**Draft Requests for Additional Information for the Review of the Hypothetical License Amendment Application for Treatment of Dogs with Synovetin OA™ Containing Sn-117m**

**General Response**

In Exubrion's pre-submittal meeting with the NRC on November 6, 2020, it was expressly discussed that this hypothetical licensing action was predicated on it being a license amendment so that the hypothetical license amendment materials we produced would not need to cover routine matters needed for a new license such as authorized user qualifications, generic radiation protection staff training, area survey procedures and similar.

The purpose of using this hypothetical license amendment process is to provide the NRC with a mechanism for it to directly discuss with Exubrion the central issue of concern, i.e., compliance with public dose limits after a dog is released and development of a Technical Evaluation on that subject. When a licensee submits an amendment request, or especially in the case of a new license application, there are many other details that the NRC license reviewer would need to review. The inclusion of such matters in this hypothetical license amendment review is beyond the originally discussed, intended, and necessary scope of the review to resolve the issue of concern. In particular, we view comments 1-10 as being beyond the intended scope. Please let us know if your intention is to broaden the scope of this review beyond our initial discussions with you.

**Requests for Additional Information (RAIs) specific on the Form 313 Supplement**

**General Response for Comments 1 through 10**

The hypothetical amendment Form 313 Supplement has been revised to generalize the contents and focus the provided content on those items relevant to ensuring that the dose to a member of the public does not exceed regulatory limits. As such, the content to which many of comments 1 through 10 apply has been removed from the revised application package. However, Exubrion does appreciate the feedback and understands that it will be helpful for an eventual specific licensing action application. The below responses to comments 1 through 10 are provided as clarification and to reflect our understanding of the NRC's concern.

**Comment 1**
*Item 8, "Training," of the Form 313 Supplement states that employees preparing the administration will be users authorized on the license or appropriately trained staff members. Please confirm that anyone preparing the administration will be a user authorized on the license (authorized user), or under the supervision of an authorized user.*

**Response**

The intention is that all preparation, handling, and administration of radioactivity will be completed by an authorized user or someone under the supervision of an authorized user. This text has been removed as discussed above.

**Comment 2**
*Item 9, "Facilities and Equipment," of the Form 313 Supplement states that a survey instrument with a pancake GM detector with a minimum detectable activity (MDA) of less than 2000 disintegrations per minute (dpm) per 100 square centimeters area (100 sq-cm) will be used for contamination analysis.*

**Response**
See 2a.

**Comment 2a**
*Appendix M of NUREG-1556, Volume 7, "Consolidated Guidance About Materials Licenses: Program-Specific Guidance About Academic, Research and Development, and Other Licenses of Limited Scope, Including Electron Capture Devices and X-Ray Fluorescence Analyzers," states that acceptable removable concentration levels are 1,000 dpm per 100 sq-cm and total contamination levels are 5,000 dpm per 100 sq-cm. Confirm that you will update the procedure to ensure that the contamination levels meet the requirements of NUREG-1556, Volume 7 and that the MDA will be less than the 1,000 dpm per 100 sq-cm.*

**Response**
This text has been removed as discussed above.

**Comment 2b**
*The package insert section titled "Facility Contamination Assessment" also states that a ratemeter may be used to count wipes used to perform surveys for removable contamination. Confirm if it is intended that wipes be counted using a survey instrument in "ratemeter mode" or "scaler mode". If the detector will be used in ratemeter mode, explain how the MDA for Sn117m is determined.*

**Response**
Empirical data using a Ludlum model 3 ratemeter and 44-9 GM probe show the efficiency for $^{117m}$Sn detection to be approximately 20% under 2π geometry. The 20% efficiency was established with triplicate measurements for both liquid scintillation and paraffin paper standards. With a background rate of 100 counts per minute (cpm), the radiation detection system has a minimum detectable activity (MDA) of approximately 400 dpm. The MDA was established using established practices where $T_{s+b}$ is 0.367min for the slow setting on the Model 3 and k is set for 95% confidence.

$$L_c = k[((R_b/ T_{s+b})+(R_b/ T_b))]^{0.5}$$
$$L_d = (k^2/ T_{s+b})+2L_c$$
$$MDA = L_d/eff$$

This text has been removed as discussed above.

**Comment 2c**
*Confirm that surveys for total contamination will be performed, in addition to surveys for removable contamination in accordance with Title 10 of the Code of Federal Regulations (10 CFR) 20.1501.*

**Response**
Confirmed. All appropriate state and federal contamination assessments will be completed for the limited use of $^{117m}$Sn. This text has been removed as discussed above.

**Comment 3**
*Item 9, "Facilities and Equipment," of the NRC Form 313 Supplement states that surveys will be conducted and documented after administration if the location of the administration is outside of the currently licensed controlled area. "Controlled area" has a specific definition in Part 20, so this statement indicates that licensed material would be used in an unrestricted area. Please confirm if that is intended. If so, provide procedures for performing activities with licensed materials in unrestricted areas that address security and control of licensed materials, and surveys that will ensure no residual radioactive materials remain in the area above levels that would exceed public dose limits. If you were using the phrase "controlled area" differently than as defined in Part 20, provide an alternate explanation of your intention.*

**Response**
This discussion should have referenced the restricted area rather than controlled area. This statement has been deleted from the hypothetical application since it is not germane to the central issue of this hypothetical licensing action, i.e., compliance with public dose limits after a dog is released. If a particular licensee wishes to conduct injections outside the restricted area, they can provide appropriate procedures at that time.

**Comment 4**
*Item 10, "Radiation Safety Program," of the NRC Form 313 Supplement states that the existing Area Survey Procedures will be followed. Based on the cover letter dated December 4, 2019, this section is applicable only if the person requesting the license amendment already is treating cats with iodine-131 (I-131) and that the survey procedures for I-131 are adequate for Sn-117m. Please confirm that Area Survey Procedures will be provided by licensees or applicants who do not currently have a license to work with radioactive materials or update the procedures to state that a licensee will provide this for review with their applications as necessary.*

**Response**
Yes, a new licensee will need to have area survey procedures. This text has been removed as discussed above.

