EXUBRION™
THERAPEUTICS

Canine Synovetin OA™ Treatment Public Dose Limitation Presentation To US NRC

July 29, 2019

Introduction

- Exubrion Background

- Exubrion Team
  - Peter Selover, CEO
  - Dr. John Donecker, Chief Veterinary Officer
  - [Dr. Steve Fox, Senior Consulting Veterinarian]
  - Dr. Nigel Stevenson, COO, Nuclear Physicist
  - Dr. Matthew Arno, CHP, PE(TX), Foxfire Scientific
  - Dr. Chad Smith, CHP, FX Masse

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Objectives and Outline

- Objective
  - Develop release criteria and instructions that the NRC would find acceptable such that individual NRC or Agreement State licensees could successfully submit radioactive materials license applications or amendments using those generic release criteria
- Outline
  - Osteoarthritic dogs – Dr. Donecker
  - Synovetin OA™ Sn-117m treatment – Dr. Stevenson
  - Address TAR issues – Dr. Arno
  - Public Dose Assessment – Dr. Arno
  - Written Instructions – Dr. Arno

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History

- January 2018 – Central Hospital for Veterinary Medicine submitted a license amendment for Sn-117m treatment of osteoarthritic dogs
- April 2018 – NRC Region 1 submitted TAR regarding release criteria and the written instructions
- October 2018 – NRC DNMS issued TAR response concluding the release criteria and written instructions were inadequate
- January 2019 – NRC DNMS distributed the TAR response to the Agreement States and Regions effectively halting all Sn-117m licensing actions
- June 2019 – Exubrion submitted proposed release criteria and written instructions template to the NRC
- Today

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Osteoarthritic Dogs

- Symptoms
  - Lameness in the elbow, stifle (knee), or hip
  - Exercise and activity intolerance
  - Inability to jump
  - Joint pain
- Most impacted breeds – large and giant dogs
  - Retrievers
  - German Shepherds
  - St. Bernards
  - Chow chows
  - Rottweilers, etc.
- Typical dog with OA
  - > 4 years old
  - > 50 lbs.
  - Overweight to obese

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Osteoarthritic Dogs

- Dogs with severe OA have trouble with normal movements.
- Veterinary instructions for caring for a dog with OA:

"Be sure the dog is able to stand on a non-skid surface while eating and drinking. Have the client explore the home for potential 'problem spots.' Steps in and out of house, patio stones, and garage floors can create unintentional challenges for the painful dog. Ramps are recommended for getting into and out of vehicles."

S Fox MS DVM MBA PhD; author of: *Multimodal Management of Canine Osteoarthritis*, CDC press, 2nd edition, 2016

