UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

October 30, 2020

ALL AGREEMENT STATES

NOTIFICATION OF ISSUANCE OF TECHNICAL EVALUATION REPORT FOR THE EXUBRION THERAPEUTICS PROPOSED LICENSE APPLICATION TEMPLATE FOR THE RELEASE OF DOGS FOLLOWING TREATMENT WITH A TIN-117M COLLOID (STC-20-074)

Purpose: To inform the Agreement States that the U.S. Nuclear Regulatory Commission (NRC) issued the technical evaluation report (TER) finding the proposed license application by Exubrion Therapeutics acceptable for the release of dogs following treatment with tin-117m (Sn-117m) colloid.

Background: By letter dated December 4, 2019 (Agencywide Documents Access and Management System (ADAMS) Accession No. ML19343C192 (package)), Exubrion Therapeutics (Exubrion) submitted a proposed license application template to support the submission of license amendments by veterinary licensees. This application template included the procedure for using Synovetin OA®, a radioactive tin (Sn-117m) colloid, to treat osteoarthritis (OA) in a dog's elbow joints. Exubrion is the manufacturer of Synovetin OA®. Exubrion's procedure included a prescreening questionnaire and release instruction template; its technical basis for release of animals following treatment; and a generic release procedure for dogs and owners following treatment. This procedure would allow veterinary licensees to release dogs following treatment of Synovetin OA®. The most recent version of Exubrion's procedure and technical basis was provided to the NRC on September 13, 2020 (ADAMS Accession No. ML20282A513).

On June 25, 2020, the NRC staff hosted a government-to-government meeting with the Agreement States to discuss the staff's review of Exubrion's proposed license application template. Feedback provided during the meeting resulted in changes and are reflected in the final TER. In addition, Agreement States provided comments on a draft version of this TER (ADAMS Accession No. ML20192A003). The NRC appreciates the thoroughness of the Agreement States' review of Exubrion's application and the draft TER. The NRC staff made significant changes in the final TER based on the comments received. On October 26, 2020, the Organization of Agreement States (OAS) provided additional comments to the NRC for consideration (ADAMS Accession No. ML20301A416). Enclosure 1 provides the NRC staff's responses to these comments.

On June 18, 2020, the NRC staff met with the Standing Committee on Compatibility to determine the level of compatibility for the use of Exubrion's procedure. The Committee's review was conducted in accordance with the "Agreement State Program Policy Statement" (82 FR 48535); October 18, 2017, and the categorization process for NRC program elements in NRC Management Directive 5.9, "Adequacy and Compatibility of Program Elements for Agreement State Programs." The Committee determined that because the staff's evaluation and guidance is only instructing NRC staff and licensees on how to meet applicable requirements, it is not a program element that is a matter of compatibility with the Agreement States, and therefore should be designated as Compatibility Category D. An Agreement State

has the flexibility to choose whether or not to adopt and implement this program element within its jurisdiction.

Discussion: Enclosure 2 provides the NRC staff's TER documenting staff's review of Exubrion's proposed procedure to release dogs following treatment with Synovetin OA®. The staff's evaluation was specific to Exubrion's request of a maximum administered dose of up to 222 MBq (6 mCi) of Sn-117m to the dog's elbows. The NRC recommends acceptance of Exubrion's release procedure contained in their application dated June 1, 2020 (ADAMs Accession Number ML20282A513) as part of an individual license amendment to treat dogs with up to 222 MBq (6 mCi) of Sn-117m as part of Synovetin OA® treatment. The NRC recommends license reviewers closely evaluate any specific licensee deviations from Exubrion's proposed release procedure analyzed in the TER before approval of the deviation. In addition to the release procedure, the license reviewer should evaluate all other pertinent information as described in the most recent revision of NUREG-1556, Volume 7. Particular attention should be given to the guidance in NUREG-1556, Volume 7, Appendix D, "Guidance for Laboratory Animal and Veterinary Medicine Uses" (ADAMS Accession No. ML18065A006).

As documented in the TER, the NRC staff found Exubrion's release procedure provides adequate measures to ensure public dose limits will not be exceeded when owners provide complete and accurate information. As there is the potential to exceed public dose limits if prescreening and release instructions are not followed, staff recommends license reviewers obtain the commitments contained in enclosure 3 from individual licensees prior to approving the use of this procedure to ensure licensees take necessary precautions to keep exposures below the public dose limits. However, as documented in the TER, the NRC staff notes that public dose limits could be exceeded to members of the household if an owner provides incomplete or inadequate information during prescreening or instructions are not followed.

If you have any questions regarding this correspondence, please contact me at 301-415-3340 or the individual named below:

POINT OF CONTACT: Katie Tapp, Ph.D. E-MAIL: Katherine.Tapp@nrc.gov
TELEPHONE: (301) 415-0236

Brian C. Anderson

Digitally signed by Brian C. Anderson
Date: 2020.10.30 10:02:05 -04'00'

Brian C. Anderson, Chief
State Agreement Liaison Programs Branch
Division of Materials Safety, Security, State, and Tribal Programs
Office of Nuclear Material Safety and Safeguards

Enclosures:
1. Response to Organization of Agreement State comments on the draft Technical Evaluation Report
2. U.S. Nuclear Regulatory Commission Technical Evaluation Report for the Exubrion Therapeutics Proposed License Application Template for the Release of Dogs Following Treatment with a Tin-117m Colloid
3. Notes to License Reviewers Evaluating License Applications to Treat Dogs with Synovetin OA®

Agreement State Comment Resolution

Exubrion Technical Evaluation Report

Comment No.	Comment	Response
1	The TER relies on dose rate and distance measurements that are difficult to obtain. Exubrion reported that because of movement during the equilibration time of the meter, it is hard to get a stable dose rate reading. It would be equally difficult holding a meter steady at the prescribed distance of 3.3 feet. The poor correlation of Wendt et al1 exposure rate/weight data seems to corroborate that assertion. Exubrion should provide protocols to be added in the TER for attaining high confidence measurements to be used in guiding release decisions.	The NRC staff believes the difficulty of performing survey measurements of dogs is no different than performing surveys of previously approved animal release, such as horses or cats. As NUREG-1556, Volume 7, Appendix D does not require licensees to submit detailed survey procedures for licensing, NRC staff does not believe there is a need for Exubrion to submit it in this generic application. However, licensees are required to ensure adequate release surveys per 10 CFR 20.1501 and surveys shall be retained for 3 years per 10 CFR 20.2103(a). This should be evaluated during inspections.
2	The Board's letter dated August 11, 2020 asked, in part, "what happens to the radiopharmaceutical if it is not injected into 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?" NRC responded "Exubrion stated that they saw no bio kinetic transfer to any other organs in a study evaluating impacts of missed injection sites." This satisfies the question regarding transfer to organs, but was an increase in excretion noted? If so, there is a risk of contamination and not just exposure that needs addressed.	Exubrion performed a study in rats to investigate this. The worst case is an intravenous injection, where the study showed the material primarily distributed to the liver with little to no excretion. For injections other than intravenous, the material remained at the injection site. In addition, during the initial dog studies, there was an injection that accidentally missed the synovial sac. In that case, subsequent imaging revealed that the injected material remained at the injection site with no biodistribution elsewhere.

Agreement State Comment Resolution

Exubrion Technical Evaluation Report

Comment No.	Comment	Response
3	The TER states that “Licensees should use the information gathered during the pre-screening evaluation and discussions with the owner, not Exubrion’s evaluation of common dogs, to determine the typical time and distances the dog has with all individuals in the household. Based on the information about the interactions in the dog’s household, the licensee will determine if release is appropriate for each dog following treatment and provide instructions to the household in order to have confidence that public dose limits will not be exceeded.” This amounts to an individual dose assessment for each household member. Will the assessments be reviewed by the NRC during inspection and what guidelines will they use for the review? A standard license commitment to retain every household members’ time studies and dose assessments should be included for each treatment.	Exubrion preformed the dose assessment for four bounding categories of dog-human interactions and demonstrated they do not exceed public dose limits with instructions. As long as the household members typical interaction patterns do not exceed the bounds of these categories, licensees will not need to perform individual dose assessments. This procedure does not allow licensees to perform their own dose assessments to allow release when household members interaction patterns do not fit into one of these categories. The information gathered during the prescreening questionnaire should be used to determine which category should apply for the household. The procedure requires the licensee to retain the prescreening questionnaire. Therefore, this should be available for inspection.