**Comment 5**
*Item 10, "Radiation Safety Program," of the NRC Form 313 Supplement states that the existing Radiation Safety Program and Radioactive Spill Procedures will be followed. Provide any modifications that would be expected for the routine program and/or emergencies (incidents/events) that may be required due to the differences between I-131 and Sn-117m. Please note that the procedures listed in package inserts are generic, and we would expect the licensee to develop site-specific procedures.*

**Response**

For a licensee approved for $^{99m}$Tc and $^{131}$I, there would be no change to the existing spill procedure. The licensee is already familiar with spills, segregation of waste, and when to conduct bioassays. This text has been removed as discussed above.

**Comment 6**

*Item 10, "Radiation Safety Program," of the NRC Form 313 Supplement states that the existing personnel monitoring program would be followed, and that routine bioassay of personnel is not required. Provide instructions for dose evaluation in the event of personnel contamination due to a needle-stick or update to state licensees will provide this for review with their applications as necessary. Follow-up for such an incident would be different for Sn-117m than for I-131.*

**Response**

This item is covered in Item 8 on the Form 313 Supplement. Training. Training including radiation safety and emergency procedures. A parenthetical (such as for an accidental needle-stick) was added to Item 8. This text has been removed as discussed above.

**Comment 7**

*Item 11, "Waste Management," states that radioactive waste may be held for decay-in-storage for 10 half-lives or until the contact exposure rates are indistinguishable from background. The NRC license condition for decay-in-storage states that:*

*i. "Before disposal as ordinary trash, the waste shall be surveyed at the container surface with the appropriate survey instrument set on its most sensitive scale and with no interposed shielding to determine that its radioactivity cannot be distinguished from background. All radiation labels shall be removed or obliterated, except for radiation labels on materials that are within containers and that will be managed as biomedical waste after they have been released from the licensee.*

*ii. A record of each such disposal permitted under this license condition shall be retained for 3 years. The record must include the date of disposal, the date on which the byproduct material was placed in storage, the radionuclides disposed, the survey instrument used, the background dose rate, the dose rate measured at the surface of each waste container, and the name of the individual who performed the disposal."*

*Please note that while the NRC no longer requires the waste to be held for 10 half-lives, some Agreement States maintain this requirement. Please confirm that you will revise your statement to require that waste be surveyed, and records maintained as required in the license condition. Also note that page 2 of the product insert states that the vial will be placed in the lead container and stored for 5 months before disposal. The vial should be removed from the lead container before the waste container and its contents are surveyed.*

**Response**

The second paragraph of Item 11 has been deleted to leave the discussion as simply referencing that existing procedures for decay in storage will be used. The germane portion of the waste management discussion to a license <u>amendment</u> to handle Sn-117m is that different waste containers should be used to handle radioactive materials with significantly different half-lives. That being said, there is no technical reason why wastes of different half-lives could not be combined as long as the waste disposal criteria mentioned in this comment are followed.

**Comment 8**
*Attachment A, "Synovetin OA Training Outline" includes a discussion of decay-in-storage and sanitary sewer disposal. In accordance with 10 CFR 20.2003, confirm that the sanitary sewer disposal training will PROHIBIT the disposal of the tin oxide material by release to the sanitary sewer, because it is NOT readily soluble in water, and is NOT readily dispersible biological material.*

**Response**
Confirmed. This was an oversight on behalf of the technical team. While Synovetin OA is readily dispersible in water, it is not a biological material. Synovetin OA liquid waste will be held for decay. The training material and provided guidance have been updated to reflect prohibition of disposal of liquid Synovetin OA into the sanitary sewer.

**Comment 9**
*Provide the amount of time that is expected to be needed to cover the training described very briefly in Attachment A, "Synovetin OA Training Outline". In accordance with NUREG-1556, Volume 7, submit a description of the assessment of training, a description of the qualifications of the instructors, and the method and frequency of training.*

**Response**
A specific licensee would provide the specific training that they intend to use, which would most likely be a modification and extension of their existing training program for I-131 therapy and any other veterinary RAM uses they may already be doing. As an example, the training made available by Exubrion is provided in accordance with NUREG 1556 Vol 7 Appendix F. The time to complete the didactic training is a function of the role of the individual in the program. Expectation of completion time can be 5 minutes to more than 40 hours for housekeeping staff to AUs respectively. Competency is determined by a quiz at the end of the training material for those handling Synovetin OA. The training is completed prior to initial use and recommended annually thereafter. The content is provided by a physicist certified by the American Board of Health Physics who holds graduate degrees in Radiological Sciences and Protection as well as Medical Physics.

**Comment 10**
*The Safety Data Sheet (SDS) and package inserts have inconsistencies and omissions that conflict with regulations in 10 CFR Part 20 or make it difficult for a licensee to determine the necessary protections necessary for an appropriate radiation protection program required per 10 CFR 20.1101.*

**Response**
The SDS and package insert are to be used in conjunction with the Pre-Screening Questionnaire process and Release Instructions to meet ALARA requirements in 10 CFR 20.1101. If there are other specific regulations of 10 CFR 20 which need clarification, please provide.

**Comment 10a**

*The chemical formula for hydrated tin(IV) oxide as "$Sn_xO_y(OH)_z$." The* CRC Handbook of Chemistry and Physics *lists a number of compounds as tin(IV) oxides including tin dioxide, $SnO_2$; stannic acid (tin oxide di-hydrate or alpha-stannic acid) $SnO_2$-$xH_2O$; and beta-stannic acid, $SnO_2$-$xH_20$. Please confirm if Synovetin OA is actually a mixture of tin oxide and stannic acid compounds or if another more accurate chemical formula is applicable.*

**Response**
The Synovetin microparticles are composed of hydrated Sn-117m enriched tin(IV) oxide (α-stannic acid) that are suspended in an aqueous solution of ammonium salts (chloride, iodide, and bicarbonate). The chemical formula for the microparticles is $SnO_2.xH_2O$. The package insert and SDS attachment has been removed from the hypothetical license amendment package.

**Comment 10b**
*The SDS does not list any potential routes of entry. In the case of any material that is injected, entry by needle is a potential route of entry and should be addressed in the SDS.*

**Response**
The updated SDS lists potential routes of entry as "Absorption (skin and eyes); ingestion; inhalation; injection" and details the potential health effects. A subcutaneous injection will have the potential to cause irritation and some possible radiation damage at the site of injection. An intravenous injection would cause some systemic spread of the product. Ingestion would cause uptake in the digestive tract. Testing of these possible modes of entry was undertaken showing unremarkable results. The package insert and SDS attachment has been removed from the hypothetical license amendment package.