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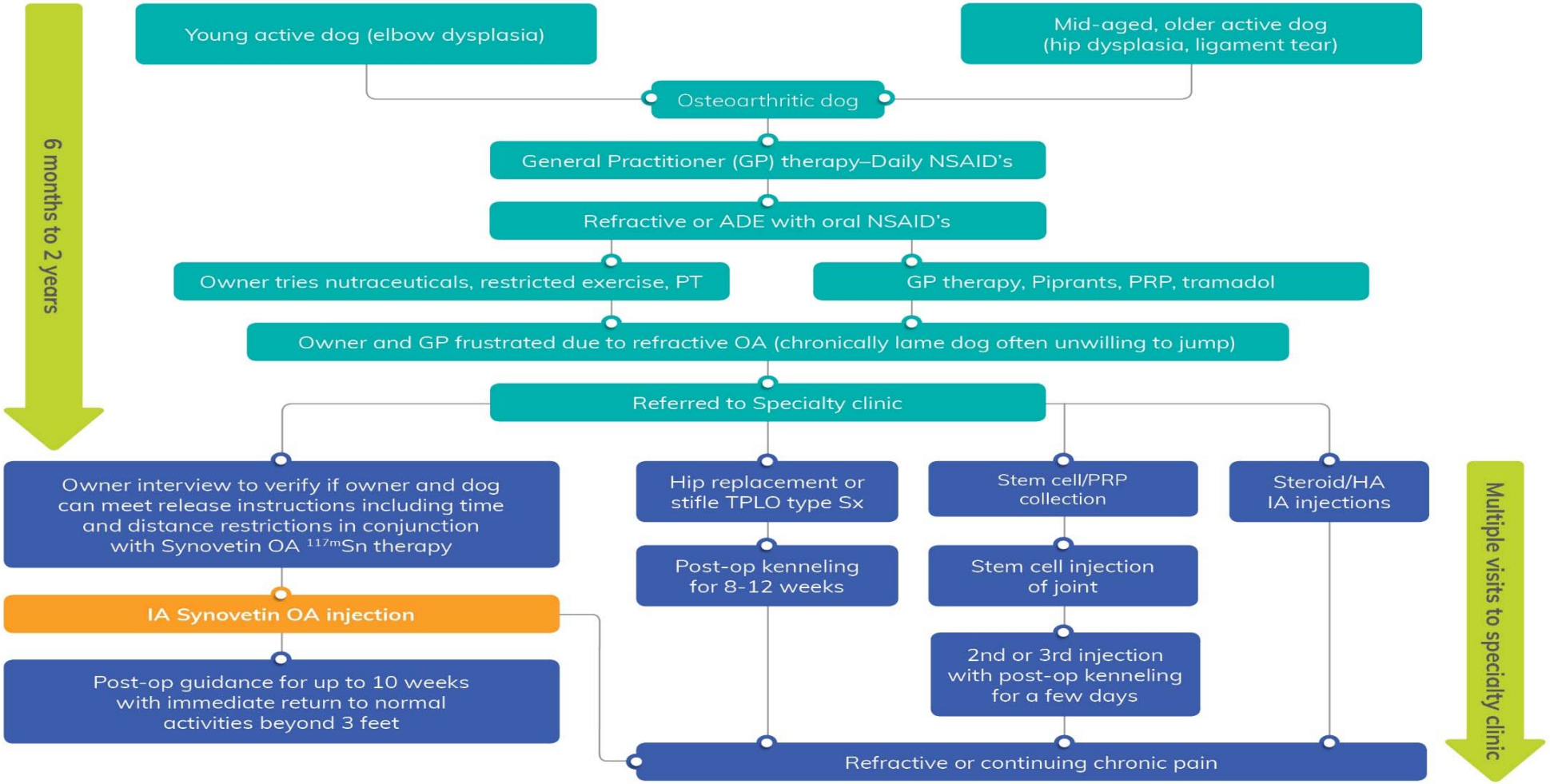
Decision Tree for Synovetin OA



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Radiosynoviorthesis (RSO)

- Successfully used in humans for over 60 years
- Radioactive colloidal particles are injected directly to local site of inflammation (synovial cavity)
- Particles are engulfed by the macrophages causing apoptosis due to radiation dose delivered
- Inflammation reduction by elimination of these pro-inflammatory macrophages
- Provides a more targeted cellular approach than does systemically administered drugs

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Sn-117m & Synovetin OA™

- Theranostic isotope (imaging and therapy)
- Decays by isomeric transition to stable Sn-117 ground state, Q = 314 keV, $t_{1/2}$= 14 d
- 158.6 keV gamma with 86% yield
  - Tissue interactions predominantly photoelectric effect
- ~140 keV conversion electrons (~112% yield)
- Lower energy (<21 keV) Auger electrons and soft (<30 keV) X-rays
- Sn-117m formulated into a colloid (suspension) for injection
- >99% of the Synovetin remains in the joint capsule
  - Effective half-life equal to physical half-life
  - Excretion is not a concern
- Treatment dosage is proportional to dog weight up to 3 mCi maximum per joint

TAR Response Concerns

- Applicable dose limit confusion especially regarding the number of treated joints
- Occupancy factors
- Duration of dose rates
- Nature of human-dog interactions
- Reliance on written instructions
- Written instruction specificity