Comment No.	Comment	Response
4	NCRP Report No. 116, Limitation of Exposure to Ionizing Radiation, recommends an equivalent dose limit for the fetus of an occupationally exposed individual of 50 mrem (0.5 mSv) per month during the pregnancy. Excluding this treatment for households with pregnant women would seem sensible if their interactions fall within those extended and prolonged close contact categories or if individual assessments result in a dose of exceeding 50 mrem per month.	The NRC does not have different public dose limits for pregnant women or fetuses. The public dose limit is 2 mrem in any one hour and 100 mrem a year. However, NUREG-1556, volume 7, Appendix D does address pregnant women and their need to limit exposure to a radioactive animal. Exubrion addresses this in their prescreening questionnaire which has licensees question if close contact interactions with pregnant women can be minimized and discuss strategies to minimize their dose prior to treating the dogs.

Comment No.	Comment	Response
5	Under Notes to License Reviewer, the first bullet on page 18 of the TER, describes that license reviewers obtain “a commitment that the licensee will not use this procedure to release a dog whose typical behavior patterns, without instructions, do not fit into the time and distance limitations listed for one of the categories described in the procedure as these categories are the only ones evaluated.” This bullet is confusing, does it intend to mean that the treatment should not be performed, or that another procedure for release should be followed?	Exubrion~~'s~~ demonstrated that public dose limits will not be exceeded for the maximum amount of times described in the four behavior categories described in the application. Therefore, this procedure can only be used to release dogs when all household members fit into one of these categories. If a licensee wishes to release a dog where a household member does not fit into one of these categories, more evaluation would need to be done to demonstrate public dose limits would not be exceeded. This would require a license amendment. The final TER provides more information on the categories.

Comment No.	Comment	Response
6	Under Notes to License Reviewer, the second bullet on page 18 of the TER, states that "…the licensee will not release a dog if a child is in the house under the age of 5 who does not fit into the common contact or extended duration or immediate contact scenarios, because the other scenario is not evaluated by Exubrion's technical basis and the typical interaction patterns could exceed the public dose limits." What is "the other scenario" that was not evaluated by Exubrion? Is the objective of this point meant to restrict releasing a dog into a household with children under the age of 5 where a pre-established contact scenario does not fit with what is discovered during pre-screening or is it to reject the candidate for treatment all together?	This language was updated in the final version of this document. The objective of this language is to not use this procedure to release dogs where household members behavior does not fit into one of the pre-established categories evaluated by Exubrion. If a licensee would like to allow release to a household where behaviors do not fit into the categories, additional evaluation and procedures would be necessary. This would require a license amendment.

Comment No.	Comment	Response
7	The TER describes "…that licensees must investigate any public exposure where limits might have been exceeded, even if it is due to individuals not following instructions, and to report those to the NRC per 10 CFR 20.2203." The Board supports this requirement; however, concern exists over the discussion of 500 mrem being an acceptable limit to protect health and safety. The TER concludes that "Even if no instructions are followed, the staff determined that the highest likely exposure to a household member, who is a member of the public, would likely be below 500 mrem. As this dose will be received by someone who would likely be benefitting from the exposure and is at a level allowable by the NRC in other circumstances where individuals benefit from the exposure, such as patient release, the staff finds the risk from this dose acceptable given the licensee provides adequate instructions and means to prevent the exposure." Licensees may lower their safety focus knowing that acceptable limits from other parts of the 10 CFR should still be upheld in worst case scenarios and ignore the need to follow up or calculate doses to adhere to 10 CFR 20.1301. An increased dose allowed to members of the public, as a consequence of patient release, is due to the life-saving or quality of life improving treatments to a human person, not an animal. The Board objects to the conclusion that an increase in dose from a treated animal is a beneficial exposure and recommends removing any discussion of other parts of regulation or the 500 mrem limit.	The NRC removed language from the TER regarding benefits to the owner and reference to other regulations other than the public dose limit. In addition, the NRC updated the TER to clarify that it is the individual licensee's responsibility to ensure compliance with public dose limits. As described in the TER, the NRC staff believes Exubrion's proposed procedure provides adequate measures to ensure public dose limits will not be exceeded when owners provide complete and accurate information. However, staff performed calculations to bound the worst case dose if an owner provides incomplete or inadequate information during prescreening or if a household member chooses to not follow instructions after the owner confirms they will. The staff finds the likelihood of such a scenario to be low given the conservatisms in the calculations and assumptions used in the scenario and that the licensee provides adequate instructions and means to prevent the exposure. Therefore, the staff finds Exubrion's proposal adequate to protect the public's health and safety.

Agreement State Comment Resolution

Exubrion Technical Evaluation Report

Comment No.	Comment	Response
8	Step A3.7 of the Procedure is confusing where it states “Note that only [one] category will apply for the entire household.” If all the household members do not fit into the same category, then is the most restrictive category used? How does that reconcile with the TER where it says Exubrion’s evaluation of common dogs should not be relied upon?	Licensees should not use Exubrion’s evaluation of typical dog behavior. Instead, licensees will need to conduct a prescreening evaluation with the dog owner to understand the individual dog’s typical behavior, including all typical dog-human interactions, in order to determine the behavior of the dog. The licensee will then use the prescreening information to choose the appropriate category for the household. The TER has been updated for clarity on this point.

U.S. Nuclear Regulatory Commission

Technical Evaluation Report for the Exubrion Therapeutics

Proposed License Application Template for the Release of Dogs

Following Treatment with a Tin-117m Colloid

October 30, 2020

Project Lead

Katie Tapp

Contributors

Vince Holahan
Betsy Ullrich
Irene Wu

Enclosure 2

Table of Contents

Introduction

By letter dated December 4, 2019 (Agencywide Documents Access and Management System (ADAMS) Accession No. ML19343C192 (package)), Exubrion Therapeutics (Exubrion) submitted a proposed license application template to support the submission of license amendments by veterinary licensees. These license amendments would allow veterinary licensees to administer Synovetin OA®, a radioactive tin (Sn-117m) colloid, to treat osteoarthritis (OA) in a dog's elbows. Exubrion is the manufacturer of Synovetin OA®. The proposed license application template included the procedure for using Synovetin OA®, which includes a prescreening questionnaire and release instruction template; its technical basis; and a generic release procedure for dogs following treatment. The U.S. Nuclear Regulatory Commission (NRC) staff (staff) notified Exubrion of the staff's decision to accept its application template for detailed technical review on December 20, 2019 (ADAMS Accession No. ML19353C760). In response to the staff's requests for additional information dated April 27, 2020 (ADAMS Accession Nos. ML20091M172), June 17, 2020 (ADAMS Accession No. ML20169A412), and August 25, 2020 (ADAMS Accession Nos. ML20238B820) Exubrion provided a revised license application template in correspondence dated May 15, 2020 (ADAMS Accession No. ML20142A291); June 26, 2020 (ADAMS Accession No. ML20178A654); September 1, 2020 (ADAMS Accession No. ML20246P521); and September 13, 2020 (ADAMS Accession No. ML20282A513). This technical evaluation report documents the NRC staff's review of Exubrion's proposed license application template including the technical evaluation and procedure provided in the September 13, 2020 submission.

Synovetin OA®

Synovetin OA® is a colloid containing Sn-117m that can be used to treat OA in a dog's elbows by radiosynoviorthesis. Synovetin OA® will be used to treat chronic pain and inflammation of OA in dogs when primary and secondary line of treatments, such as nonsteroidal anti-inflammatory drugs and opioids, are found to be ineffective. Relief from joint pain does not occur immediately following treatment and can take weeks following treatment, and therefore a dog's behavior should not change in the first few weeks following treatment.

The dosage of Sn-117m is proportional to the weight of the dog, up to 111 megabecquerels (MBq) (3 millicuries (mCi)) being injected in each joint for the largest dogs and a maximum of 222 MBq (6 mCi) per dog per treatment. Sn-117m decays to Sn-117 by releasing an internal conversion electron and a predominant 158-kiloelectronvolt gamma ray. The half-life of Sn-117m is 13.6 days. The types of dogs most often affected with OA tend to be large and giant breed dogs, but Synovetin OA® can be used to treat dogs weighing 10 pounds or more. Studies referred to in Exubrion's application have demonstrated that 99 percent of the injected Sn-117m colloid remains in the treated joint; therefore, there is almost no biological elimination, and excretion is not of concern.