**Comment 10c**
*The SDS requires additional information. The SDS does not include hazards identified for non-radioactive tin oxides on Material Safety Data Sheets readily available on the internet. Tin(IV) oxide is listed as hazardous in case of inhalation, and slightly hazardous (irritant) in the event of skin contact, eye contact, or ingestion. It is listed as toxic to mucous membranes and may be toxic to lungs and the upper respiratory tract.*

**Response**
Section 3 of the SDS has been updated to include the non-radiological hazards. The package insert and SDS attachment has been removed from the hypothetical license amendment package.

**Comment 10d**
*The SDS chronic health hazard statement is not consistent with the U.S. system of regulatory protection. The system is based on linear no threshold. There is no threshold below which no stochastic effects may be induced. The text must be changed accordingly. Also, remove genetic effects as a potential chronic health hazard in Section 11 of the SDS.*

**Response**
The SDS Section 3 chronic health hazard description has been updated accordingly. The package insert and SDS attachment has been removed from the hypothetical license amendment package.

**Comment 10e**
*The SDS section for protective clothing or equipment should include shielded containers for handling and storage of the radioactive material.*

**Response**
Section 8 of the SDS has been updated to note shields and shielded containers are appropriate. The package insert and SDS attachment has been removed from the hypothetical license amendment package.

**Comment 10f**
*The SDS states that the molecular weight is "N/A (polymeric)." This is not a polymer; molecular weight can be known, without hydration if hydration is unknown. Please confirm that the SDS will be revised to include the molecular weight.*

**Response**
SDS has been updated with the molecular weight of anhydrous $SnO_2$ = 150.7. The package insert and SDS attachment has been removed from the hypothetical license amendment package.

**Comment 10g**
*Section 12 of the SDS states that, because this product is intended for use by a veterinary hospital or clinic patients, it is expected to be treated by standard wastewater treatment facilities. <u>This statement must be corrected</u> because 10 CFR 20.2003 prohibits disposal to the sanitary sewerage system unless the material is readily soluble or is in readily dispersible biological material. Tin oxide hydrate is a solid in colloidal suspension; the solid is not readily soluble in water and is not a readily dispersible biological material.*

**Response**
The option for sanitary sewer disposal has been removed. The package insert and SDS attachment has been removed from the hypothetical license amendment package.

**Comment 10h**
*In the package insert, section "Preparation for Use" states that the prescribed dose should be administered on the date noted on the accompanying certificate; however, it could be administered the day before or after if circumstances require. This may not make much difference for doses below the 3 mCi maximum but injecting a day earlier may require the dog be held if radiation levels exceed the release criteria. Please confirm that a reminder of the need for a survey will be added to the procedure to ensure that the maximum activity is not exceeded. Also note that there is no statement on the vial regarding the concentration of radioisotope (e.g., mCi per mL). Without this information, how will the veterinarian know how much solution should be withdrawn for the appropriate dose? Update the procedure or package insert to ensure the veterinarian knows how much solution should be withdrawn.*

**Response**
The package insert provides the activity concentration ranges in the "Name" and "Net Quantity" sections. Since the public dose assessment and duration of precautions is based on the pre-screening questionnaire and release exposure rate measurement, the allowance to inject one day

before or after (+/- 5%) is not viewed as a possibility to exceed public dose limits. In all cases the release exposure rate measurement is conducted post injection so the additional 5% is taken into account. Several layers of conservatism are built in to ensure that the 0.45 mR/h maximum exposure rate would not be exceeded for the largest dogs. Further, section 7 addresses release and indicates what to do if the measured net exposure rate exceeds 0.45 mR/h. A certificate of compliance accompanies each unit dose vial which contains the activity concentration and the exact volume to use for each patient. The package insert and SDS attachment has been removed from the hypothetical license amendment package.

**Comment 10i**

*The package insert does not address the use of dosimetry or shielding for radiation. Step 5 of the preparation for use states "Where practical, use a syringe shield...". Add use of syringe shield, as well as whole body and extremity dosimeters for the persons administering the dose and handling the animal, to procedure.*

**Response**

While syringe shields are recommended where practical, the decision to use a syringe shield will be at the discretion of the authorized user. Field experience indicates that syringe shields increase handling time and limit dexterity. The package insert and SDS attachment has been removed from the hypothetical license amendment package.

**Comment 10j**

*The package insert instructions for owners states that "The dog will, however, retain a low level of radioactivity in the treated joint(s) for a short period of time." This is misleading, as 10 half-lives is 136 days (more than 4 months). Based on our calculations using point sources for dogs receiving 3 mCi and released at measuring 0.45 mR/h at a distance of 1 meter from the elbow, the radioactivity in the dog could be measurable for at about 1 mR/h at 1 cm from the elbow at approximately 5.5 months after administration, dropping to about 0.02 mR/h after 8 months. Update the package insert, licensee's procedure, and instructions to clearly define a duration (e.g., 4 to 5 months) that the dog will contain measurable/detectable radioactive material to ensure this is not misleading.*

**Response**

The package insert has been updated to remove "short" from "short period of time". Note that the release instructions clearly indicate the duration for distance/behavior restrictions. The package insert and SDS attachment has been removed from the hypothetical license amendment package.

**RAIs specific on the Procedure for Use of Synovetin OA**

**Comment 11**

*The entire procedure is difficult to follow. As strict adherence to the procedure is necessary to ensure public dose limits are not exceeded, the procedure should be updated to ensure each step in the procedure, including the use of the table in Appendix B, is easily understood to minimize mistakes in its use. The following are just some examples of items that should be clarified, but staff recommends the entire procedure be evaluated and updated to ensure those without detailed knowledge of the technical basis can follow it without mistakes.*

**Response**
See updated procedure. In addition to changes made in response to the comments below, the procedure has been test-run with veterinarians to gauge the procedure clarity and ease of use and their comments and suggestions have been incorporated.

