively safe agent, 700 hours is not warranted and overly burdensome. Compared to Xofigo, $Na^{131}I$ presents much greater radiation safety issues, including: higher dose rates due to high energy emissions, higher administered activity, longer half-life, the fact that I-131 is a leaky source while Xofigo is excreted mostly in feces so internal contamination is highly improbable, the emesis issue due to the oral administration and the need for complicated patient release instructions to minimize external dose to others.

Reducing T&E requirements will still ensure adequate radiation protection for Xofigo use

Given its documented radiation safety record, requiring 700 hours pursuant to 35.390 for limited AU status in the case of Xofigo is not warranted. It also conflates a single specific use with the ability to use all forms of radionuclide therapy with unlimited flexibility. Mandating 700 hours of training may be necessary for some agents, and if a physician intends to use all available therapies, but this number of hours is indeed burdensome to those physicians desiring to attain limited authorization for Xofigo-only use, when such extensive training has been shown to be unnecessary to ensure adequate radiation protection to patients and workers.

Physicians, such as medical oncologists, hematologists and urologists) may desire to incorporate only a single FDA-approved and commercially available radioactive therapeutic agent into their practice and should be encouraged to do so if they have received training deemed sufficient to ensure appropriate and adequate radiation protection to patients and workers. Xofigo (Ra-223 dichloride) is an alpha-emitting therapeutic administered in only microcurie quantities provided as a unit dosage in a syringe ready to be injected with no additional manipulation, is of minimal external exposure concern and since it is excreted mainly in the feces it is not a likely source of internal contamination. The potential dose to others is so low that patient release instructions are not even required pursuant to 35.75. Since Ra-223 does emit photons, albeit minimally, conventional nuclear medicine equipment (such as dose calibrators and survey meters) have been shown to be appropriate for measurement and detection purposes; alpha-specific instrumentation is not required.

Thus, from a radiation safety perspective, Xofigo is no more, and generally much less, hazardous than oral $Na^{131}I$ administrations. The training requirements for ANY physician wishing to treat their patients with Xofigo should therefore not exceed those for ANY physician treating thyroid disorders with oral $Na^{131}I$. This should therefore be considered a practice of medicine issue rather than a radiation safety issue and would be consistent with NRC's Medical Use Policy Statement that "NRC will not intrude into medical judgments affecting patients, except as necessary to provide for the radiation safety of workers and the general public." The NRC did not increase the duration of training for

endocrinologists in the revised Part 35 over the previous requirement for such use in part due to consideration of the following comment submitted by endocrinologists (as published in the Federal Register on April 24, 2002): Any increase over the existing 80 hour training requirement would conflict with NRC's guidelines of minimizing intrusion into medical judgments affecting patients and into other areas considered to be a part of the practice of medicine. That is, additional training hours are not justified by the risk to patients, as would also be the case for Xofigo only use.

In conclusion, T&E requirements should be appropriately rigorous and tailored to reflect the radiation risks involved, being more extensive for those types of uses of byproduct material for which potential hazards are greater. This may increase the complexity of regulatory oversight, but when justified, would be a more risk-informed approach and of great benefit to patients and their treating physicians. The NRC considers that the alternate "tailored" 80-hour training pathway for any physician to attain AU status for oral $Na^{131}I$ use is justified and sufficient for radiation safety purposes, because, as published on April 24, 2002 (67 FR 20264), these physicians are only seeking *limited* authorization – for only the oral administration of $Na^{131}I$ in dosages ≤33 mCi (pursuant to 10 CFR 35.392) or in dosages >33 mCi (pursuant to 10 CFR 35.394) – AND they are not seeking authorization to prepare radioactive drugs using generators and reagent kits. Nor are they seeking to administer any other agents, let alone a wide variety of radionuclides, which would increase the associated radiation risks of use, justifying the increased 700-hour alternate pathway required pursuant to 10 CFR 35.390. An additional tailored reduced training pathway is even more justified for a physician (such as a medical oncologist, hematologist or urologist) seeking limited authorization use of only Xofigo, due to the fact that the associated radiation protection concerns are minimal in comparison to $Na^{131}I$. Therefore, a new requirement needs to be codified (e.g., 10 CFR 35.395) to indicate that only 80 hours of training, perhaps even less, is appropriate and adequate for Xofigo-only use. Restricting physicians' access to, and ability to use an FDA-approved and commercially available agent by imposing unwarranted and unduly burdensome T&E regulations, is detrimental to them and their patients, conflicts with NRC guidelines of minimizing intrusion into medical judgments and is most assuredly not risk informed.

As an interesting aside, there is a disconnect between the expertise necessary for the release of patients administered radioactive material and training requirements – blindly following flawed guidance should not be acceptable for compliance with the patient release rule

Medical licensees are required to comply with NRC regulations pertaining to the release of patients administered radioactive material. This is an extremely important requirement so compliance should not be achieved based on NRC guidance as published in NUREG-1556, Vol. 9. Given NRC's necessary current T&E focus, I would be remiss if I did not say a few words about this.

In 1997, the NRC amended its regulations pursuant to 10 CFR 35.75 concerning the criteria for the release of patients administered radioactive material. According to 10 CFR 35.75, the guidance provided by NUREG-1556, Vol.9, Appendix U represents acceptable procedures to comply with the patient release regulation. However, as I have written and communicated to the Commission, this appendix sets back the practice of radiation protection science almost 20 years, with material that is scientifically baseless, disregarding the large body of published literature demonstrating the proper methodology. Using erroneous assumptions and parameter values, the "calculated" doses to others are highly inflated and therefore of limited value, making it impossible to properly issue release instructions to patients.

The NRC's Advisory Committee on the Medical Uses of Isotopes (ACMUI), published its "Patient Release Report" on December 13, 2010, indicating that NRC guidance overestimates doses, and recommended that it be updated with assistance from experts. Interestingly, NRC staff apparently disagreed with the ACMUI and my numerous publications, asserting that over-conservatism is appropriate and that any criticism of this practice "reflects a misunderstanding of the guidance." Pursuant to SECY-12-0011, "Data Collection Regarding Patient Release," dated January 25, 2012, even though the patient release rule has no built-in conservatism, "The calculations performed by NRC and described in the NUREG, and the tables that are based on these calculations, are intended to serve as screening tools for the convenience of licensees who may not wish to do their own calculations, or *who do not have the technical expertise* to do them [emphasis added]." Thus, NRC, through its guidance, apparently finds it "acceptable" to massively overestimate doses to others in order to allow licensees, who either don't wish to do calculations or who may lack the requisite expertise to even do them, to treat and release radionuclide therapy patients. Although it is true that guidance carries no regulatory weight, most licensees adopt it anyway without critical assessment, thereby adding an unfounded extra-regulatory burden. Given that many licensees not only implement this guidance without question but also may not even be capable of performing their own calculations, it is apparently acceptable to NRC that AUs may possess limited understanding and expertise in the areas of radiation physics, radiation protection and mathematics pertaining to use and measurement of radioactivity, despite their having received this mandated training. This expertise is particularly important for release of $Na^{131}I$ patients; not so much for Xofigo patients