Regulatory Overview

NRC has allowed the release of animals treated with byproduct material for over 20 years when licensees demonstrate public dose limits listed in Title 10 of the *Code of Federal Regulations* (10 CFR), Section 20.1301 are not exceeded. Regulations in 10 CFR 20.1301(a)(1) state that licensees shall conduct operations so that the total effective dose equivalent (TEDE) to individual members of the public from licensed operation does not exceed 0.1 rem (1 millisievert (mSv)) in a year. Regulations in 10 CFR 20.1301(a)(2) state that the dose in any unrestricted

area from external sources does not exceed 0.002 rem (0.02 mSv) in any 1 hour. In addition, 10 CFR 20.1101(b), "Radiation protection programs," states that the licensee shall use, to the extent practical, procedures and engineering controls based on sound radiation protection principles to achieve doses to members of the public that are as low as is reasonably achievable (ALARA). Therefore, the licensee must demonstrate that these public dose limits will not be exceeded and ensure doses are ALARA, to the extent practical, before it schedules the administration of Sn-117m and the subsequent release of the dog following treatment. The higher public dose constraint of 0.5 rem (5 mSv) provided in 10 CFR 35.75, "Release of individuals containing unsealed byproduct material or implants containing byproduct material," is for the release of human patients following a medical treatment and does not apply to animal release.

Overview of Exubrion's Release Procedure

Exubrion's proposal contains procedures to allow release of a dog with a measured dose rate of less than 0.45 milliroentgen (mR) per hour (h) at 3.3 feet (1 meter (m)) from the treated elbow joint(s). To be confident that an animal released at this rate does not cause an individual to receive a dose exceeding the public dose limits listed in 10 CFR 20.1301, "Dose limits for individual members of the public," the application described a multilayer approach. First, Exubrion conducted a technical assessment to evaluate the common dog-human interactions that could potentially result in an individual exceeding a public dose limit. Second, as Exubrion identified some behaviors that could result in a member of the public who has daily interactions with the dog to exceed the annual public dose limit, Exubrion's proposed procedure instructs the licensee to use a prescreening questionnaire. The purpose of the prescreening questionnaire is to determine whether any of the dog's typical dog-human interactions need to be stopped or modified for a specified duration to ensure public dose limits are not exceeded. The procedure states the licensee will only provide the treatment if the licensee is confident that the owner understands the need to comply with public dose limits and the household members can and are able to stop or modify these behaviors for the necessary duration. Owners will sign the prescreening questionnaire and the proposed release instructions acknowledging them before treatment.

Exubrion's proposal states that the licensee will provide instructions to the dog's caregivers to minimize dose. The instructions will include any dog-specific restrictions, and the licensee will ask the caregiver to acknowledge the instructions by signature prior to release of the dog to confirm the caregiver's intent and ability to comply. Finally, the procedure directs the licensee to follow-up with the dog's owner approximately one week after the procedure to remind the owner how to keep doses ALARA and review compliance with the release instructions. The procedure also directs the licensee to investigate any instances where public dose limits may have been exceeded including instances when owners have self-reported not following instructions and report to the NRC if it is determined any public dose limits have been exceeded per 10 CFR 20.2203.

Discussion

Evaluation of Common Dog-Human Interactions

Exubrion's Analysis of Common Interactions

Exubrion's technical evaluation provided the results of its assessment of common dog-human interactions to determine occupancy factors for a typical osteoarthritic dog. These occupancy factors are not intended to be used for individual dogs without pre-screening. These common occupancy factors provide a general view of dog behavior to categorize dogs into different groups of behavioral patterns and determine what behaviors could result in public dose limits to be exceeded without modification. Exubrion's evaluation included a review of the published literature and observing interactions of 69 severely arthritic dogs and their owners involved in Exubrion's three studies. Exubrion also had discussions with dozens of practicing veterinarians who see arthritic dogs on a daily basis and numerous dog owners (including focus groups conducted by Exubrion to assess dog-owner interactions).

Exubrion evaluated three groups of typical dog-human interactions: standing, sitting, and cosleeping. For standing, Exubrion evaluated typical feeding, petting, and walking scenarios. For sitting, Exubrion evaluated both situations in which a dog sits by an owner, which would include both resting at the owner's feet or by the side of the owner's chair, and a dog who sits on an owner's lap for up to 3 hours a day. Exubrion's evaluation assumes the dog either sits by an owner or on the owner's lap but not both. Exubrion's analysis also considered a dog who sits at the feet of or close by someone for 8 hours a day, such as someone who works from home ("officing"). Exubrion's evaluation also considered cosleeping. Table 1 below summarizes the distances and durations that Exubrion found were typical for common dog-human interactions. Distances are defined from the center of the individual's torso to the dog's elbow, where the source is located. Exubrion's technical evaluation provides more details on how Exubrion derived duration and distances of typical dog-human interactions. It should be noted the distances and times listed in this table were used by Exubrion in their evaluation of common dog-human interactions. Specific times and distances for individual dog's interactions should be confirmed by licensees while completing the prescreening questionnaire prior to scheduling the treatment of each dog.

Table 1 – Exubrion's Listed Common Dog-Human Daily Interaction Patterns

Interaction	Distance	Time
Feeding	1 foot	< 1 min/day
Petting	1 foot	5 min/day
Walking	3 feet	1 h/day
Sitting[1]	3 feet	3 h/day
Lap sitting[1]	1 foot	3 h/day
Cosleeping	1 foot	8 h/day
Officing	3 feet	8 h/day

1 Exubrion's analysis assumes a dog either sits by an owner or lap-sits but not both.

Exubrion found the typical dog-human interactions, other than lap sitting, cosleeping, or officing, are 1 minute per day at less than one foot (30 cm), 6 minutes per day at 1 foot (30 cm) and 4 hours a day at 3 feet (0.9 m). For conservatism, Exubrion rounded up values for typical interactions at less than one foot (30 cm) to 5 minutes a day and at 1 foot (30 cm) to 15 minutes a day in calculations. Exubrion increased the duration of time to 5 minutes per day at less than

one foot (30 cm), 11 hours per day at 1 foot (30 cm) and 9 hours a day at 3 feet (0.9 m) for dogs which exhibit lap sitting, cosleeping, and officing behaviors.

Exubrion's technical evaluation also included an analysis of close contact interactions. Exubrion stated that a distance of 1 foot is assumed for typical lap sitting due to simple geometry separation of the elbow and center of the human torso. In addition, Exubrion states there would be increased shielding as the dog's legs would be separated from the human torso by the dog's torso in typical lap-sitting geometries. Therefore, Exubrion did not include lap sitting as a close contact activity. Exubrion's technical evaluation of typical dog behaviors only considered close contact to occur in situations for which the dog requires assistance, such as getting into and out of a vehicle, standing up on slick surfaces, and climbing up or down stairs. Exubrion conservatively defined close contact in the geometry that leads to the highest dose to a person, with the dog's elbows directly against the human's torso. Exubrion provided videos (ADAMS Accession No. ML20219A709) showing people transferring a dog from a vehicle. These videos showed the time to lift a dog into and out of a vehicle only involves a few seconds of direct contact with the dog and the person's body. Assuming a dog needs to be helped multiple times throughout the day, Exubrion bounded direct contact at 5 minutes a day for typical dog-human interactions.

Staff Evaluation

The staff finds Exubrion's evaluation provided sufficient evidence to support their summary of typical dog-human interaction patterns for many dogs. However, staff finds the most important part of Exubrion's findings is that these typical interaction patterns cannot be assumed for all dogs and some dogs may have interactions that could result in the public dose limits being exceeded if they are not stopped or modified. Therefore, licensees will need to conduct a prescreening evaluation with the dog owner to understand the individual dog's typical behavior, including all typical dog-human interactions, in order to determine whether a dog is a candidate for treatment and if any behaviors need to be stopped or modified to ensure the public dose limit is not exceeded following release. Exubrion developed a prescreening questionnaire for this purpose. Per the release procedure, licensees will need to use the information gathered during the prescreening evaluation, not Exubrion's evaluation of common dogs, to determine the typical time and distances the dog has with all individuals in the household. For each release, the licensee will need to ensure that public dose limits will not be exceeded based on the information about the interactions in the dog's household and confidence that the owner of the owner can and are able to follow any necessary instructions.

Total Effective Dose Equivalent Rate

Regulatory Basis

Per 10 CFR 20.1301, licensees must conduct operations to ensure that the TEDE to individual members of the public does not exceed 100 mrem in a year. As defined in part 20, TEDE is the sum of effective dose equivalent (EDE) for external exposures and committed effective dose equivalent (CEDE) for internal exposures. In addition, 10 CFR 20.1301(a)(2) state that the dose in any unrestricted area from external sources does not exceed 0.002 rem (0.02 mSv) in any 1 hour. As this regulation is intended to ensure the 100 mrem annual limit is not exceeded by any member of the public, TEDE is also used for dose as defined in Part 20.

