Annual Update on Medical Isotopes from the Department of Energy Isotope Program—FY 2020

Background

The DOE Isotope Program (DOE IP) supports a network of national laboratories and universities to produce and sell isotopes including the medically relevant Ac-225/Bi-213, Ac-227, As-72, At-211, Co-60, Cu-67, Ge-68, Lu-177, Pb-212/Bi-212, Ra-223, Th-227, Th-228/Ra-224, Sr-82, Sr-89, Sr-90, W-188/Re-188, Y-86, and Zn-65. The DOE IP produces isotopes in short supply or when no other production capability exists domestically, for research, industry, and other applications. The DOE IP also makes investments in R&D to develop new production and processing capabilities for critical isotopes. The snapshots below highlight select progress made within the DOE IP over the past year. For more information on the availability of isotopes mentioned below or new isotopes that are not in the catalog, please contact the National Isotope Development Center (NIDC) at **contact@isotopes.gov**.

For a full list of the isotopes produced by the DOE IP and to request a quote, please visit the NIDC website: **www.isotopes.gov**. While there, be sure to sign up for the mailing list at **www.isotopes.gov/subscribe** to receive announcements and newsletters from the DOE IP. Newsletters are published regularly and include feature-length articles. Announcements occur more frequently (approximately one per week) and focus on information about isotope availability, DOE IP funding opportunity announcements, or breaking news from the DOE IP.

Response to COVID-19 and Supply Constraints

The DOE IP is the only mission essential program within the Department of Energy Office of Science. Throughout the COVID-19 pandemic, DOE IP operations have been staffed and operational. Irradiations, processing, and purification operations continue with shipments made to both domestic and international users. Individuals or entities with concerns about supply constraints are encouraged to contact the NIDC at **contact@isotopes.gov**.

Updates to Initiatives

Enriched Stable Isotope Production—DOE discontinued producing enriched stable isotopes in the Y-12 Plant calutrons in 1998. To re-establish this domestic capability, the DOE IP commissioned a prototype stable isotope enrichment plant at Oak Ridge National Laboratory (ORNL). Using an electromagnetic isotope separator (EMIS) machine, it produced the world's only supply of ruthenium-96. ORNL is now using the machine to develop methods for producing highly enriched ytterbium-176 for use in the production of no-carrier-added lutetium-177. Meanwhile, a small cascade of gas centrifuges was effective at enriching small quantities of molybdenum-98 and -100. The DOE IP is supporting a substantial scale-up of the prototype plant and has provided funds to install several additional EMIS machines to expand production in the next few years. Starting by 2025, the Stable Isotope Production Facility will host an expanded centrifuge capability dedicated to producing enriched xenon-129 for polarized lung

imaging. Finally, further expansions are planned in the $230M Stable Isotope Production and Research Center. With commissioning of the center planned around 2028, DOE will be capable of using multiple technologies and making multiple products simultaneously under one roof.

FRIB Isotope Harvesting—The DOE Office of Nuclear Physics is constructing the Facility for Rare Isotope Beams at Michigan State University; the DOE IP will establish isotope harvesting there to provide large quantities of rare isotopes starting around 2024.

Nuclear Data—The accelerators at Brookhaven National Laboratory (BNL) and Los Alamos National Laboratory (LANL) both recently underwent upgrades to increase their production and analytical capabilities. A collaborative effort of BNL, LANL, and Lawrence Berkeley National Laboratory is underway to provide nuclear data of importance to the isotope community and allow the DOE IP to take full advantage of the improvements to increase production yields at these facilities.

University Isotope Network (UIN)—In response to a Funding Opportunity Announcement, two universities were selected for research funding in FY 2019 and an additional four universities were selected in FY 2020 to encourage the development of routine isotope production capabilities or production-related technologies. These awards aim to bolster the DOE IP's efforts to establish a regional production network for short-lived medically relevant isotopes or boutique isotopes for which there are no commercial suppliers. The six funded universities are being integrated into the UIN, which currently consists of the University of Missouri and the University of Washington.

