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August 14, 2020

Kathryn Tapp and Irene Wu
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Dear Dr. Tapp and Ms. Wu:

The OAS Executive Board (Board) appreciates the opportunity to comment on the Nuclear Regulatory Commission's (NRC) draft technical evaluation report (TER) entitled, "Technical Evaluation Report for Exubrion Therapeutics' Proposed License Application Template for the Release of Dogs Following Treatment with a Tin-117m Colloid."

The Board has reviewed the information provided in the TER as well as the information provided by Exubrion in their response to additional information (RAI) requests, model runs from Microshield, and the shielding study. Based on our review of the information, the Board has the following questions and comments.

1. There is no justification provided for eliminating low energy gammas from the Microshield modeling. Including the 0.0034 Mev gamma increases the dose for close distances.
2. Dogs with an average weight of 67 pounds were used for the modeling and for the distance to human measurements. Wouldn't larger dogs have closer torso to elbow distances, thus increasing the dose? Particularly a shorter person walking a Great Dane, for example.
3. The Board could find no justification or modeling results for one 6 mCi activity source located halfway between the dog elbows versus modeling one 3 mCi activity source in each elbow. In fact, all the models are run with a 3.046 mCi source activity. Are there any models showing the dose from 3.046 mCi in each elbow?
4. When the same inputs are used in Microshield Version 9 versus Microshield Version 7.02 (used by Exubrion), higher results are obtained. This is concerning considering the tolerances are so low to ensure public dose limits are not exceeded.
5. Microshield calculations include shielding from tissue ($1.81E4 \text{ cm}^3$). Exubrion then takes credit for more shielding determined from their shielding study. Is this double counting the shielding provided by the dog's torso? Or is the shielding in Microshield

Alabama, Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Minnesota, Mississippi, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, Virginia, Washington, Wisconsin, Wyoming

for the human torso? This is complicated by the fact that the model used a cylinder source to a point receptor instead of a point source (elbow) to a cylinder receptor (human torso). If the cylinder is the source, then is the shielding from tissue in the Microshield run an overestimation of the shielding afforded by elbow tissue?

6. The shielding study presents its own inconsistencies. Left lateral dose rates should be nearly identical to right lateral dose rates in the same dog. However, there are some readings that are over 50% different. Other inconsistencies can also be seen in the data. Did the sources move? Should that invalidate the rest of the readings for that particular dog? Also, does combining all the dose rates from different locations make sense for a shielding factor? Are there other shielding studies that use this technique as a precedence?
7. The procedure states the licensee will only schedule the procedure if it is confident the owner understands the need to comply with public dose limits and can comply with the Release Instructions. This is subjective and relies on the subjective responses of the owner who is motivated to alleviate the pain of their dog.
8. Exubrion states that due to the geometry of a dog's elbow to a person's torso and increased shielding the closer the dog is to a person, distances of 6 inches (15.2 centimeters [cm]) are not reasonable for situations such as lap-sitting. Distances of 6 inches or closer seem very reasonable for lap-sitting depending on the dog and how it orients itself on the lap. The elbow could be in direct contact with the torso.
9. On page 15 of the Exubrion technical evaluation, it states: "To normalize the results, the activity of the point source was chosen such that the dose rate at a point one meter from a point source was 0.45 mrem/hr, equal to the maximum allowed dose rate for release of a dog. This activity was then evenly distributed within the volume of consideration for the MicroShield calculations." That point source activity is 3.046 mCi. Why would that activity be evenly distributed since this is only half the activity that will be injected into a large dog?
10. On page 16 of the Exubrion technical evaluation report it states that modeling was performed for the on contact dose using 1.7 cm as the distance, taking into account the distance to the center of the "elbow" modeled as a cylinder, and 3mm of skin shielding. This model run was not included in Appendix D. What was the contact dose with buildup? Since the contact dose is not provided, the inverse square calculations could not be verified.
11. On page 17 of the Exubrion technical evaluation report states: "Using the maximum dose rate at release of 0.45 mrem/hr at 1 meter, the torso sizes based on the above table, and the 1.7 cm radius of the elbow (including the skin), the following dose rates using MicroShield were determined. To simplify the calculation, it is assumed all the activity is in one elbow." However, there is no Microshield run that uses 6 mCi as the source. Was the "elbow" located in the center of the animal or to one side? How could you have

a maximum dose rate at release of 0.45 mrem/h at 1 meter using 6 mCi as the source? These calculations can not be verified because the runs are missing from Appendix D.