Exubrion's Calculation of Effective Dose Equivalent Rate

Exubrion used principles of the compartment factors methodology described in Regulatory Guide 8.40, "Methods for Measuring Effective Dose Equivalent from External Exposure," issued July 2010, to calculate dose to an individual, as dose will be nonuniform across the individual's body at close distances. This method divides the whole body into seven separate compartments (head and neck, thorax, abdomen, upper right arm, upper left arm, right thigh, left thigh). Each compartment's dose is measured separately and has individualized weighting factors that are used to determine TEDE. Dose to the thorax and abdomen make up 88 percent of the total dose.

Exubrion used MicroShield® Pro Version 12.07 to calculate the dose to an individual's abdomen and thorax from Sn-117m contained in a single elbow located at 0.7 inch (1.7 cm) (i.e., contact), 1 foot (30 cm), and 3.3 feet (1 m) from the center of the torso. A distance of 0.7 inch (1.7 cm) was chosen for contact due to the distance from the elbow cavity to the surface of the skin. In the calculation, the activity in the elbow cavity was normalized such that the dose rate at 3.3 feet (1 m) to a release dose rate of 0.45 mrem per hour at 3.3 feet (1 m). This simulated activity was 129 MBq (3.5 mCi), which is less than the injected activity as the MicroShield® calculation does not include shielding from the dog. This is to be expected as Exubrion used a bare source in air instead of modeling a dog's elbow cavity.

The photon emission data in MicroShield® for Sn-117m, with emissions less than 15 kiloelectronvolts excluded, were used. Exubrion derived anatomical data from International Commission on Radiological Protection Publication 89, "Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values," issued May 2003; Tanner (1978);[1] and Regulatory Guide 8.40 to develop its human model. Exubrion modeled a male adult and also modeled 1-, 5-, 10-, and 15-year-old children.

To calculate the dose contribution from the head and neck, upper arms, and thighs to the effective dose equivalent, Exubrion assumed a point source for simplicity. Exubrion calculated the distance to each of these compartments, assuming the source was midline to the torso and the minimum distances to each compartment. The on-contact distance for adults was 13.0 inches (33 cm) to both legs and head and neck and 10.2 inches (26 cm) to the arms. For a 1-year-old, the minimum distance was approximately 5.5 inches (14 cm).

Exubrion's Shielding Analysis

Exubrion's technical evaluation points out that an individual's exposure to the dog will not always be at the point of the maximum dose rate but will occur at locations around the dog. Due to inherent shielding by the dog's body, the dose rates at other locations around the dog will be lower than the maximum dose rate. Exubrion's proposal uses average shielding factors to account for different geometries of interactions. Exubrion described the evaluation used to determine its shielding factor (ADAMS Accession No. ML20142A296). In its evaluation, Exubrion collected dose rate measurements at distances of 1 foot (30 cm) and 3.3 feet (1 m) from 10 dogs in nine geometries. In three of the geometries, not all of the measurements could be taken at the 1 foot (30 cm) distance because of the size and the shapes of the dogs. These geometries were the posterior, upper posterior, and dorsal measurements. Exubrion instead

[1] Tanner JM, "Fetus into Man, Physical Growth from Conception to Maturity," Harvard University Press, Cambridge, MA, 1978.

replaced these measurements with representative measurements as described in their evaluation. Exubrion determined the average dose measurement for each dog and divided that by the maximum dose rate to determine the dog's isotopic shielding reduction. Exubrion conservatively selected the lowest shielding reduction to determine the shielding factor for distances of both 1 foot (30 cm) and 3.3 feet (1 m), which were 32 percent and 28 percent, respectively.

Staff's Evaluation

The staff notes there is conservatism in Exubrion's calculations. All calculations assume the maximum duration, and shortest distance for each category. Additionally, Exubrion's calculations conservatively assume a maximum dose rate at time of release of 0.45 mrem/h (0.0045 mSv/h) at 3.3 feet (1 m), when procedure uses maximum exposure of 0.45 mR/h at 3.3 feet (1 m). Calculations also conservatively assume point source approximation for determining the dose contribution from the head and neck, upper arms, and thighs. Calculations also assume all activity will be present in one elbow joint. This is conservative when both elbows are treated as one elbow would likely be located at a further distance away and the dose would be lower if only one elbow is treated. Additionally, Exubrion chose the lowest (most conservative) shielding factor derived from the 10-dog survey.

Exubrion showed the colloid will not be excreted, hence individual CEDE is 0. Therefore, it is acceptable that Exubrion used only EDE for TEDE. As defined in part 20, EDE is the sum of the products of the dose equivalent to the organ or tissue and the weighting factors (W_T) applicable to each of the body organs or tissues that are irradiated. In place of individual organ weighting factors, Exubrion used compartment factors described in table 1 in RG 8.40. In place of compartmental deep dose equivalent calculations as described in RG 8.40, Exubrion used Microshield® to model EDE to the combined thorax and abdomen compartment from a source located at the most conservative location (i.e., middle of the torso). Staff finds this appropriate for EDE calculations to hypothetical persons, in place of a more sophisticated simulation containing individual organs. Exubrion used significant conservatism in their assumptions which contain significant uncertainty when calculating a dose to a hypothetical person. These uncertainties include exact location of source, size and shielding of the dog's elbows, and specific time the source remains at the location. Exubrion conservatively assumes EDE to the other compartments is the highest dose calculated using the point source assumption.

The staff finds Exubrion's Microshield calculation acceptable. Staff finds it acceptable to exclude emissions less than 15 kiloelectronvolts as these low energy emissions would not penetrate into human tissue. Normalization of the activity to the maximum allowable release dose rate is appropriate as dogs will be released based on dose rate and not activity administered. In addition, using a bare source in air for normalization removes variability and errors, which would be introduced due to variations in geometry and shielding between different dogs' elbows. Staff finds Exubrion's use of multiple sized torsos appropriate to demonstrate doses to various members of the public. Finally, the use of point source approximation and use of minimum distances between compartments is conservative to calculate dose contributions from the head and neck, upper arms, and thighs.

Staff performed an independent assessment of dose to members of the public following release of dogs. To verify if the Exubrion analysis was conservative, NRC simulated the dose to an adult male using MCNP 6.2 to compare to Exubrion's calculated dose using Microshield®, Pro

Version 12.07, and the shielding evaluation. This MCNP simulation assumed a Sn-117m point source using ICRP 38 database within a sphere of bone with a radius of 0.6 inch (1.5 cm) and a density of 1.85 g/cm^3 and covered in skin which has a thickness of 2 mm and a density of 1.0 g/cm^3. The human torso was modeled as a right circular cylinder of ICRU 4-component tissue that is 22.8 inch (58 cm) high with a radius of 5.55 inch (14.1 cm) and had the mass of the modeled torso is 36,200 grams. Calculations were conducted for a source centered at 0.7 inch (1.8 cm), 1 foot (30 cm), and 3.3 feet (1 m) laterally from the torso and at locations at the base of the torso, at the umbilicus, and at mid-torso. The simulation provided the energy deposition per nuclear transition in the torso, which was then converted to dose using the maximum activity of 222 MBq (6 mCi). For simplicity, the simulation only modeled dose to the torso and was not weighted with dose to the arms, head and neck, or legs. This geometry is conservative as the dose to these other areas would be lower due to the greater distance to the source. All standard errors in the MCNP simulations were less than 0.5%.

The results from the MCNP simulation are compared to Exubrion's in table 2 below. As shown, Exubrion's analysis results are approximately double that of the MCNP simulation. Staff therefore finds Exubrion's method to use Microshield® in combination with their shielding evaluation is adequate to calculate dose to members of the public from interactions with released dogs following treatment.

Table 2 – Comparison MCNP versus Exubrion's Analysis Calculations of Adult EDE

Distance from the middle of the torso	Exubrion's Analysis (mrem)	MCNP Simulation (mrem)
0.7 inch (1.7 cm) (i.e., contact)	7.7	3.1
1 foot (30 cm)	0.98	0.6
3.3 feet (1 m)	0.22	0.1

The staff finds it appropriate to use an isotropic shielding factor as exposure will occur over a long period of time and through a variety of different geometries. The staff also finds the use of the lowest shielding factor from the 10 dogs measured provides adequate conservatism in measurements. While Exubrion's shielding factor calculations are conservative, staff wanted to verify that use of alternative measurements for the posterior and upper posterior locations at the 1-foot distance did not change the final outcome. Therefore, staff removed these measurements and calculated an independent staff 1 foot (30 cm) shielding factor. The staff retained the dorsal measurements, as staff believed the replacement measurements were unlikely to be significantly greater than 1 foot (30 cm) and the staff did not find the values to skew the average shielding factor. After removing the 1-foot (30-cm) measurements for the upper posterior and posterior geometries, the staff determined its own independent shielding factor of 26 percent for the 1-foot (30-cm) measurements. The staff determined Exubrion's shielding factor of 28 percent at 3 feet (0.9 m) was appropriate as all measurements were taken at 3 feet (0.9 m). Table 3 below shows staff's calculated effective equivalent dose using Exubrion's methodology with the staff's reduction factor at 1 foot which staff used in all confirmatory calculations below.