α-Emitter Updates

Actinium-225—The DOE IP has historically used a thorium-229 cow to provide actinium-225 and its bismuth-213 daughter. This product is distributed weekly to various groups for R&D and early-stage clinical trials. However, the limited supplies of this material are insufficient to support multiple advanced-stage clinical trials. The Ac-225 Tri-Lab Effort between BNL, LANL, and ORNL has made substantial progress toward increasing production capacity over 100-fold via accelerator-based production. New production and processing methods as well as planned facility upgrades will enable further applications of Ac-225 and Bi-213 to a broader scope of researchers and patient populations. A Drug Master File (DMF) was recently filed on the accelerator-produced Ac-225 product, and a DMF is scheduled to be completed in FY 2021 for the Th-229 cow product. Accelerator-produced Ac-225 samples have been evaluated by the community in dosimetry and toxicology studies, some of which were recently presented and discussed in a virtual forum at the annual Ac-225 User Group meeting. Accelerator-produced Ac-225 is routinely available on an approximately 6-week basis.

Actinium-227—An Ac-227 cow is used to produce very high-purity Ra-223 and Th-227, both alpha-emitting isotopes. The DOE IP is also the sole producer of Ac-227 for Bayer's FDA-approved drug Xofigo®.

Astatine-211—The University of Washington is currently supplying At-211 for several preclinical studies and one Phase 1 clinical trial through the DOE IP. A weekly production schedule enables regional distribution of highly pure At-211, one of the short-lived radionuclides produced through the UIN. Four of the universities that received UIN FOA funding, as described above, have begun R&D to enable an At-211 production capability. Upon completion of this R&D effort, the UIN will include five universities, in geographically diverse locations, producing and distributing At-211. The At-211 User Group meeting recently convened for its annual discussion.

Lead-212/Bismuth-212 Generator—Ra-224 is the parent of candidates for new therapeutic alpha-emitting radiopharmaceuticals using Pb-212 and Bi-212. Ra-224 generators are produced at ORNL and can be used to provide both Pb-212 and Bi-212. Preclinical evaluations are being conducted at multiple domestic sites. Additional R&D is also underway to improve the design and capacity of the generators. The Pb-212/Bi-212 User Group meeting recently convened for its annual discussion.

Thorium-228/Radium-224 Generator—Th-228 is being supplied as a generator for Ra-224, which is currently in clinical trials to develop novel treatments for ovarian, colorectal, and various skin cancers such as metastasized melanoma.

Emerging Isotopes

Titanium-44/Scandium-44 Generator (theranostic isotope)—the NIDC is currently identifying potential test batch recipients for evaluation of this material.

Newly Available Isotopes:

Copper-67—The capability to produce Cu-67 has been developed at both Argonne National Laboratory (ANL) and BNL. ANL routinely produces 2 Ci batches of high-specific activity (400 Ci/mg at end of batch) material by phototransmutation using an electron linac. BNL provides lower specific activity material (20 Ci/mg) using a proton linac.

Strontium-89—pain palliation agent—now available

Isotopes Under Development

Bromine-76 and Bromine-77—PET and SPECT imaging agents respectively—under development

Cerium-134—PET imaging analogue of α therapeutic agents—under development

Lutetium-177—large-scale production of no-carrier-added Lu-177—under development

Manganese-52g—bimodal imaging agent—under development

Niobium-90—PET imaging agent—under development

Platinum-191, Platinum-193m, and Platinum-195m—radioisotopes to be used with current chemotherapy agents—under development

Rhenium-186—theranostic isotope—under development

Scandium-43 and Scandium-44—PET imaging agents that can be theranostically paired with Sc-47—under development

Scandium-47—therapeutic agent—under development

Selenium-72/Arsenic-72—generator (PET imaging agent)—under development

Tellurium-119m/Antimony-119—generator (Auger e-therapy)—under development

Xenon-129—stable isotope used in MRI lung imaging—enrichment under development

Uranium-230/Thorium-226—generator (α therapeutic agent)—under development

Other Routinely Available Medically Relevant Isotopes

Cobalt-60—source applications for cancer radiotherapy, cancer radiosurgery (Gamma Knife®), and industrial gamma radiography—high specific activity and low specific activity available

Iron-52—radiotracer for early-stage medical and biological studies—available

Lutetium-177—partnership with University of Missouri Research Reactor to supply quantities for research use only

Tungsten-188/Rhenium-188—available

Yttrium-86—PET imaging agent and theranostic pair to Y-90—available

Yttrium-88—can be substituted for Y-90 in development of therapeutic agents—available

A Note About Molybdenum-99

While it's not within the DOE IP's production purview, the program provides technical support to NNSA in its ongoing mission to ensure a stable domestic supply of molybdenum-99.