**Comment 11a**
*The statement "Determine which of the four categories of contact is applicable and explain to owner" in Section A3.6 is difficult to understand and leaves a lot up to the user for interpretation, some of which would not align with the technical basis and could lead to overexposures. Instructions on how to use the table are necessary. In addition to including steps, providing a few examples in an appendix might help. In the instructions, ensure to:*

**Response**
See comment 11a(i).

**Comment 11a(i)**
*Describe if it is possible that multiple contact categories would be applicable to an owner? Please clarify what the licensee should do if the animal falls into multiple categories or in-between two categories.*

**Response**
There is no situation where multiple categories apply. If the "common contact" scenario does not apply, then only one of the other three does. A dog with both extended duration close contact and extended duration intermediate contact falls into the 4$^{th}$ category.

To decomplicate the procedure, the owners are asked open ended questions about their physical proximity relationship with their pets. The licensee is then in a position to make the best possible informed decision on which of the four categories best fits that owner/dog relationship. Note that this is done for each member of the household (see Section A3.2). This process is similar (but much more complicated) to the selection of the occupancy factor described in NUREG 1556 Vol 9 Appx U for human release post $^{131}$I therapy.

**Comment 11a(ii)**
*Please clarify that licensees must round down to the nearest distance if the distances described by the owner does not match those used in the table.*

**Response**
Section A3.3.4 of the Procedure has been updated with rounding down instruction.

**Comment 11a(iii)**
*Please clarify terms like "most common," "extended intermediate contact," and "extended close contact" as it is not clear what they encompass. Explain the activities that they typically involve and distances to avoid confusion.*

**Response**

We were explicitly instructed to include open ended questions which did not coerce or suggest an answer from an owner. At the end of the open ended question section on the Pre-Screening Questionnaire, examples are provided for each of the three distance categories. It is then up to the licensee to make an informed decision, based on the questionnaire, which category should be employed in the release. This approach provides the most confidence for the licensee to ensure that all behaviors are captured and public dose limits are met.

**Comment 11b**
*It is not easily understandable that Step A3.1 is walking the licensee through each step of the pre-screening questionnaire. Clarification that this step is intended to help the questionnaire would avoid misuse. Possible options would be to include which item number in the questionnaire each step is referring to or at least specify that the licensee should record the information in the questionnaire.*

**Response**
The Procedure has been updated to include additional instruction. Section A3.9. indicates that the Pre-Screening Questionnaire is to be completed with a copy retained for inspection purposes.

**Comment 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.*

**Response**
There are seven questions with asterisks in the Pre-Screening Questionnaire. Guidance for the asterisked questions is provided near the end of the Pre-Screening Questionnaire:
"Any "No" checkmark may be contraindicated for the procedure. The authorized user may make an informed decision based on responses, proposed dose to pet, or other clinical factors."

**Comment 11d**
*The note in Step A3.7 states to reduce interactions to fit into one of the categories listed in the table. However, two of the categories (prolong close and intermediate contact categories) would exceed the public dose limit. Please revise this note.*

**Response**
All the categories except "most common" would result in the public dose limit being exceeded. The point of assigning interactions to one of these categories is to make sure that the Release Instructions duration is chosen properly later in the procedure which in turn will prevent the public dose limit from being exceeded. No change made.

**Comment 11e**
*Step A3.3.4 provides four separate questions (i.e., what activity, who, duration, and distance), but the table in item II only has two blanks (i.e., activity and duration). Therefore, it is unclear how the licensee is meant to fill out this table. The questions in the step should match the table. The table should include distances. Also, please clarify if the licensees should document exposure to different individuals in the household (i.e., whether or not they fill out two tables).*

**Response**
The Pre-Screening Questionnaire under Item III. General Contact Information is again designed for the owner to provide a description of the activity in their own words. This table, in this format, was added specifically at the request of the Technical Staff of the NRC. Distances are inherent in the activity and at the discretion of the licensee to bin appropriately.

**Comment 11f**
*Revise Section C2.1 to add "If both elbows were treated, measurements should be made for each treated elbow."*

**Response**
The survey is made from the nearest treated elbow as stated. If both elbows are treated, the left lateral measurement would be made from the left elbow and the right lateral measurement would be made from the right elbow. Dorsal, posterior, and anterior are the same regardless. No change made.

**Comment 11g**
*The language in the flow chart step "Veterinarian reviews all post-treated behavior restrictions can pet owners comply" is confusing. Revise as appropriate.*

**Response**
Revision included in Flow Chart.

**Comment 11h**
*The flow chart should include a step to hold the animal if the dog measures above 0.45 mrem/hr at 1 meter.*

**Response**
Edited Flow Chart to indicate that patient is held until the release exposure rate is ≤0.45 mR/h at 1m.

**Comment 11i**
*Appendix A includes a possibility "Patient not released" in the event that an owner will not sign the release instructions after the dog is treated. Please submit contingency actions if a dog cannot be released.*

**Response**
Flow Chart has been updated.

**Comment 12**
*The procedure should include all limitations necessary to ensure public dose limits are not exceeded, such as the maximum activity per joint and per dog and that only one animal should be treated with radioactive material per household per year.*

**Response**

The condition of 1 animal treated per year per house was added to the "Other" section of the Pre-Screening Questionnaire. Please clarify the need for the maximum activity per joint to be included in the procedure. The activity will be determined on the animal weight and clinical condition (one or two elbows). Release restrictions are based on animal/owner behavior and release exposure rates.

**Comment 13**
*As instructions are necessary to ensure public dose limits are not exceeded, the procedure should be updated to ensure all individuals who have the potential to exceed the public dose limits are given instructions. In addition, as the procedure relies on a person's interactions with the animal, the procedure needs to be updated to explain what a licensee should do if more than one individual is exposed to the dog on a daily basis. For example, if one individual co-sleeps with a dog but another individual lets the dog sit on their lap, how would the licensee provide conservative instructions? Please ensure the procedure is updated to clarify how licensees develop instructions when multiple individuals will be exposed to the dog.*

**Response**
The Pre-Screening Interview adequately addresses this concern and it is part of the procedure. See sections A3.3.4-A3.3.5 where the licensee asks the "open ended" questions which captures individualized human/dog interactions. Item A3.7 was edited to include the statement "Determination should be conservatively based on all household member interactions."