Table 3 – Staff's Calculated Effective Equivalent Dose Rates

	Effective Equivalent Dose Rate (mrem/h)		
Age	**On Contact**	**1 foot**	**3 feet**
Adult	7.7	1.0	0.22
15	9.3	1.2	0.24
10	13.7	1.4	0.26
5	19.4	1.6	0.28
1	29.6	1.8	0.30

The staff additionally finds the shielding study demonstrated that the dose rate to humans from most dogs will be below 0.45 mR/h (0.0045 mSv/h) at 3.3 feet (1 m) following this treatment and could be immediately released. The shielding study was conducted with a total activity of 6.76 mCi administered to each dog; a dosage which is approximately 10 percent greater than the maximum activity to be administered. Most of the dose rate measurements from the ten test subjects were less than 0.45 mR/h (0.0045 mSv/h) at 3.3 feet (1 m). However, the results from the shielding study demonstrate the importance of surveying the dog after treatment as a few were over 0.45 mR/h (0.0045 mSv/h) at 3.3 feet (1 m). Exubrion's procedure states the licensee will take survey measurements at 3.3 feet (1 m) from the nearest elbow in three geometric directions expected to have the highest dose, anteriorly and right and left laterally. If the dog has a measurement above 0.45 mR/h at 3.3 feet (1 m), the dog will be held by the licensee until the dose rate decreases below this threshold.

Household Member Exposure

Regulatory Basis for Prescreening and Behavior Modifications

Per 10 CFR 20.1301, licensees must conduct operations to ensure that the TEDE to individual members of the public does not exceed 100 mrem in a year. In addition, 10 CFR 20.1301(a)(2) states that the dose in any unrestricted area from external sources does not exceed 0.002 rem (0.02 mSv) in any 1 hour. In addition, 10 CFR 20.1101(b), "Radiation protection programs," states that the licensee shall use, to the extent practical, procedures and engineering controls based on sound radiation protection principles to achieve doses to members of the public that are as low as is reasonably achievable (ALARA).

Prescreening Questionnaire

Exubrion's evaluation showed that the public dose limits could be exceeded upon exposure to some dogs based on their normal dog-human interactions. Therefore, Exubrion proposes a prescreening questionnaire to identify dogs that are candidates to be released immediately after treatment. If prescreening finds a dog is a candidate for treatment, the prescreening questionnaire is also used to identify if any of the dog's normal behaviors need to be stopped or modified and for how long. Exubrion's procedure states that the licensee shall conduct an evaluation using a prescreening questionnaire with the owner, who has full knowledge of the dog's interaction with people, to determine whether the common behavior patterns of the dog could create a risk for any individual to exceed the public dose limits. If behavior patterns of potential risk are identified, then the licensee would inquire as to whether or not the household members could stop or modify the behaviors to provide confidence that public dose limits will not be exceeded.

Exubrion's prescreening questionnaire procedure has licensees asking owners to describe the general interactions the dog has with each household member using leading and specific questions. The intent of the specific questions is to identify behaviors which Exubrion's evaluation found could potentially cause the public dose limit to be exceeded if not modified. If these behaviors cannot be modified, the procedure allows the licensee to make an informed decision to contraindicate the therapy. The prescreening questionnaire also has a section for additional items, which the licensee may use for a focused discussion on any item applicable to that household, such as minimizing public dose with attention to children and pregnant women. After gathering this information, the licensee will compile the amount of time each person spends at distances of less than 1 foot (30 cm), at 1 foot (30 cm), and at 3 feet (0.9 m) daily. While compiling the information, the procedure states that distances should be rounded down for conservatism.

After the licensee completes the prescreening questionnaire, Exubrion's proposed procedure directs the licensee to sum the typical daily time each individual spends at various distances to the dog. The licensee will then use this information to place the dog into the most conservative category based on individuals' interactions. The four categories are: common contact, extended duration at intermediate contact, extended duration at close contact, and prolonged close and intermediate contact. The "common contact" category is for dogs which have typical behavior patterns of up to 5 minutes a day with direct contact, 15 minutes a day at 1 foot, and 4 hours a day at 3 feet. If a dog's normal behavior includes more interactions at 3 feet, like a dog who sits with someone while they work, this dog would move into the extended duration at intermediate contact category. This category allows up to 12 hours a day at 3 feet and the dog would still need to have less than 5 minutes a day with direct contact and 15 minutes a day at 1 foot. If a dog instead typically has more interactions at 1 foot, like a dog which sits on a couch next to someone, this dog would be in the extended duration at close contact category. This category allows up to 3 hours a day at 1 foot and the dog would still need to have less than 5 minutes a day with direct contact and 4 hours a day at 3 feet. If a dog typically has even more contact at the 1 foot distance, such as a dog which cosleeps, or the dog has increased interactions at both the 1 foot and 3 feet distances, this dog would be categorized in the prolonged close and intermediate contact group. This category allows for a dog to have typical interactions of up to 5 minutes a day with direct contact, 11 hours a day at 1 foot, and 9 hours a day at 3 feet. The specific times for each category are provided in table 4 below.

Table 4 – Behavioral Categories

Category	Maximum time at direct contact	Maximum time at 1 foot	Maximum time at 3 feet
Common contact	5 minutes	15 minutes	4 hours
Extended duration at intermediate contact	5 minutes	15 minutes	12 hours
Extended duration at close contact	5 minutes	4 hours	4 hours
Prolonged close and intermediate contact	5 minutes	11 hours	9 hours

[1] Calculations were completed for 4 hours a day at 1 foot for extended duration at close contact category, but the procedure conservatively limits this to 3 hours a day.

Exubrion's evaluation demonstrated instructions would be necessary for varying amounts of time based on these typical interaction patterns. Therefore, Exubrion proposed using these

categories to determine the duration (2 to 6 weeks) necessary for the release instructions. The release instructions will be customized based on discussions between the licensee and owner during the prescreening. Instructions are described in more detail below.

Household Member Exposure

For each category, Exubrion calculated the dose for all age groups. In these calculations, Exubrion assumes an individual interacts with the dog on a daily basis for the maximum amount of time allowed during the instructional period. After the instructional period is over, calculations assume the dog interacts with individuals at the maximum amount of time described in the category on a daily basis. If a dog's typical interactions exceed any of these categories, the dog would not be a candidate for treatment. Therefore, as no category allows typical interactions to exceed 5 minutes a day on direct contact with the elbow joint, a dog with typical contact interactions of more than 5 minutes a day would not be a candidate for treatment as there is no category which the dog could fit into. The licensee cannot use instructions to fit a dog's behavior into these categories as the calculations assume these will be the interaction patterns after the instruction window is completed.

Exubrion's calculated annual dose to adults is below the public dose limit of 100 mrem (1 mSv) for all categories, assuming individuals follow instructions. Exubrion also calculated the dose to children and found the maximum calculated dose was 61 mrem (0.61 mSv) for the common contact scenario assuming a 1-year-old baby who is present for the maximum amount of time described in the instructions and scenario. The calculated dose to the 1-year-old increases to a maximum of 84 mrem (0.84 mSv) in the prolonged close and intermediate contact scenario. Exubrion's technical evaluation report provides more information on the calculated doses for each category.

Exubrion proposed that a dog may be released with a maximum dose rate of 0.45 mR/h (0.0045 mSv/h) at 3.3 feet (1 m). Exubrion calculated the maximum hourly dose rate if someone follows the instructions to be 0.5 mrem (0.005 mSv) for an adult and 1.1 mrem (0.011 mSv) for a 1-year-old. After the 2-week minimum duration for instructions, Exubrion calculated the maximum dose to be 0.8 mrem (0.008 mSv) in 1 hour for an adult and 2.0 mrem (0.02 mSv) in 1 hour for a child assuming a scenario of 5 minutes of direct contact of the torso with the elbow and the remaining 55 minutes at 1 foot (30 cm). Exubrion chose this scenario as the procedure only allows for release of dogs using this evaluation if they have behavior patterns which typically have less than 5 minutes a day in close contact with an individual.

Staff's Evaluation of Household Member Dose

The staff's evaluation found that Exubrion's proposal to release dogs containing a Sn-117m colloid has the potential to result in doses exceeding the public dose limits in 10 CFR Part 20 without appropriate screening and written instruction. Exubrion proposed to allow immediate release of dogs who are administered up to 222 MBq (6 mCi) of Sn-117m colloid. Because of the half-life of Sn-117m and because there is almost no biological decay in the colloid form, the Sn-117m will remain in the dog's elbow for a substantial amount of time. Therefore, staff agrees with Exubrion that prescreening is necessary prior to releasing a dog to ensure public dose limits are not exceeded.