12. The NRC TER determined that even if the owner disregards all instructions, the occupational dose limit would not be exceeded. The Board finds this conclusion very disturbing. Not only could the public dose limit be exceeded, but the Board finds that release of these dogs does not follow ALARA principals, nor does it account for other doses that an individual may incur. In addition, the TER clearly demonstrates and acknowledges that the dose rate in the near vicinity of the treated animal, which is unrestricted once released, can without question exceed 2 mrem in an hour.
13. The Board has serious doubts that spending the amount of time with the owner on the pre-screening questionnaire will result in not administering the drug. Economic factors on the part of the licensee would seem to lean toward administering the drug, not being objective in evaluating the responses to the questionnaire.
14. More than any other licensed use of RAM, this therapy depends on strict owner compliance with instructions, and for an extended duration. The public dose limit can be exceeded by a SINGLE failure to follow instructions (child co-sleeping with dog for one night). The Board finds this unacceptable.
15. The NRC TER states: “After the 2-week minimum duration for instructions, Exubrion calculated the maximum dose to be 0.7 mrem (0.007 mSv) in an hour for an adult and 1.9 mrem (0.019 mSv) in an hour for a child assuming a worst-case scenario of 5 minutes of direct contact of the torso with the elbow and the remaining 55 minutes at 1 foot (30 cm). These calculations demonstrate that the hourly limit of 2 mrem (0.02 mSv) in any 1 hour would not be exceeded if individuals follow instructions.” Does that mean if a child spends 6 minutes of direct contact with the elbow, then the 2 mrem in any 1 hour will be exceeded? The Board believes this is unacceptable.
16. The NRC TER states that “as long as the caregiver is willing and able to limit or avoid these behaviors, the dog will not engage in them.” Anyone who has had a dog would not believe this statement. Also, instructions do not ensure that certain behaviors will stop. The owner may agree to stop them, but the dog may display other behaviors to make the owner comply with the dog’s wishes.
17. The NRC initially said this drug would be used only on large dogs, however, there is no such prohibition in the Exubrion materials or in the package insert. The drug may be administered to dogs weighing 10 pounds. While the dose would be smaller, there is more opportunity for close contact with smaller dogs.
18. Section C1.4.1 of the procedure and instructions (ML20142A294) states “If the injection site is missed, the owner must be informed that re-treatment can be scheduled 1 year from the initial treatment date.” What happens to the radiopharmaceutical if it is not injected in the correct spot, is it then excreted? Does it travel to a different physical location within

the animal where the owner needs to be aware of a different radiation hazard? Is it appropriate to release the dog?

The Board believes that even if all the technical comments are addressed satisfactorily, there is too much reliance on the owner's ability to follow instructions. There is little evidence that a child can socially distance from a dog. Also, there is no objectivity in the screening questionnaire on the owner's behalf. The Board believes there is too much uncertainty surrounding the doses from the use of this drug and the tolerances are too low to rely on subjective questionnaires and the owner's ability to follow instructions.

In conclusion, the Board supports the Compatibility D designation, but the Board does not support the NRC's conclusion that the Exubrion proposal is adequate to protect the public health and safety. We appreciate the opportunity to express our views and stand ready to answer any questions you may have.

Sincerely,

A handwritten signature in blue ink that reads "Jennifer T. Opila". The signature is written in a cursive style.

for

Terry Derstine, Chair
Organization of Agreement States
Radiation Protection Program Manager
Department of Environmental Protection
Southeast Regional Office
2 East Main Street
Norristown, PA 19401