**Comment 14**
*The procedure does not discuss modifications that should be changed if there are children in the home. Young children, such as toddlers, are unlikely to follow instructions and also would have shorter distances when interacting with an animal in similar situations. Please describe how the licensees should ensure that the public dose limit will be not be exceeded when children, or other individuals who may have difficulty following instructions, are present in the home where the animal resides.*

**Response**
The Pre-Screening Interview adequately addresses Comment 14. Open ended questions are asked to describe household member interactions with their pet. The very next question asks if they are willing to modify their household member interaction with their pet – and if so, how will they modify it. Further, the following question specifically addresses children and pregnant women and how they will minimize their close contact. Further, the Additional Items Discussed with Animal Owner(s) section of the Pre-Screening Questionnaire addresses added precautions for children and pregnant women and again in the Release Instructions.

**Items below are for the pre-screening questionnaire found in Appendix B**

**Comment 15a**
*Ensure situations where individuals who do not have the ability to follow instructions, such as children, cannot be kept away from the dog on a daily basis should clearly preclude treatment in the questionnaire and procedure.*

**Response**
The procedure has been updated to indicate that the questionnaire is completed for each member of the household, including children. The normal flow of the procedure then addresses the situation where compliance cannot be obtained or ensured.

**Comment 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.*

**Response**
The Pre-Screening Questionnaire has been updated 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 less than 1 minute.

**Comment 15c**
*The cover paragraph on the pre-screening questionnaire makes it appear that there is no emission outside the dog's elbow joint. Revise to add that there are radiation emissions that leave the dog's joint and can lead to public exposure. The phrase "very low" and the word "energy" should be removed in the phrase "very low amounts of radiation energy" as the maximum dose rate almost classifies as a radiation area and that terminology could lead to non-compliance with instructions.*

**Response**
Non-compliance was not the intention as those words were carefully chosen (from NCRP 148) to reduce an alarmist response. On the Pre-Screening Questionnaire, the words very low and energy were changed to say "emits ionizing radiation".

**Comment 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.*

**Response**
The topic of boarding and spending time outside of the home was included in the "Additional Items Discussed with Animal Owner(s)" section. Further, the Release Instructions were updated to further address boarding and traveling. A discussion on boarding has been added to the technical evaluation.

**Comment 15e**

*Add a question to ensure dogs are not working service animals whose close contact with individuals would likely cause exposure exceeding public dose limits.*

**Response**
"Service animal" is a broad category. Some service animals may have close contact for whom treatment would not be indicated, such as a guide dog for a blind person. Others may not, such as a police K-9 or bomb sniffing dog. Exubrion prefers to rely on the questionnaire to elicit the normal behaviors and judge suitability of treatment on that basis rather than make categorical treatment exclusions.

**Comment 15f**
*The pre-screening questionnaire has a space for another person besides the owner to be interviewed. Clarify in the procedure that the person being interviewed should have full knowledge of the dog's behavior and should be able to control behaviors after the procedure as necessary to ensure public dose limit is not exceeded.*

**Response**
The Pre-Screening Questionnaire was updated to include a statement in item A.3. that the "Owner interviewed shall have full knowledge of household member's interaction with the proposed patient."

**Comment 15g**
*At the end of the questionnaire, the application states that any "no" checkmark may contraindicate the procedure. However, the application allows for modifications in many cases. Update this statement to clearly state when a licensee will consider a procedure contraindicated due to radiation safety, such as the procedure would be contraindicated if modifications appear not to be able to be made to ensure members of the public will receive less than public dose limits or the licensee is not confident the public dose limits would not be exceeded following treatment of the animal.*

**Response**
The statement has been updated to state that if modifications cannot be made, treatment is contraindicated.

**Comment 15h**
*Clearly explain in the procedure how the table at the end of Appendix B is intended to be used and ensure this is consistent with the technical basis. Currently, if more than one category is applicable, it appears that each category may be viewed individually. For example, an owner might restrict direct contact during common activities to 1 minute each day for 2 weeks, restrict direct contact for holding the animal in direct contact on the lap to 1 minute each day for 5 weeks, and limit direct contact to 1 minute each day while sleeping in the owner's bed for 9 weeks. As this does not align with the technical basis, additional instructions are necessary.*

**Response**

There is no situation where multiple categories apply. If the "common contact" does not apply, then only one of the other three does. A dog with both extended duration close contact and extended duration intermediate contact falls into the 4th category. All the instructions apply for the same length of time.

**The items below are specific to the instructions.**

**Comment 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.*

**Response**
As noted in the response to Comment 15b, the Pre-Screening Questionnaire has been updated 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 1 minute.

**Comment 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.*

**Response**
The technical basis does not assume limitations on contact. The technical basis is based on categorizing the routine interactions and contact and developing one set of instructions applicable for one interval and then allowing interactions to return to the previous routine interactions and contact. As these are the normal behaviors, no additional limitation is needed.

**Comment 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.*

**Response**

As discussed in the response to Comment 11a(iii), at the end of the open ended question section on the Pre-Screening Questionnaire, examples are provided for each of the three distance categories.

**Comment 16d**
*Without strict adherence to instructions, staff's analysis indicates that the exposure to members of the public could potentially exceed public dose limits. Therefore, the instructions need to clearly articulate the following:*

**Response**
See below.

**Comment 16d(i)**
*The phrase "very low" and the word "energy" should be removed in the phrase "very low amounts of radiation energy" as the maximum dose rate almost classifies as a radiation area and that terminology could lead to non-compliance with instructions.*

**Response**
Non-compliance was not the intention as those words were carefully chosen (from NCRP 148) to reduce an alarmist response. On the Release Instructions, the words very low and energy were changed to say "emits ionizing radiation".

**Comment 16d(ii)**
*The instructions should prohibit having a dog lying directly next to you as well as holding a dog on the lap as one would expect a large dog to lay next to someone instead of directly on their lap.*

**Response**
The wording was changed to "hold the dog in or near your lap".

**Comment 16d(iii)**
*The instructions state that walking and playing with your dog can continue as usual. However, this would not be the case if the owner plays with an animal in close contact or in another manner that could result in public dose limits to be exceeded. Therefore, this statement needs to be revised.*

**Response**
The Pre-Screening Questionnaire would capture any irregular behavior which would then be included in the individualized section. Note that this method was added at the request of NRC Headquarters. The Release Instructions have been edited to say: "…Activities such as walking or playing with your dog can continue with distance limitations maintained."