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Westgarth Study

- TAR Response requested further evaluation to determine conservative occupancy factors
- Westgarth study (2008) surveyed dog-human interactions
- 83% of large/giant dogs rarely or never lie on a person's lap
  - 49% of medium dogs
  - 29% of small dogs
  - Young dogs more likely to lap sit than older dogs
- Only 14% of dogs sleep on a human bed
  - Reasonable to assume more likely with small dogs than large dogs
- Only 19% of large dogs walked 3 or more times per day.
  - ~65% of medium and large dogs walked once or twice per day
  - Walk duration range is 16-60 minutes
  - Younger dogs walked more

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Human-Dog Interactions

- Standing
  - Feeding
  - Walking
  - Grooming
  - Petting
- Sitting
  - Lap-sitting
  - Resting by owner's chair
- Co-sleeping

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Feeding

- Short duration activity in close proximity to the dog
- < 1 min at a distance of one foot as the food bowl is filled and placed
- Owner moves away as the dog starts to eat
- Most of the time is at distances >> 3 feet
- Conclusion: Assume 1 minute per day at a distance of 1 foot

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Walking

- Conservatively assume a dog is walked twice a day for 30 minutes each time based on Westgarth data
  - OA dogs will be walked less and for shorter durations than healthy dogs
- Most dogs walk at or near the extent of the leash
- Most leashes are at least 3-4 feet long, 6 ft common
- The treated joint is lower than the dog's neck
- A distance of 3 feet or greater from the dog's elbow to the center of owner's torso is reasonable and conservative
- Conclusion: Assume one hour per day at a distance of 3 feet

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Grooming

- Breed-specific – short-haired dogs groomed much less than long-haired dogs
- Owner-controlled activity, frequency and duration
- Grooming more than once per week is rare
- Each grooming session lasts no more than one hour
- Grooming can be avoided or deferred if necessary
- Conclusion: Assume 1 hour per week (9 min/day average) at one foot

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Petting

- Owner-controlled activity, frequency and duration
- Each petting session typically short
  - 15-20 seconds each time
  - 8-10 sessions each day
  - 20 x 10 = 200 seconds/day, round up to 5 minutes
- Most petting is on the head or upper torso
  - Consider arm length
  - Distance from head to treated joint
  - 2 feet is a reasonable average distance
  - Use 1 foot to be conservative
- Conclusions: Assume 5 minutes per day at a distance of 1 foot

Lap-sitting

- The opportunity for this behavior is limited for most people
  - Mostly in the evenings after dinner before bedtime
  - 3 hrs./day is a conservative estimate of the time available
- A dog in a person's lap will have its legs under it or pointed away from the person's torso
  - Under the dog, the dog's torso functions as a shield
  - Away from the person's torso, the distance is increased
  - 1 foot or more from the treated joint(s) to the center of the human torso is reasonable
- Conclusion: Assume 3 hours per day at 1 foot

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Resting & Officing

- A dog may rest beside or at the feet of a person seated
  - While working from home or for elderly/sedentary individuals
    - 8 hr/day
  - While watching TV/videogames/web browsing
    - 3 hr/day, same as lap-sitting
- Distance considerations
  - The joints of a dog lying down are effectively at floor height
  - Standard chair seat height is 18"
  - Add distance from the chair seat to the torso center
  - Add horizontal offset to side or to feet
  - 3 feet is a reasonable distance from treated joint to human torso center.
- Conclusion: Assume 3 hours per day at 3 feet (resting) and 8 hours per day at 3 feet for officing

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Co-Sleeping

- Co-sleeping is the behavior with the closest and most prolonged contact.
- Patel (2017) data gives a conservative estimate of 8 hours per day with human and dog sleeping
- Sleep position
  - Next to legs
    - Most common
    - Distance 2 feet or greater
  - Next to torso
    - Dorsal more often than pectoral
    - Dog torso serves as shield
    - Distance >1 foot
- Conclusion: Assume 8 hours per day at 1 foot

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Behaviors Summary

Interaction	Distance	Time
Feeding	1 ft	1 min/day
Walking	3 ft	1 hr/day
Petting	1 ft	5 min/day
Grooming	1 ft	1 hr/wk, 9 min/day
Resting	3 ft	3 hr/day[a]
Lap-sitting	1 ft	3 hr/day[a]
Co-sleeping	1 ft	8 hr/day
Officing	3 ft	8 hr/day