Exubrion's proposal includes an evaluation using a prescreening questionnaire to identify each dog's typical dog-human interactions in order to determine whether the dog would be a

candidate for treatment and could be safely released after treatment. The staff determined that the prescreening questionnaire should identify individual dog's behaviors that would require modification or cessation to ensure the public dose limits are not exceeded. The prescreening questionnaire can be used to identify behaviors that could cause public dose to be exceeded if they are not able to be modified. The staff finds it acceptable for the licensee to decide on a case-by-case basis if treatment should still be allowed if a dog-owner cannot modify any of these flagged behaviors, which provides flexibility in situations where the licensee determines that the dog's specific situation will not cause the public dose limits to be exceeded. The staff finds Exubrion's procedure requires any necessary behavior modifications be discussed with the owner. In addition, the focused discussion will help the licensee determine whether the owner has any unique situations that would require further modifications and whether all individuals who have frequent interactions with the dog will be able to meet the necessary time and distance restrictions.

Staff finds Exubrion's maximum calculated dose for each category to be conservative, as they assume a maximum release dose rate at the time of release per category and the maximum time, minimum distance in each category, and use of a singular source for dose on contact. Staff additionally finds the calculations for young children, such as the calculation for a 1 year old in the prolonged close and intermediate contact scenario, to be conservative as it is unlikely a young child would typically remain at a 1 foot distance for 11 hours a day and 3 feet distance for 9 hours every day following release. In addition, the prescreening questionnaire and instructions include additional steps to inform the owner to minimize the dog's interactions with children and pregnant women following release of the dog.

The staff independently calculated the maximum public dose for individuals in each behavioral category and assumes they follow instructions. The staff's calculations assume the maximum dose at time of release and that the individual has the maximum daily interactions with the dog allowed for each distance during and after the instructional period until infinity. Table 5 below lists the staff's calculated maximum dose for each category for adults, a five-year-old, and a one-year old child. The staff used the same methodology as Exubrion to calculate the dose as it was shown to be conservative, except for using the staff's 1-foot (30-cm) shielding reduction factor of 26 percent as described above.

Table 5 – Staff's Maximum Calculated EDEs

Dog Category	Maximum dose to an adult (mrem)	Maximum dose to a 5 year old (mrem)	Maximum dose to a 1 year old (mrem)	Maximum Instruction Duration (weeks)
Common Contact	29	47	61	2
Extended Duration at Intermediate Contact	45	67	84	2
Extended Duration at Close Contact	59	94	114	3
Prolonged Close and Intermediate Contact	59	90	106	6

As demonstrated in table 5, younger children have a larger dose when they follow the same interactions as larger adults. Exubrion did not calculate the dose for a 1-year old child for the extended duration at close contact or prolonged close and intermediate contact categories as they did not believe the interaction patterns described in these categories would be realistic for children this young. Therefore, a 5-year old is the youngest average age showed to not exceed the public dose limit for these two categories. To ensure licensees do not use these categories for children younger than the age of 5 as they could potentially lead to public dose limits being exceeded, future license applicants would need to commit to not using these pathways specifically for children younger than the age of 5 in their license application. However, a licensee could use these pathways if adult interactions require it as long as all children under the age of 5 in the household fit into common or extended duration at intermediate contact categories. An example would be a dog that has a typical interaction pattern with an adult fitting the prolonged close and intermediate contact category and with a four-year old fitting the common contact. In that case, the release instructions will be at the level of prolonged close and intermediate contact, because that is the highest level of contact in the household, but the dog can be released because the interaction with the child under 5 fits into the common contact category. Staff's calculations demonstrate with reasonable assurance that the common contact and extended duration at intermediate contact categories will result in doses below the annual public dose limit for young children.

The staff also evaluated Exubrion's calculations to provide reasonable assurance that the hourly limit of 2 mrem (0.02 mSv) in any 1 hour would not be exceeded with adequate prescreening and if household members follow instructions after release. In this calculation, Exubrion assumed a dog elbow would be at a distance of 1 foot for the entire hour except for the 5 minutes which the dog's elbow is in direct contact with the individual's torso. Staff finds this acceptable as the procedure only allows treatment of a dog which has less than 5 minutes a day of direct contact interactions prior to treatment. Therefore, staff finds assuming an individual is in close contact for 5 minutes and at 1 foot for the remaining 55 minutes in an hour is appropriate.

The staff also reviewed the close contact dose beyond the instruction duration. The proposed shortest duration for instructions is 2 weeks, which is approximately equal to one half-life of Sn-117m. Using Microshield with all activity located in one joint similar to Exubrion, staff identified that, at the end of the first two weeks, it would take almost 8.3 minutes for a 1-year-old child and almost 32 minutes for an adult to reach 2 mrem (0.02 mSv) assuming the most conservative geometry (i.e., direct, center of the torso contact with the dog's elbow). As the procedure only allows dogs to be treated if prescreening shows the owner normally has less than 5 minutes of contact with the animal and the unlikeliness of a dog with severe OA to allow significant physical contact with the joint, it is unlikely these times would be exceeded. In addition, this calculation has significant conservatism as the maximum release dose rate would unlikely be from a dog with one elbow treated, and this calculation assumes direct contact in the center of the abdomen to a singular elbow containing all activity. Furthermore, it is unlikely the maximum release dose rate (0.45 mR/h at 1 m) will be exceeded if only one elbow is treated with 3 mCi. After 2 weeks, dose rate would be less than 2 mrem (0.02 mSv) per hour at 1-foot (30 cm) even without considering shielding factors. Therefore, the staff finds that the procedure provides reasonable assurance that the hourly public dose limit will be met for dog's which

normal behavior fits into one of the categories analyzed. To ensure that licensees understand that this evaluation is only intended to be used when all household members' typical interaction patterns fit into the categories described in the procedure, future licensees must commit that they will not use this procedure to release a dog whose typical behavior patterns do not fit into the categories described in the procedure.

Staff's Evaluation of Dose to Individuals Outside the Household

If dogs are properly prescreened and release instructions are followed, Exubrion's evaluation showed the annual dose limit of 100 mrem (1 mSv) in a year will not be exceeded by those who have frequent contact with the dog. Adequate prescreening by the licensee should identify any dog who has significant daily contact with individuals outside the household, and licensees will need to be confident that the dog owner will modify or limit these behaviors before scheduling treatment. To ensure individuals who have random, infrequent contact with the dog also do not exceed the public dose limit, the staff evaluated the total amount of time someone would need to be near the dog to exceed the annual dose limit. For simplicity and conservatism, the staff used the dose rates calculated above using Microshield with staff's shielding factors without decay considerations. The staff determined it would take 13 hours on contact, 97 hours at 1 foot (30 cm), and 454 hours at 3 feet (0.9 m) for an adult to exceed the pubic dose limit of 100 mrem in a year. Staff also determined that a 1-year-old might exceed the public dose limit after 3.4 hours on contact, 54 hours at 1 foot (30 cm), and 333 hours at 3 feet (0.9 m). Even if a dog ran away from its owner, it is unlikely that another individual would exceed these durations before the dog would be reunited with its owner. It is highly unlikely that an individual who does not have frequent interactions with the dog would meet these criteria. The staff finds Exubrion's proposed maximum release dose rate is adequate to ensure the annual dose limit is not exceeded for individuals who have infrequent encounters with the dog.

The staff also validated the isotropic dose at 1 foot (30 cm) and 3 feet (0.9 m) would be less than 2 mrem (0.02 mSv) per hour immediately following release. This includes the grooming scenario, which Exubrion's proposed instructions state to avoid for 2 weeks following treatment. Even if an owner took their dog to the groomer immediately following treatment, the maximum dose to the groomer would be 1.0 mrem (0.010 mSv), assuming the groomer's torso is at an average distance of 1 foot (30 cm) from the elbow for an entire hour and the groomer moves around the animal during the grooming session.