**Comment 16d(iv)**
*The instructions state to avoid boarding of an animal. Either specifically state long term/daily boarding is prohibited, or provide the information requested above.*

**Response**
The Release Instructions and technical evaluation have been updated to specifically address "long term/daily boarding".

**Comment 16d(v)**
*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.*

**Response**
Commercial grooming is an activity that occurs at a distance of 1 foot. Given that the maximum release doserate is 0.45 mrem/hr at 1 meter, a 2-week delay in commercial grooming and factoring in the dog torso shielding factor results in a doserate of 1.67 mrem/hr at 1 foot,,is sufficient to meet the 2 mrem in any one hour criteria for even the largest dogs. This is conservative in that no credit for shielding by the dog's torso is taken.

**Comment 16e**
*More instructions are needed in the case of a death of an animal. Specifically, the instruction regarding cremation needs to discuss where and how the animal carcass would be stored to ensure doses are ALARA if it is not immediately able to be cremated. In addition, justification for allowing cremation at 4 months should be added to the technical basis document as a dog injected with 6 mCi would still contain approximately 12 microcuries at 4 months.*

**Response**
The four month term was removed in the Release Instructions. Guidance is also provided to the Owner during the Pre-Screening Interview in the "Additional Items Discussed" section. Additional items of discussion are covered in the site specific training. The training recommends storing an expired therapy patient in a freezer and treated as decay in storage (DIS), following DIS procedures thereafter.

**Comment 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.*

**Response**
The point being made with that statement is that the instructions are designed to optimize the probability of owner compliance with the instructions. It is pointless to design instructions with which compliance is unlikely due to their intrusiveness. Previous discussions with the NRC were very clear that the NRC is concerned about owner compliance with changes to normal behavior and these instructions are designed to maximize the ability of owners to comply. It is reasonable to design instructions to maximize the ease and thus likelihood of achieving compliance.

**Comment 16g**
*If follow-ups are expected to be conducted by the licensee before the duration of the instructions ends, update the procedure to ensure the licensee re-enforces the need to follow instructions for the entire instructional period during this follow-up to ensure the public dose limit is not exceeded.*

**Response**
The Procedure was updated to address Comment 16g under Procedure C: Treatment and Release with the wording "Additionally, the licensee should review the Release Instructions with the owner(s) should any follow up care be provided to ensure public dose limits are met."

**Comment 16h**
*10 CFR 20.2203(a)(2)(iv) requires the licensee to report if public dose limits are exceeded. Update the procedure to ensure the licensee appropriately reports if they find the public dose limit has been exceeded. Include a description of how the licensee may determine if the public dose limit has been exceeded based on discussions with the owner or individuals close to the animal following treatment.*

**Response**
The Release Instructions were updated to include instructions to contact the licensee if the owner believes that the distance and duration restrictions were exceeded.

**Comment 16i**
*Throughout the application, including in the instructions, Synovetin is referred to as a device. Synovetin is not considered a device for the purposes of NRC regulations. Please use a more appropriate term for owners such as "medical treatment" or "solutions" throughout the application. However, the term "device" can be used in the package insert if necessary for classification by the U.S. Food and Drug Administration.*

**Response**
"Device" references removed except where needed for FDA classification.

**RAIs specific on the "Technical Basis for Release Criteria", "Evaluation of potential dose to members of the public from treatment of dogs with Synovetin AO containing Sn 117m" attachment.**

**Comment 17**
*The technical basis uses many assumptions based on an average dog which would not be applicable for all dogs. Ensure all assumptions would be met using the pre-screening questionnaire and instructions for all animals released to demonstrate the public dose limit will not be exceeded. Provide a description in the technical basis of how the pre-screening questionnaire and instructions will be used to ensure that all assumptions in the technical basis are met.*

**Response**

The technical basis uses the behaviors of an average dog as a conservative estimate of the behavior of an osteoarthritic dog as a starting point. This is reflected in the common behaviors summary. Exubrion believes these common behaviors bound the behavior of the vast majority of osteoarthritic dogs. As has been previously discussed with and requested by the NRC, the other categories of behavior are designed specifically to address all other dogs. The other categories are simplified into 3 groups based on the pre-screening based on daily durations at various distances regardless of the specific behavior which results in time at that distance. Any dog determined suitable for treatment will fit into one of these categories. Any dog that does not fit one of these categories is deemed not suitable for treatment.

**Comment 18**

*The technical basis assumes the center of the human torso as the point on the body which is used to calculate exposure. However, 10 CFR 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.*

**Response**

Skin is the only organ for which addressing dose to the maximally exposed portion is a regulatory issue and even for the skin the dose to a minimum of 100 $cm^2$ is evaluated. For all other organs, the average dose to the entire organ is used. Additionally, organ dose is not relevant for evaluating dose to a member of the public.

In the reviewer notes for the December 21, 2001 response to the May 18, 2001 technical assistance request for release criteria for cats treated with radioactive iodine, the NRC states "The distances provided are put into perspective by relating them to distances from the highest activity measured from the cat to the center of the area of the person that NRC defines as the 'whole body.'" The center of the torso is the center of the area of the person that NRC defines as the "whole body."

The maximally exposed part of the body for long duration close contact, as with lap-sitting, is not the center of the torso but rather the upper leg. NRC Regulatory Guide 8.40 Table 1 assigns each upper leg a weighting factor of 0.005 for external dose. Even for an anatomic region as small as the thigh, the dose rates are highly non-uniform when close to what is effectively a point source. The dose to the skin closest to the dog's elbow is not the dose to the anatomic region of the thigh. The average dose to the entire anatomic region of the upper leg is much lower. We submit that the center of each anatomic region provides a much more accurate estimate of the average dose to that anatomic region than using the maximally exposed portion. Given that the torso accounts for 88% of the total weighting factor, and a further 10% is on the head, use of the center of the torso is a reasonable means of estimating the average dose to an individual.

**Comment 19**

*Average shielding factors cannot always be assumed. For example, a dog sitting or lying across a person's lap, who has direct contact with a person's leg such as shown in Figure 6, or dogs who lay on their side with their legs extended and elbows up cannot have credit for torso/body shielding in the exposure to the legs. In addition, one would expect that close contact activities,*

*such as carrying, petting, and feeding, would be done in a similar geometry every day, especially when the time is limited to less than 15 minutes a day. Therefore, the use of average shielding factors is not justified in all geometries. Therefore, average shielding factors cannot be conservatively applied in these scenarios and close contact doses and criteria must also be revised.*

**Response**
As discussed in the response to the previous comment, the legs compose a very small portion of the total external dose weighting. Exposure to the human torso is much more important that exposure to the legs.