[a] A given dog exhibits one of these behaviors or the other, but not both

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Most Common Behaviors Summary

Interaction	Distance	Time
Feeding	1 ft	1 min/day
Walking	3 ft	1 hr/day
Petting	1 ft	5 min/day
Grooming	1 ft	1 hr/wk, 9 min/day
Resting	3 ft	3 hr/day

- OA dogs don't jump or climb up due to pain and stiffness
- OA dogs are typically larger and heavier
- Therefore:
  - No co-sleeping
  - No officing
  - No lap-sitting
- Occupancy factors
  - 15 min/day at 1 foot
  - 4 hr/day at 3 feet

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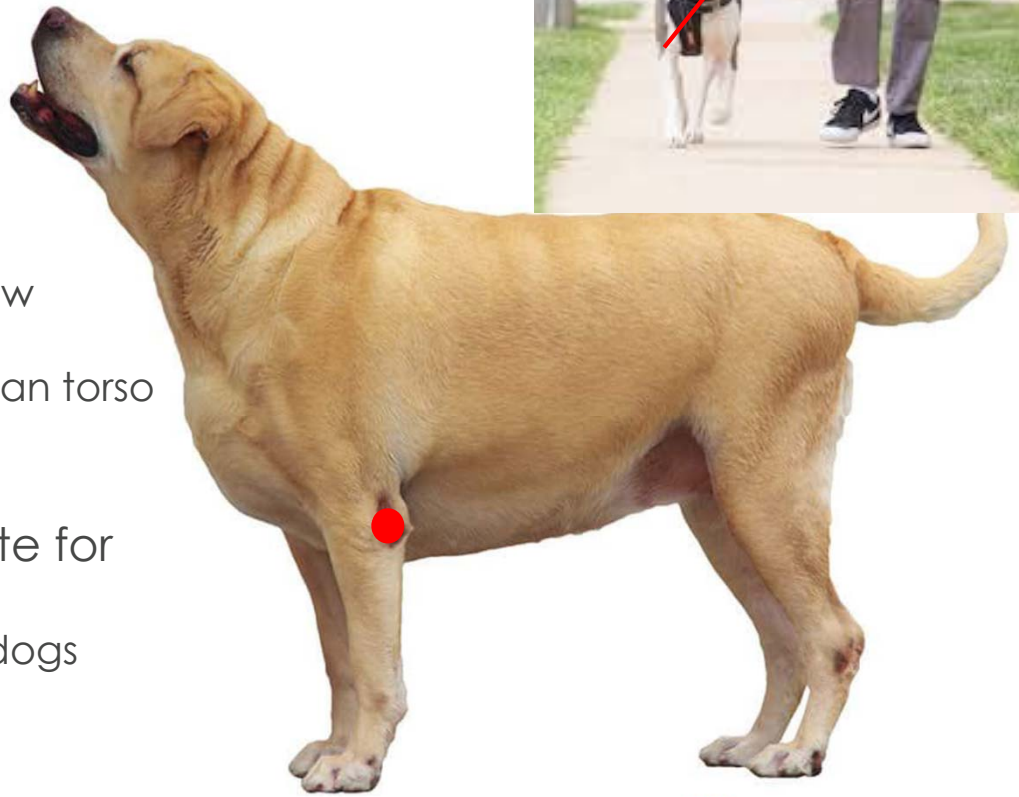
How common?