The staff also evaluated the boarding scenario. Exubrion stated the worst case scenario for a worker at a boarding facility would be a worker who spends 30 minutes a day at a distance of 1 foot (30 cm) interacting with a dog. Staff estimate that this scenario would result in a calculated annual dose of 10.2 mrem (0.102 mSv) using a 0.26 shielding factor at 1 foot (30 cm) and assuming a dog who had the maximum release dose rate at time of release went back to the boarding facility immediately following treatment and was at the boarding/daycare facility every day. Exubrion instructs the owner to avoid long-term or daily boarding for one half-life, or 2 weeks. Following this instruction reduces the conservatively calculated dose to 5.0 mrem (0.05 mSv) for 30 minutes a day at a distance of 1 foot (30 cm) and 10 mrem (0.010 mSv) for 1 hour a day at a distance of 1 foot (30 cm). This conservative calculation shows a worker at a boarding facility would need to be exposed to a minimum of at least 10 dogs before the public dose limit would be exceeded. Therefore, the staff does not believe it is likely that a member of the public working at a boarding facility would exceed the public dose limits from a dog treated with Sn-117m. As the maximum contact dose rate is 7.7 mrem/h (0.077 mSv/h), it would take

approximately 16 minutes of direct contact with the dog's elbows on the workers torso to exceed 2 mrem in any one hour. As staff finds this an unlikely scenario, staff believes the 2 mrem in any one hour limit will not be exceeded in the boarding scenario.

Instructions

Exubrion's Instructions

As stated above, some owners will need to modify behaviors for a period of time following treatment to ensure public dose limits are not exceeded. Exubrion's proposal uses categorization of dogs based on the dog's normal behavior patterns to determine the instructional duration (anywhere between 2 to 6 weeks). After the duration of the instructions, individuals can return to their normal behavior patterns. The procedure only allows treatment of dogs that have normal behavior patterns that Exubrion has shown to not cause doses to exceed public dose limits with the proposed instructions.

The instructions inform all individuals to limit direct activities, which typically occur at distances less than 1 foot (30 cm), to less than 1 minute a day, close activities, which typically occur at a distance of 1 foot (30 cm), up to 15 minutes a day, and intermediate activities ,which typically occur at a distance of 3 feet (0.9 m), up to 4 hours a day. These average daily durations at these distances should keep household members exposures below the public dose limits. To support owners' understanding of these time limitations and distances, given their specific dog's behavior patterns, the instructions will include individualized behavior modifications from the prescreening questionnaire. In addition, the instructions recommend minimizing time to sensitive populations, such as children and pregnant women, and provide owners with how to keep doses ALARA. Finally, the instructions inform the owner that, after the expiration of instructions, they may return to normal interactions with the dog but should continue to be prudent about extended close contact.

Exubrion's procedure states that, before treating the dog, the licensee will confirm that the owner is willing and able to follow the instructions for the specified duration and that all household members can comply with the instructions. The licensees will provide written instructions with a minimum duration of 2 weeks, whether or not behavior modification is needed to ensure that all public exposures are ALARA. In response to requests for additional information, in a letter dated May 15, 2020, Exubrion stated that customizing the instructions based on an individual owner's behavior increases the likelihood of compliance and therefore keeps doses ALARA. The procedure and prescreening questionnaire have a step to ensure the licensee discusses ALARA principles with the owner to support the owners' understanding of how the general radiation protection principles (i.e., time, distance, and shielding) should be used to keep their doses as low as possible. In addition, the procedure requires licensees to discuss with owners how they can keep the doses ALARA at a follow-up approximately one week after treatment. The instructions will also provide owners with the information necessary to reduce exposure to other members of the public.

As described below in the staff's independent evaluation, most infrequent or random encounters with the animal would not likely exceed dose limits. However, if an individual is in close contact with a dog for an extended period of time or has almost daily contact with the animal, the interaction may need to be limited. Therefore, the instructions inform the owner to avoid long-term or daily boarding or commercial grooming for 2 weeks and avoid air travel and large organized events where the animal would not be able to move easily for the entire duration of

the instructions. If the dog were to need emergency care, the instructions state the owner should immediately inform the emergency provider about the Sn-117m treatment and immediately contact the licensee for directions. Additionally, the prescreening questionnaire would help to identify unanalyzed situations in which an animal is out of the house for a significant period, allowing the licensee to provide behavior modification instructions, if necessary. Finally, the instructions inform the owner to contact the licensee if the dog dies within 20 weeks of treatment. Exubrion chose 20 weeks because this is the time it would take for the maximum treatment activity of 222 MBq (6 mCi) to decay to less than 0.37 MBq (10 microcuries).

Staff's Evaluation

The staff finds Exubrion's proposed duration of instructions adequate to ensure public dose limits will not be exceeded for dogs appropriately prescreened. The procedure only allows treatment of dogs that have normal behavior patterns that Exubrion has shown to not cause dose to exceed public dose limits if instructions are followed. Exubrion has demonstrated these dogs can resume their normal behavioral patterns after the instructional period, but the instructions still provide guidance to owners to minimize extended close contact following the instructional period.

The staff finds that Exubrion's prescreening discussions with the owner and customizable instructions will provide owners with the information necessary to reduce their exposure and provide adequate assurance that household members will not exceed public dose limits. While direct contact needs to be limited to less than 1 minute a day during the instructional period, dogs will only be allowed to be treated per this procedure if their normal behavioral patterns have less than 5 minutes a day at direct contact without instructions. Exubrion's procedure also only allows treatment of the dog if the licensee feels confident that the household will follow release instructions to provide adequate assurance that the public dose limits are not exceeded. Therefore, staff finds Exubrion's proposed instructions provide adequate assurance that public dose limits will not be exceeded. In addition, the staff finds the use of customizable instructions and the required discussions with the owner on how to keep doses ALARA, both before and after treatment, provides reasonable assurance that doses will be ALARA.

<u>Dose with Inadequate Prescreening or Disregard for Release Instructions</u>

Exubrion's technical evaluation provided evidence that the most common interaction pattern with a severely arthritic dog who would be a candidate for this treatment would lead to a dose below 100 mrem (1 mSv) even without instructions. However, Exubrion's evaluation also identified that some interaction patterns that could lead to public dose limits being exceeded by household members. The staff found that the public dose limits will not be exceeded with adequate prescreening and if household members follow their customized release instructions. The staff determined that the prescreening questionnaire is adequate to identify any unique dog-human interactions that would need to cease or be modified to ensure that the public dose limits are not exceeded. In addition, the staff determined the procedure's use of both standard and customized instructions, and only allowing release if the licensee has confidence that household members can comply with these instructions, provides adequate assurance that the household members know how to keep their exposure below the public dose limits and ALARA. However, if individuals who reside with the dog choose not to provide complete and accurate information during the prescreening, or choose not to follow licensee's instructions, it is possible

that their exposures could exceed the public dose limits. Therefore, staff evaluated several potential situations to determine the maximum likely dose if members of the public do not provide adequate prescreening information or do not follow instructions.

First, the staff calculated the amount of time on a daily basis that it would take for an individual to reach the annual 100 mrem (1 mSv) dose limit. For an adult, the staff found it would take approximately 40 minutes a day of direct on-torso contact with the elbow to exceed the public dose limit. The duration would be longer for further distances. If adults had no contact with the treated dog for 2 weeks post-treatment, the amount of time needed to exceed the annual 100 mrem (1 mSv) dose limit if they interacted with the dog on direct torso contact increased to more than 74 minutes a day. For a 1-year-old child, after the minimum 2-week instructional period, approximately 41 minutes a day of direct contact or approximately 4.5 hours a day at 1 foot (30 cm) is needed to exceed the public dose limit. These calculated values demonstrate the importance of minimizing time in close contact with the animal for several weeks after treatment. The staff finds the prescreening questionnaire will adequately identify a dog who typically has interactions that exceed these times at these distances. The procedure only allows dogs to be treated if prescreening shows the owner normally has less than 5 minutes of contact with the dog's elbow. To ensure that licensees understand that this evaluation is only intended to be used when all household members' typical interaction patterns fit into the categories described in the procedure, staff recommends license reviewers obtain a commitment from future license applicants that they will not use this procedure to release a dog whose typical behavior patterns do not fit into the categories described in the procedure.

The staff calculated the dose to an individual who has daily interactions that match those described in the prolonged close and intermediate contact scenario (5 minutes on contact, 11 hours at 1 foot (30 cm), and 9 hours at 3 feet (0.9 m) per day) but disregards instructions such as cosleeping. This is a worst-case scenario based on Exubrion's evaluation of typical dog-human interactions. If an adult cosleeps with the dog, offices with the dog, and allows the dog to lap sit for 3 hours a day, this adult could receive a 273 mrem (2.73 mSv) exposure. If the individual follows the instructions for only the first 3 weeks of the 6 week instructional period, this dose drops to 110 mrem (1.10 mSv). These calculated values demonstrate the importance for licensees to ensure individuals understand and are willing to comply with instructions for the full duration. The staff finds it acceptable to use the proposal to use the prescreening questionnaire to allow the licensee to develop necessary customized instructions. Prescreening also allows the licensee to have directed conversations with the owner to ensure the owner understands which activities would lead to high doses, especially those which need to stop or be modified to ensure the public dose limit is not exceeded, and allows the licensee to gauge if the household can follow necessary instructions. If the licensee's staff does not have confidence that all household members will and can follow the necessary instructions, the procedure states the dog will not be treated. The staff finds this proposal provides adequate assurance that public dose limits will not be exceeded.