Carrying, petting, and feeding are all separate activities which collectively comprise the time spent at close distances. Each of these activities, and any other close contact activities identified during the pre-screening questionnaire, is done in a different geometry even if all are routinely done every day. Given the multiple activities in multiple geometries, use of an average shielding factor is appropriate.

**Comment 20**
*The statement that the dog's leg joints are much lower than the dog's torso is not acceptable for the elbow joint, which is very close to the base of the dog's torso. This statement is used to consider additional distance between the dog's elbow and the human torso (whole body). Although this may be true for lower joints such as the knee, it is not true for the elbow. Instead, the paper "Canine Torso Attenuation from Elbows Treated with Synovetin OA (Sn 117m)" states that the "Canine anatomy is such that the dog's elbows are approximately at the same height as the lower extent of the dog's torso when in a standing position." If distances used to support the calculations were based on locations much lower than the elbow, please revise those calculations. If not, revise the statement saying that dog's leg joints are much lower than the dog's torso to avoid future licensee confusion.*

**Response**
The intent of this statement and this entire paragraph in the technical evaluation is to make the point that the distance being considered in this evaluation is different than what is commonly thought of the distance between a dog and a person. As pointed out in the quote in the comment, the elbow is at the lower extent of the dog's torso and thus by extension is lower than the center of the dog's torso, the upper torso, or the head which would be closer to the center of the human's torso as discussed in this paragraph of the technical evaluation.

The technical evaluation text has been revised to clarify this point.

**Comment 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 adult 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 basis and instructions to ensure children or small adults do not exceed the public dose limit.*

**Response**
Based on human anatomic data from ICRP 89, the approximate height of the center of mass of a 5-year old is 64 cm. For a Labrador retriever, a typical treated large dog, the height of the elbow is approximately 12", or 30 cm. Without accounting for any increase in distance due to lateral offset, this still results in a height difference of 34 cm, more than one foot.

It is not reasonable to postulate that a person would remain in such close contact with a dog that there is essentially no horizontal separation for an extended length of time while awake, especially in the context of a household that has received written instructions regarding how to behave. Therefore, the conclusion that a foot is a reasonable distance is deemed appropriate.

**Comment 22**
*As 2 mrem can be exceeded within minutes at close distances, such as 1 inch, justification is needed to demonstrate that short-term close-distance encounters, such as young child coming up to pet the dog during a walk, would not exceed the public dose limit of 2 mrem in any 1 hour. As doses at close distances are not uniform, use of non-uniform dosimetry such as that described in Regulatory Guide 8.40, "Methods for Measuring Effective Dose Equivalent from External Exposure," could be considered in this calculation. In addition, stronger instructions are necessary to ensure that members of the public do not have close contact with the animal, specifically spelling out activities, distances, and timeframes which should be prohibited.*

**Response**
A distance of 1 inch is not attainable. The minimum distance possible (dog elbow in contact with a human torso) results in distances of calculational significance of greater than one inch. As discussed in the response to Comment 18, the dose to the skin closest to the dog's elbow is not the dose to the underlying anatomic region. For calculation of the potential dose or dose rate to a person resulting from exposure at small distances, the anatomic region with the greatest weighting factor is the most significant, i.e., the abdomen. For an adult male, the distance from the skin surface to the center of abdomen is approximately 9.25 cm, or almost 4 inches. In the worst case scenario (the largest dog injected with the highest activity, 6 mCi total), a joint radius of 1.7 mm (including skin) is added to this resulting in a total distance of 11 cm, just over 4 inches. Calculating the dose to both the abdomen and the thorax under these assumptions results in a maximum doserate of 20 mR/hr. At this doserate, 6 minutes is required to result in a total dose of 2 mrem which exceeds the written instructions limitation for close contact. This is a highly conservative calculation given that it does not properly account for geometric attenuation or self-shielding throughout the volume of the anatomic region.

The doserate to smaller individuals would be higher as detailed in the revised technical evaluation. Even for the 1-year-old, 2 minutes are needed to result in a total dose of 2 mrem. It is unreasonable to assume that a 1-year-old would remain in that close of contact with a large osteoarthritic dog for 2 minutes while awake and contact while sleeping has been ruled out. The natural behavior for a dog is to avoid pain, which includes avoiding letting a person touch a painful osteoarthritic joint. The dog would naturally take action should a child try to repeatedly touch the dog's elbow or otherwise remain in contact with it. Such action would be to move away or in more extreme cases nip at the person making the contact.

**Comment 23**
*Routine veterinarian exams could result in an exposure of greater than 2 mrem in any on 1 hour if the examination is performed by an individual who does not know about the radioactive material. Describe any limitations, or instructions, that would be given to the dog's primary veterinarian if they are not associated with the licensee.*

**Response**
The release instructions have been updated with a statement regarding follow up care. Emergency care instruction is provided in the Release Instructions with the licensee's contact information for guidance as needed.

**Comment 24**
*The technical basis states that the worst-case scenario for evaluating whether a person could receive 2 mrem in any 1 hour, from a dog released at 0.45 mR/h measured at 1 meter from the dog's elbow, is that for a person that spends 1 minute at 6 inches from the dog's elbow, plus 15 minutes at 1 foot away, plus the remaining 44 minutes at 3 feet away. However, the NRC does not believe this is the worst-case scenario, but rather the maximum dose that would be received by owners performing only the activities allowed by the instructions. Please confirm that our understanding is correct or provide an explanation that clarifies the statement.*

**Response**
The activities allowed by our instructions include 1 minute per day at effectively 6 inches (the direct contact scenario), 15 minutes per day at 1 foot, and 3 three hours per day at 3 feet. Although it is highly unlikely, it is possible that the 1 minute at 6 inches and 15 minutes at 1 foot could occur in the same hour along with additional time at 3 feet. Thus the scenario we evaluated is the worst case scenario for an owner performing only the activities allowed by our instructions.