- 83% of large healthy dogs rarely/never lap-sit
  - OA dogs even less likely
  - ∴ >>90% rarely/never lapsit
- Only 14% of dogs co-sleep
  - Large dogs less likely
  - OA dogs even less likely
  - ∴ >> 90% do not co-sleep
- Most people do not work from home or are not sedentary
  - Even of those that are, the dog may not rest at their feet/by their chair
  - Most dogs will choose to rest where their dogbed is located
- The vast majority of dogs with severe OA will fit this description

Canine self-shielding

- A dog's torso functions as a shield for radiation emitted from the leg joints for many common exposure geometries
  - Dorsal
  - Lateral
  - Torso height of standing person
- Consider 9 geometries
  - Anterior, Posterior, L lateral, R lateral at elbow height
  - Anterior, Posterior, L lateral, R lateral at human torso height
  - Dorsal (directly above)
- Average doserate is 60% of max doserate for medium-large dogs
  - Assume shielding scales linearly for smaller dogs



Public Dose Assessment

- Inputs:
  - Occupancy factors – Distance & duration
  - Dose rates
  - Controls
- Identified behaviors that substantially impact public dose (lap-sitting, officing, co-sleeping)
- Veterinarian will screen for those behaviors prior to treatment
- Most patient candidates do not engage in those behaviors
  - For those dogs, no limitations are necessary (although some are included out of conservatisim)
- For those patients that do engage in those behaviors
  - Short-term restrictions will keep the public dose under the limit
  - If caregiver cannot adhere to the restrictions, the patient will not be treated

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Typical Behavior Dose Evaluation

- Doserate based release criteria are specified at 1 meter
  - Vet techs are used to making measurements at 1 meter for RAM shipping and receiving
- Doses are based on distances of 1 foot and 3 feet
  - Most dog owners are more comfortable using Imperial units
- Maximum anticipated doserate is ≤ 0.5 mR/hr at 1 m
  - This yields a maximum average doserate of 0.36 mR/hr at 3 feet
- Using 4 hours/day at 3 feet and 15 minutes/day at 1 foot, an "infinite" dose of 44 mrem is calculated for the largest dogs/maximum treatment activity
  - Less than the 100 mrem public dose limit
- Conclusion: No written instructions are needed for the most common dog-human interaction pattern

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Dose Evaluation – Other Scenarios

- Lap-sitting – 213 mrem
- Co-sleeping – 530 mrem
- Officing – 100 mrem
- All three behaviors – 776 mrem
- These doses are for the largest dogs and maximum treatment activities, smaller dogs would be proportionately less

Dog Weight, lbs.	mCi Synovetin per Joint
10-19	0.6
20-29	0.9
30-39	1.2
40-49	1.5
50-59	1.7
60-69	1.9
70-79	2.2
80-89	2.4
90-99	2.6
100-109	2.8
110+	3.0

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Restricting Dose to Members of Public

- Owners/caregivers will receive the most dose; other people are simply not close enough long enough to receive an appreciable amount of dose.
- Objective – Limit the amount of behavior modification required
- Allowed (unmodified) behaviors
  - Feeding
  - Walking
  - Grooming
  - Petting
  - Resting
- Controlled behaviors
  - Lap-sitting
  - Officing
  - Co-sleeping

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Restricting Dose to Owners

- Most common behavior scenario
  - No written instructions necessary to comply with public dose limit
  - Issue written instructions regardless applicable for 2 weeks, one half-life, when 50% of the potential dose could be delivered to provide a margin of dose reduction
  - The written instructions don't actually modify expected behavior but simply raise owner awareness of behavior
- Other scenarios
  - Make compliance easy and minimize intrusiveness
  - Allow common behaviors to continue unmodified
  - Limit the less common behaviors

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Veterinary Screening

- Prior to treatment, the veterinary staff must pre-screen patients and determine that the dog owner understands and is willing to follow the written instructions for the length of time necessary
  - If the owner is unable or unwilling to do so, then their dog is not a candidate for treatment
- Upon release, the dog owner is provided with the written instructions and signs that they understand and will comply with the instructions

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Written Instructions

Your dog has been treated with Synovetin OA™ (tin-117m) in one or more arthritic joints. Synovetin OA™, a radio-therapeutic device, emits very low amounts of radiation energy within the joint to relieve pain and inflammation over an extended time period. Your dog's coat and surroundings will not be affected, and the activity will naturally decrease over time. To maintain overall exposure below federally-established limits*, follow these recommendations for the next ____ weeks:

