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NUCLEAR REGULATORY COMMISSION
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SUBJECT: LICENSING OF THORIUM GENERATORS

The purpose of this memorandum is to support regulators in the licensing of thorium generators. Thorium generators use thorium (Th)-229, Th-228, and Th-227 to produce alpha/beta emitting progeny for targeted alpha therapy (TAT). The key nuclides currently being researched by industry for TAT coming from Th generators as progeny include actinium-225 (Ac-225), bismuth (Bi-212), lead-212 (Pb-212), radium (Ra)-224, and Ra-223.

Production Overview

Thorium can be licensed as either byproduct material or source material. The licensing determination is based on how the thorium was originally produced or generated. Below lists the known pathways for how thorium is produced or generated at the time of this memorandum for use in thorium generators and explains that the production pathways all point to thorium being licensed as a byproduct material. License reviewers should note that production processes could change with technological advancements and result in revised licensing guidance.

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Thorium 227. Th-227 is being researched as both a generator for Ra-223 and as a TAT. The definition of byproduct material under 10 CFR 30.4(1) includes "any radioactive material (except special nuclear material) yielded in, or made radioactive by, exposure to the radiation incident to the process of producing or using special nuclear material." Because Th-227 is currently being produced as a decay product of material produced in a nuclear reactor, this material meets the definition of byproduct material under the NRC regulations. The NRC determined that Th-227 chloride treatment (TTC) meets the definition of byproduct material via memorandum ML19197A327 posted in 2019.

Thorium-228. Th-228 has a decay chain that includes Ra-224, Pb-212 and Bi-212. There is interest for these radionuclides in the medical community with multiple early-phase investigational clinical trials in the United States using the radiopharmaceutical Pb-212. In February 2024, a Pb-212 treatment received FDA's breakthrough therapy designation. Th-228 is used to make Ra-224/Pb-212 generators. Ra-224/Pb-212 generators are the preferred radionuclide source over Th-228 to minimize radiation hazards.

The Th-228 used for research and development (R&D) generators are currently known to come from four (4) different sources: (1) accelerator produced by the United States Department of Energy (DOE); (2) a byproduct of Ac-227 production via irradiation of Ra-226 in a reactor operated by the DOE; (3) accelerator produced in Australia; or (4) extracted from UK uranium (U)-232 that is created through neutron activation of U-235 or Th-232. Th-228 from these four (4) sources meet the definition of byproduct material found in 10 CFR 30.4(1). Therefore, this use of Th-228 would be licensed as byproduct material under 10 CFR Parts 30 and 35 or equivalent NRC Agreement State provisions for R&D use.

Th-228 can also be produced through extraction from natural sources, such as from the decay of U-232, which is found in small quantities in natural uranium ores. However, this memo does not address the licensing of Th-228 produced through this method as the staff is unaware of any initiatives by industry to use such derived Th-228 for generators. Submittals from licensees who want to use source material thorium-based generators should be brought to the attention of Medical Safety and Events Assessment Branch (MSEB).

Thorium-229. Th-229 decays to Ra-225 and then to the TAT nuclide Ac-225.Th-229 is produced from neutron transmutation of Ra-226 targets in the ORNL High Flux Isotope Reactor (HFIR). Th-229 can also be produced through neutron irradiation of Ra-228, Ac-227, and Th-228. These production pathways meet the definition of byproduct material in 10 CFR 30.4(1).

In summary, the above production pathways all point to thorium for use in thorium generators being licensed as a byproduct material. All radioisotopes produced or derived from thorium generators produced in this manner would be considered byproduct material. The licensee and regulator should nonetheless always confirm the production methodology of the thorium parent generator.

Licensing Considerations for Research and Developmental Use

Research and Developmental Use. From discussions with several vendors, the generators will likely be placed within a network of radiopharmacies in a distribution manufacturing scenario. Radiopharmacies may use the generators to prepare and transfer the radioactive drugs during R&D. In accordance with 10 CFR 32.72, licensees may prepare the radioactive drugs for use by

persons authorized pursuant to 10 CFR 35, provided that the radioactive drug is prepared by an authorized nuclear pharmacist (ANP) or an individual under the supervision of an ANP.

At this time, it is expected the medical institutions may receive the unit dose of radioactive drug containing the alpha/beta emitting progeny for TAT for use under 10 CFR 35.300. During research, the Investigational New Device (IND) protocol will have appropriate controls on training and experience, breakthrough and impurity testing, tracking and reporting. Therefore, in accordance with 10 CFR 35.300, a licensee may use the radioactive drug for research if it is obtained from and prepared by an NRC or Agreement State licensee for use in research in accordance with an IND protocol accepted by the FDA. This scenario is subject to change if TAT radioactive drugs receive FDA approval.

Future Considerations. MSST staff is evaluating the appropriate licensing pathway for future clinical use of thorium generators approved by the FDA. This evaluation includes determining if further conditions for breakthrough testing, limits, or reporting are needed. Similar to breakthrough of the parent, breakthrough of an impurity could also be a concern. Currently, we do not have any evidence of impurity breakthrough with any generators during clinical trials but if the NRC becomes aware of such evidence, the staff may provide additional guidance. If the NRC becomes aware of future developments regarding the production, distribution, or medical use of these novel radionuclide generators that could negatively affect radiation safety, NRC staff may provide further guidance or considerations.

LICENSING OF THORIUM GENERATORS DATE April 4, 2025

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