**Comment 25**
*In a published presentation, there was a note of a past unintentional misadministration where the material was administered outside the elbow. Please describe if the material could be excreted or end up migrating if it is administered outside the elbow. Update the licensee release procedure as necessary to instruct licensees of what they should do if the treatment is injected somewhere other than the elbow.*

**Response**
This content was omitted intentionally. Small animal studies were conducted for missed injection sites and it was determined that a missed injection site will result in a reduction of the efficacy of the treatment but no biokinetic transfer to any other organs of interest. Organs were harvested after missed injection sites and found to be statistically similar to successful injections. The Procedure was updated to indicate that the owner must wait a year to attempt the therapy again (Section C.1.4.).

**Comment 26**
*Please describe common interactions that owners might have with dogs with osteoarthritis that are not common with other dogs. For example, is massaging recommended for some dogs with*

*osteoarthritis and if so, describe the dose one would get from a conservative massage? If massaging needs to be halted to meet public dose limit, could it be and what would be the consequences to the dog? Include in the instructions if necessary. In addition, do dogs with osteoarthritis need help up-stairs or in other normal interactions? If so, describe how 1 minute a day would cover those who need to help a dog up and down flights of stairs on a daily basis.*

**Response**
The most common interaction utilized with osteoarthritic dogs is assistance to climb stairs or jump up onto furniture. If this action is needed when appropriate the dog caretaker can use a bath towel around the posterior abdomen to assist the patient. Of course, the patient's difficulty in climbing stairs or jumping up can also be used to stop co-sleeping and other intimate interactions with caretakers especially during the immediate post-treatment period. With regard to physical therapy such as massaging etc. this is not a treatment modality typically prescribed by a veterinarian. Any massaging or other tactile treatment by the dog's owner would have to be conducted within the limits of the written instructions. Professional massaging or other tactile treatment would be considered the same as grooming and is prohibited in the first two weeks.

**Comment 27**
*Regulations in 10 CFR Part 20 require licensees to maintain doses ALARA. Principles of ALARA include time, distance and shielding. Describe the feasibility to include shielding to minimize public exposure, such as use a small elbow shield.*

**Response**
The use of an elbow shield is not feasible for dogs in general. In the past, some dogs afflicted with elbow hygromas have been attempted to be treated with elbow pads. These pads have not been consistently successful in provided padding to the elbow area, primarily due to excessive movement of the pads and the individual dogs not tolerating having such a device attached to them. Having such pads now thickened with shielding to attenuate gamma radiation will only increase the non-acceptability of these pads to dogs at the very least. The worst case scenarios would be a dog that either chews the pads and ingests the fabric, shielding material, and pad or in which the dog becomes tangled in the pad and constricts the blood supply to the forelimb.

**RAIs specific on the "Contact Doses from Dogs that Have Been Treated with Sn-117m Radiosynoviorthesis" attachment.**

**Comment 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.*

**Response**
This report pre-dates the discussions with the NRC regarding limiting the dose to a member of the public. It provides useful information regarding self-shielding that occurs once the material is injected into the elbow, i.e., once the material is not an unshielded point source) but is not explicitly relied upon for the public dose assessment. This report has now been published in Operational Radiation Safety and is presently available at http://journals.lww.com/health-

physics/Fulltext/publishahead/Radiation_Safety_Considerations_in_the_Treatment.99800.aspx. This report has been removed from the hypothetical license amendment package.

**Comment 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.*

**Response**
The dose rates in that report are a modeling of dose rates based upon administered activity. Rather than project the dose rate based on the administered activity, Exubrion has chosen to directly measure the dose rate and determine the necessary written instructions accordingly. Calculations and models are not necessary when direct measurements are made. This report has been removed from the hypothetical license amendment package.

**RAIs specific on the "Canine Torso Attenuation from Elbows Treated with Synovetin OA (Sn-177m)" attachment**

**Comment 30**
*Explain how the following terms are used in this paper:*

**Comment 30a**
*Anterior – the paper states that anterior measurements of 1 foot are under or within the body of the dog, and therefore 1-foot anterior measurements were taken at the rump of the dog regardless of the distance. However, "anterior" in other common documents use "anterior" to be towards the front of the dog, in which case anterior measurements of the elbow would not be in the body of the dog at all. Explain how your anterior measurement locations are different from your "posterior" and "dorsal" measurements.*

**Response**
"Anterior" was a typographical error. The statement should say "posterior."

**Comment 30b**
*Explain the difference in locations upper anterior, upper posterior, and dorsal.*

**Response**
Upper anterior is taken at a 45 degree vertical angle from the dog's elbow forward (towards the dog's head horizontally). Upper posterior is taken at a 45 degree vertical angle from the dog's elbow and towards the animal's rump horizontally. Dorsal is taken directly above the dog's spine centered between the shoulders when in a standing position.

**Comment 31**
*In 2 of the 10 dogs measured, the anterior and lateral measurement were not the highest at 1 meter. Update the release procedure to ensure all geometries which have the potential for having the highest dose rate are measured.*

**Response**
The release procedure was updated to reflect the request.

**Comment 32**
*One would expect the dorsal or posterior positions to have the lowest dose rate due to having the most shielding through the dogs' body. As these shielding factors are used to demonstrate public dose limit is not exceeded, provide an explanation on how the dorsal and posterior measurements had either the maximum or close to the maximum dose rate in several of the measurements.*

**Response**
Experimental measurements rarely 100% follow theoretical expectations. None of the 1 meter posterior measurements were close to the maximum. In only one measurement at 1 meter was a dorsal measurement close to the maximum and in that case, the anterior measurement was the maximum. This measurement was taken on a Golden Retriever, a long-haired dog, which caused difficulty in affixing the Sn-117m source to the inside of the dog's elbow in a reliable fashion causing variation in the measurements. This particular dog also had a higher 1 meter shielding reduction than the shielding effectiveness recommended by the evaluation. Therefore, use of the recommended shielding reduction factor remains conservative.

At 1 foot, only 1 posterior measurement is near the maximum and that is on the smallest dog for which shielding considerations would be expected to have the least impact and geometry considerations can play a greater role. Two dorsal measurements are at or near the maximum but are exceeded by the anterior measurement. One of these results is the smallest 1 foot shielding reduction factor which is the one used.

In all these cases, the data do demonstrate that the radiation field around the dog is far from uniform and thus a shielding reduction factor is warranted.