- Do not sleep with the dog or hold the dog in your lap
- Each member of the household should limit close contact to _**15**_ minutes and should limit intermediate contact to _**4**__ hours. Activities such as walking or playing with your dog can continue as usual
- Minimize the time that young children and pregnant women spend in close contact with the dog
- Avoid boarding your dog or traveling with it by air or across any international borders or very large, organized events (professional sporting events, parades, etc.). Keep a copy of this document should any questions arise
- Minimize use of public transportation and staying in public accommodations (e.g., hotels). Transport your dog in its carrier as far from passengers as is reasonable and safe for the dog
- If your dog needs emergency care, please inform the provider about its treatment with radiotherapy, and to contact (*RSO of facility, at RSO's phone number)* with any questions

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Written Instructions

If for any reason your dog dies within four months of treatment and you plan to have it cremated, this may be delayed until the radioactivity has decreased to an appropriate level

If you have any questions, please contact (*RSO of facility, at RSO's phone number)*

Veterinarian signature: _____Date: _____

I have received this information orally and in writing, and I understand it. I have had the opportunity to ask any questions

Dog owner signature: _____Date: _____

Examples of routine activities

1 foot: feeding, petting, grooming or bathing

3 feet: walking or running on a leash, dog sitting or lying down at your feet

Copies of this document shall be provided to the Pet Owner and retained by the Radioactive Materials Licensee

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Written Instruction Durations

- 8 scenarios evaluated
  - Simplified to 4 scenarios
  - Co-sleepers
  - Lap-dogs but not co-sleepers
  - Officing but not lap-dog or co-sleeper
  - None of the above (most common)
- In each case, limit co-sleeping, lap-sitting, and officing for the duration of the written instructions

Exposure Rate (mR/h @ 1 m)	0.5	0.4	0.3	0.2	0.1	0.05
Dogs that do not co-sleep, lap-sit, or office						
Instruction Duration (weeks)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)
Average daily time @ 1 ft (min)	15	15	15	15	15	15
Average daily time @ 3 ft (hrs)	4	4	4	4	4	4
Dogs that co-sleep						
Instruction Duration (weeks)	8	7	6	5	3	2 (1)
Average daily time @ 1 ft (min)	15	15	15	15	15	15
Average daily time @ 3 ft (hrs)	4	4	4	4	4	4
Dogs that lap-sit						
Instruction Duration (weeks)	5	4	3	2	2 (0)	2 (0)
Average daily time @ 1 ft (hr)	15	15	15	15	15	15
Average daily time @ 3 ft (hrs)	4	4	4	4	4	4
Dogs that office						
Instruction Duration (weeks)	2 (1)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)
Average daily time @ 1 ft (min)	15	15	15	15	15	15
Average daily time @ 3 ft (hrs)	4	4	4	4	4	4

Reliance on Written Instructions

- The NUREG-1556 Vol 7 Rev 1 Appendix D release criteria implicitly rely on the written instructions to limit dose to members of the public
  - In particular, the requirement to not co-sleep
- NCRP 148 allows credit to be taken for written instructions
- The approach should be that the majority of the dose limitation is based on factors other than the written instructions
- The written instructions should be a secondary factor
- The proposed written instructions for Sn-117m treatment of dogs parallel the NUREG guidance for I-131 treatment of cats in the types of behaviors limited and the degree of reliance on those instructions
- Written instruction specificity modeled after the NUREG guidance for I-131 treatment of cats as well

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Conclusions

- The TAR response concerns regarding human-dog interactions and occupancy factors have been addressed and factored into the public dose evaluation
- For the vast majority of patients, written instructions are not required but simply heighten owner awareness and provide a margin of dose reduction
- When written instructions are required, they have been formulated to minimize disruption of normal behaviors, i.e., allow most normal behaviors to proceed unimpacted, increasing ease of compliance
- The written instructions have been revised to provide greater specificity and match the feline I-131 therapy written instructions level of detail

Next Steps

- NRC thoughts and questions about the public dose evaluation and proposed written instructions
- Once agreement in principle is reached, how do we move forward?

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