



UNITED STATES
NUCLEAR REGULATORY COMMISSION
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June 3, 2020

MEMORANDUM TO: Duane White, Acting Chief *Duane E. White*
Medical Safety and Events Assessment Branch
Division of Materials Safety, Security, State,
and Tribal Programs
Office of Nuclear Material Safety
and Safeguards

FROM: Irene Wu, Project Manager
Medical Safety and Events Assessment Branch
Division of Materials Safety, Security, State,
and Tribal Programs
Office of Nuclear Material Safety
and Safeguards

SUBJECT: SUMMARY OF THE MAY 7, 2020, CLOSED MEETING WITH
EXUBRION THERAPEUTICS TO DISCUSS THE STAFF'S
REQUESTS FOR ADDITIONAL INFORMATION

On May 7, 2020, the U.S. Nuclear Regulatory Commission (NRC) staff met with representatives from Exubrion Therapeutics (Exubrion) to discuss the staff's requests for additional information. Please see the enclosed meeting summary for more details (Enclosure 1). The meeting attendance list is also enclosed (Enclosure 2).

Enclosures:
As stated

CONTACT: Irene Wu, NMSS/MSST
301-415-1951

SUBJECT: SUMMARY OF THE MAY 7, 2020, CLOSED MEETING WITH EXUBRION
THERAPEUTICS TO DISCUSS THE STAFF'S REQUESTS FOR ADDITIONAL
INFORMATION

DATE: JUNE 3, 2020

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DATE	05/19/20	05/20/20	05/20/20	06/03/20

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Meeting Summary

Meeting with Exubrion Therapeutics, Inc. to Discuss the
Staff's Requests for Additional Information
May 7, 2020
1:00 PM – 4:00 PM ET

During the U.S. Nuclear Regulatory Commission (NRC) staff's review of a hypothetical license amendment submitted by Exubrion Therapeutics (Exubrion) containing generic dog release procedures and instructions, the NRC staff determined that additional information would be necessary to prepare a draft technical evaluation (TE) report. On April 27, 2020, the NRC staff transmitted the requests for additional information (RAIs) to Exubrion (Agencywide Documents Access Management System Accession No. ML20091M172). A teleconference was scheduled on May 7, 2020, to ensure that Exubrion has a clear understanding of the RAIs. Following introductory statements by the NRC and Exubrion, the NRC staff provided an overview of the schedule and the plan for discussing the RAIs at the meeting. At the meeting, all of the RAIs were discussed. A summary of the RAIs that were discussed in greater detail and key discussion points from the meeting are contained below:

RAIs #1-10

The NRC staff indicated to Exubrion that RAIs #1 to 10 were provided because this information was included as part of the hypothetical license amendment application submitted to the NRC. However, this information would be specific to a licensee and would be included as part of a specific licensing action and therefore, is not necessary for NRC staff to review as part of its review of the hypothetical license amendment. Exubrion indicated that they will remove this information and instead add placeholders to the NRC Form 313 when they submit their RAI responses.

RAI #11c

Step A3.7 states to flag any asterisked question where the answer is yes; however, it does not reference which questions this is referring to and there are no asterisked questions in the pre-screening questionnaire. Clarify this step.

- Exubrion indicated that they have added clarity to the procedure, pre-screening criteria, and instructions and these will be included in their RAI responses. Exubrion indicated this step will be clarified in the pre-screening questionnaire as to what other clinical factors are considered as part of the authorized user's informed decision.

RAI #11f

Revise Section C2.1 to add "If both elbows were treated, measurements should be made for each treated elbow."

- Exubriion indicated that they would update their process flowchart in Appendix A of the Procedure for Use of Synovetin OA to account for multiple survey locations.

RAI #11g

The language in the flow chart step “Veterinarian reviews all post-treated behavior restrictions can pet owners comply” is confusing. Revise as appropriate.

- Exubriion indicated that they would update their process flowchart in Appendix A of the Procedure for Use of Synovetin OA for clarification purposes.

RAI #15b

The technical basis relies on an individual not spending any time within 6 inches and an average of 1 minute a day between a foot and 6 inches from the dogs’ elbows for months following the procedure. Include an overarching screening question to see if modifications are needed to meet these criteria. The procedure should prohibit release when close contact is necessary, and these criteria cannot be met.

- Exubriion indicated that they will update the pre-screening questionnaire to include a question that addresses the owner’s full understanding that direct contact with the treated joint to the human torso is limited to one minute.

RAI #15d

Add a question to the pre-screening questionnaire to determine if dogs spend significant time outside the home, including at a daily boarding facility or dog park. Provide instructions to the licensee on how to respond if a dog does spend a significant amount of time in public facilities. For boarding facilities, either include in instructions that boarding facilities cannot be used for a specified number of weeks or provide additional justification in the technical basis how public doses at the boarding facility would be kept as low as reasonably achievable (ALARA) and below limits.

- Exubriion and NRC staff agreed to discuss this RAI in further detail to better understand the justification for dogs spending significant time outside of the home to limit doses to members of the public who do not receive instructions.

RAI #16a

The instructions do not match the technical basis assumptions used to demonstrate the public dose limit is not exceeded. Please update the procedure and instructions to include all necessary limitations described in the technical basis to ensure the public dose limit and doses are ALARA if the instructions are followed. For example, the technical basis assumes the closest distance between the dog and an individual is not less than 6 inches; however, the

instructions do not prohibit contact under 6 inches. It should be noted in the procedure and instructions that instances where distances less than 6 inches to the dog's elbow should be minimized or avoided for a specified timeframe. The timeframe should be justified in the technical basis.

- Exubriion indicated that they would provide additional explanation in the procedure and instructions for how they intend to ensure the doses to members of the public are ALARA for real close distances.