Finally, the staff calculated the dose to an individual who was not appropriately prescreened and had daily interactions beyond those described in the categories of the procedure. To bound the worst case dose, staff chose a highly unlikely scenario where an individual has a dog directly on contact with their torso for 2 hours a day in addition to daily interactions of 8 hours at 1 foot (30 cm) with a 26-percent shielding factor and 9 hours at 3 feet (0.9 m) with a 28-percent shielding factor would receive 502 mrem (5.02 mSv) for the entire duration of Sn-117m decay. Staff

conservatively assumed maximum dose rate at time of release and assumed the individual did not follow any instructions after release. Staff finds this calculation to be conservatively bounding as it is highly unlikely that a dog released with the maximum dose rate would have this long of close contact with an individual on a daily basis. Staff did not calculate this scenario for a young child as it would be extremely unlikely that a dog to have their elbows directly on contact with a small child for 2 hours every day. Staff assumes the prolonged close and intermediate contact scenario appropriately bounding for a one year old. The calculations for the staff's worst case scenario demonstrate that, if an owner does not provide complete or accurate information during prescreening or chooses not to follow the release instructions, exposure to the released dog could cause public dose limits to be exceeded amongst household members who have frequent, close contact exposure to the dog. The procedure contains steps to avoid releasing dogs whose typical interactions would cause this level of exposure and does not allow licensees to release dogs from licensee control if they are not confident the household members will follow instructions based on discussions during prescreening with the owner. Therefore, this type of scenario causing exposures to exceed the public dose limit would only occur if an owner did not provide complete or accurate information during the prescreening or a household member did not to follow instructions even after the owner provided the licensee with assurance that all household members will do so.

As described above, the prescreening questionnaire is meant to identify if an individual dog has behaviors that could cause the dose limits to be exceeded. If behaviors are identified, the procedure has the licensee and owner discuss ways which these behaviors could be stopped or modified for a duration of time and develop customized written instructions to keep exposures below the public dose limit. In addition, the procedure, prescreening criteria, and release instructions have additional measures to ensure that the licensee discusses, and the owner knows, how to minimize dose specifically to children and pregnant woman. The procedure tells the licensee not to treat a dog if the licensee does not feel confident that the owner understands the need to keep doses below the public dose limit and that the household will not be able to follow the instructions. This would prohibit the licensee from treating a dog which they know will spend time with an individual, like a young child, who could not follow instructions. In addition, the procedure states the licensee will follow-up with the dog's owner approximately 1 week after the treatment, review the household members adherence to the instructions, and remind the owner to keep doses ALARA. Therefore, the staff finds Exubrion's proposal acceptable to ensure public health and safety as it provides adequate assurance that public dose limits will not be exceeded when owners provide complete and truthful information during prescreening and household members follow instructions agreed to prior to treatment.

The procedure also directs the licensee to follow-up with owners and to perform an assessment of the dose to individual household members if someone does not follow the release instructions. This follow-up will provide the licensee an opportunity to ensure that the owner is abiding by the release instructions and understands the necessity to continue following the release instructions. If the licensee becomes aware of the owner not following the release instructions, the licensee has an opportunity to re-emphasize the need to follow the release instructions and modify those instructions, if necessary. In addition, the procedure states that licensees must investigate any instance where public exposure limits might have been exceeded, even if it is due to individuals not following instructions, and to submit a written report to the NRC per 10 CFR 20.2203. In this case, the NRC would evaluate this event to determine if any corrective actions are necessary to avoid future exceedance of the public dose limits.

Conclusion

Exubrion's proposal is to allow veterinary licensees to be authorized to release dogs following Synovetin OA® treatment with a maximum dose rate of 0.45 mR/h at 3.3 feet (1 m). As demonstrated above, it is unlikely that normal encounters with a dog released at a dose rate proposed by Exubrion would cause a member of the public to exceed the public dose limits without daily interactions. However, it is possible that individuals who have certain frequent, close interactions with the dog, such as cosleeping, could exceed the public dose limit. The prescreening questionnaire and release instructions ensure that the licensee has discussions with individuals knowledgeable of the dog's behavior to determine whether any dog-human interactions need to stop or be modified for a certain amount of time. The prescreening questionnaire and release instructions also facilitate discussions with these owners to support their understanding of the importance of these instructions and how to keep their exposures ALARA. The proposed procedure states that, if the licensee is not confident that a household can comply with or will follow the necessary instructions to ensure public dose limits will not be exceeded, then the dog will not be scheduled for treatment. The procedure also requires the licensee to follow-up approximately one week after treatment to remind the owners of how to keep doses ALARA, review the owner's adherence to instructions, and remind them of the instructions. The staff finds Exubrion's proposed generic procedure to release dogs following Synovetin OA® treatment with a maximum activity of 222 MBq (6 mCi) provides adequate assurance that public dose limits will not be exceeded when licensees perform adequate prescreening and instructions are followed.

It is the individual licensee's responsibility to ensure compliance with public dose limits in 10 CFR 20.1301, not the dog owners, who are members of the public. It is possible that the exposure to a household member could exceed public dose limits for dogs that have close contact with individuals on a daily basis or otherwise have behavior patterns that do not fit into categories evaluated by Exubrion. With accurate prescreening, these dogs can be identified and should not be treated in accordance with the procedure. In addition, it is possible for exposure to household members to exceed the public dose limits if household members do not follow instructions. If the licensee does not have confidence that household members can follow or are able to follow instructions, the dog should not be treated in accordance with the procedure. Therefore, the staff finds Exubrion's proposal provides adequate measures to ensure public dose limits will not be exceeded when owners provide complete and accurate information. However, staff notes that if an owner provides incomplete or inadequate information during prescreening or if a household member chooses to not follow instructions after the owner confirms they will, public dose limits could be exceeded to members of the household. Staff calculated the maximum exposure in this scenario would be approximately 500 mrem (5 mSv). The staff finds the likelihood of such a scenario to be low given that the licensee provides adequate instructions and means to prevent the exposure. Therefore, the staff finds Exubrion's proposal adequate to protect the public's health and safety.

Notes to License Reviewers Evaluating License Applications to Treat Dogs with Synovetin OA®

NRC license reviewers should accept Exubrion's release procedure contained in their application dated June 1, 2020 (ADAMs Accession Number ML20282A513) as part of an individual license application to treat dogs with up to 222 MBq (6 mCi) of Sn-117m as part of Synovetin OA® treatment. The veterinarian requesting authorization to use Sn-117m for veterinary treatment of dogs should submit this procedure along with all other pertinent information requested in the most recent revision of NUREG-1556, Volume 7. Particular attention should be given to the guidance in NUREG-1556, Volume 7, Appendix D, "Guidance for Laboratory Animal and Veterinary Medicine Uses."

In addition to the guidance in NUREG-1556, Volume 7, Revision 1, the staff recommends that license reviewers obtain the following:

- Acknowledgement from the licensee that the licensee is responsible for ensuring that dogs are released with instructions that will not cause a member of the public to exceed dose limits.

- A commitment that the licensee will not use this procedure to release a dog whose typical behavior patterns, without instructions, do not fit into the time and distance limitations listed for one of the categories described in the procedure as these categories are the only ones evaluated.

- A commitment that the licensee will not release a dog if a child is in the house under the age of 5 who fits into the "Extended Duration at Close Contact" or "Prolonged Close and Intermediate Contact" categories. The dog can be released if the overall category for the dog is either of these categories based on the behavior of an individual over the age of 5. A request to amend the license to approve such a release may be submitted to the NRC with additional, specific calculations that demonstrate the public dose limits will not be exceeded based on the expected dog-child behavior.

- A commitment that there will only be one release per household each year, although a request to amend the license to approve additional releases of the same animal treated multiple times or release of an additional dog to the same household may be submitted, with the additional calculations provided to the NRC that demonstrate that the public limits will not be exceeded; if approved, the license would be amended to authorize the additional release to the same household.

- A commitment that all individuals who conduct the prescreening interviews using the prescreening questionnaire or provide instructions to the staff or clients/owners, will be trained on basic radiation safety principles and the importance of adherence to the procedure and instructions.

- A commitment to retain a copy of prescreening questionnaires and household instructions.

- A commitment to document and retain dose assessments made if household members indicate they have not followed written instructions per 10 CFR 20.2107.