RAI #16b

To demonstrate that public dose limits are not exceeded, the technical basis assumes limitations on interactions well beyond the proposed duration of the instructions. The procedure and instructions should be modified to ensure instructions and necessary limitations on interactions are maintained as long as necessary to ensure the public dose limits are not exceeded and to ensure doses are ALARA. Note, there can be multiple sets of instructions with different durations, if necessary.

- Exubriion provided some additional basis for ensuring doses are ALARA during the meeting and indicated that they plan to include this information in their revised application.

RAI #16c

Define "direct contact," "close contact," and "intermediate contact" in the instructions. These definitions should include the distances meant by these terms. Also, the term "direct contact" could be easily confused to mean actual touching of the animal, but the instructions are using this term to mean a distance of 6 inches. Ensure the terms are clearly understood as to what behaviors usually assume to fall under these terms.

- Exubriion and NRC agreed to review how these terms are used in the instructions to ensure that it is clear what these words mean to recipients of the instructions.

RAI #16div

The instructions state to avoid boarding of an animal. Either specifically state long term/daily boarding is prohibited, or provide the information requested above.

- This RAI is related to RAI #15d. Exubriion and NRC staff agreed to discuss this RAI in further detail to better understand the justification for dogs spending significant time outside of the home to limit doses to members of the public who do not receive instructions.

RAI #16dv

Commercial grooming could result in an exposure of greater than 2 mrem in any 1 hour to a member of the public who does not know about the dog's treatment. Therefore, instructions for limitations on grooming for a specified period of time should be included. The timeframe should be justified in the technical basis document.

- Exubrion indicated that they would verify the calculations related to this RAI.

RAI #16f

Please describe how the instructions will be used to ensure public dose is maintained ALARA. Specifically, describe how the statement on page 13 of the technical basis document which states "the minimum possible change to normal behavior for each dog is required" would be considered ALARA. Update instructions as necessary to ensure public doses will be maintained ALARA.

- This RAI is related to RAI #16b. During the meeting, Exubrion provided some additional basis for ensuring doses are ALARA and indicated that they plan to include this information in their revised application.

RAI #18

The technical basis assumes the center of the human torso as the point on the body which is used to calculate exposure. However, Title 10 of the Code of Federal Regulations Part 20 defines the whole body, for the purposes of external exposure, to include the head, trunk, arms above the elbow, or legs above the knee. Explain your rationale for using this methodology versus a more conservative method such as assessing exposure to the maximally exposed portion of the body.

- Exubrion indicated that they would add more information to the technical basis about the maximally exposed part of the body for a long duration at close contact.

RAI #21

The technical basis states that for a child or small adult, the distance from the human torso to the dog's torso can easily be a foot or more than the distance from the human's leg to the dog's torso even for a child or small adult. Small children or small adults standing next to an animal will be much closer to the dog's elbow than an average-sized adult and can easily be within a foot distance. This statement should be revised, and more consideration is needed in the technical basis and instructions to ensure children or small adults do not exceed the public dose limit.

- The NRC staff expressed concern for doses to small children. The NRC staff indicated that they would be reviewing the application to ensure that the technical basis and instructions take into consideration behaviors and distances for small children and there is adequate protection in place to ensure public dose limits are not exceeded.

RAI #28

Please describe how this information is being used to develop instructions and the technical basis for release. For example, the paper suggests limiting touching the dog's elbow for 34 days, but the minimum duration for instructions is 2 weeks.

- Exubrion indicated that this report has now been published. Exubrion plans to revise their application to only including necessary information, with a reference from this report to avoid confusion as to what parts of the report are applicable to the application.

RAI #29

As the technical basis states that it is not reasonable to treat dose rates found in this report as applicable to calculating a whole-body dose, provide calculations or a model that is applicable to calculating whole dose on contact or at close distances as requested above.

- This RAI is related to RAI #28. Exubrion indicated that this report has now been published. Exubrion plans to revise their application to only including necessary information, with a reference from this report to avoid confusion as to what parts of the report are applicable to the application.

Following the discussion on the RAIs, the NRC staff reviewed the revised schedule including the following milestones with estimated dates:

- RAI responses received with a revised application (~May 27, 2020)
- Public meeting held on the revised application to help inform the NRC staff's TE (~June 10, 2020)
- Draft TE report to NRC regions and Agreement States for parallel review (~July 1, 2020)
- Draft TE Report issued to Exubrion (~July 23, 2020)
- Final TE Report issued to Exubrion (~September 11, 2020)

The NRC staff indicated that these estimated dates are predicated on a single round of RAIs with acceptable RAI responses and no Congressional Review Act review needed on the TE report by the Office of Management and Budget.

Meeting Attendees

Meeting with Exubrion Therapeutics, Inc. to Discuss
Requests for Additional Information
May 7, 2020
1:00 PM – 4:00 PM ET

	Name	Organization
1	Irene Wu	NRC
2	Katie Tapp	NRC
3	Betsy Ullrich	NRC
4	Vincent Holahan	NRC
5	Christian Einberg	NRC
6	Michael Layton	NRC
7	Ian Irvin	NRC
8	Lisa Dimmick	NRC
9	Daniel Dimarco	NRC
10	Peter Selover	Exubrion Therapeutics
11	John Donecker	Exubrion Therapeutics
12	Steve Fox	Exubrion Therapeutics
13	Nigel Stevenson	Exubrion Therapeutics
14	Eric Schreiber	Exubrion Therapeutics
15	Martin Manco	Exubrion Therapeutics
16	Matthew Arno	Foxfire Scientific, Inc.
17	Chad Smith	F.X. Massé Associates
18	Josie Piccone	Consultant to Exubrion Therapeutics