Isotope Program
U.S. Department of Energy

DOE IP Accelerator Production of Ac-225

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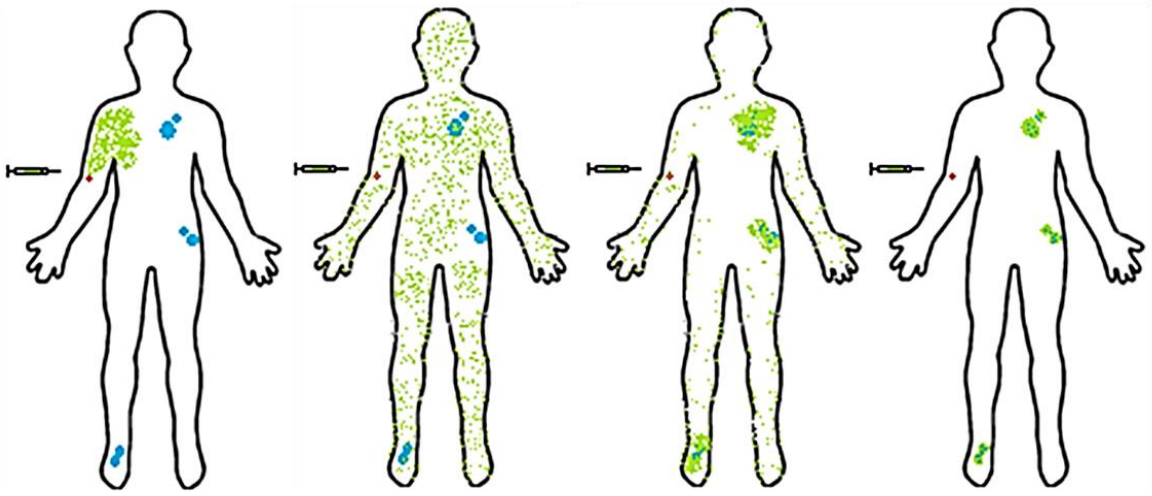
Medically-relevant alpha emitters have been a priority

Isotope	Half-life
^{225}Ac	9.92 d
^{211}At	7.2 h
^{212}Bi	60 m
^{213}Bi	46 m
^{212}Pb	10.6 h
^{223}Ra	11.43 d
^{226}Th	31 m
^{227}Th	18.7 d

Alpha emitters are well suited for treatment of cancer and infectious diseases

- Short range (50 to 80 microns or ≤ 5 cells)
- High linear energy transfer (5 to 8 MeV)



1. Administration 2. Distribution 3. Localization 4. Retention

Priority alpha emitters that DOE IP is routinely producing or development production capabilities.

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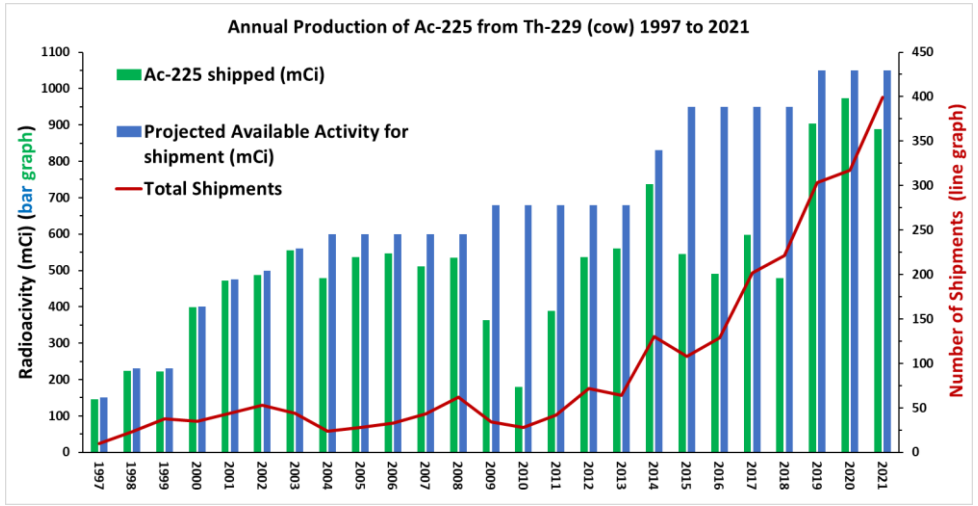
Actinium-225 Production at ORNL

- ORNL has been the main supplier of ^{225}Ac (via decay of existing ^{229}Th stock) since 1997
- >10 Ci of ^{225}Ac shipped in >2000 packages
- Approximately 1 Ci of ^{225}Ac is harvested annually from 130 mCi ^{229}Th stock at ORNL
- Thirteen 4-week campaigns are performed per year, with weekly customer shipments
- **Present supply fully subscribed**

Rationale for pursuing additional routes for production of ^{225}Ac

- The present supply is insufficient to meet the growing research and medical applications demands for ^{225}Ac



^{233}U
↓ α 1.6x10^5
^{229}Th
↓ α 7.9x10^3
^{225}Ra
↓ β 15 d
^{225}Ac
↓ α 10 d

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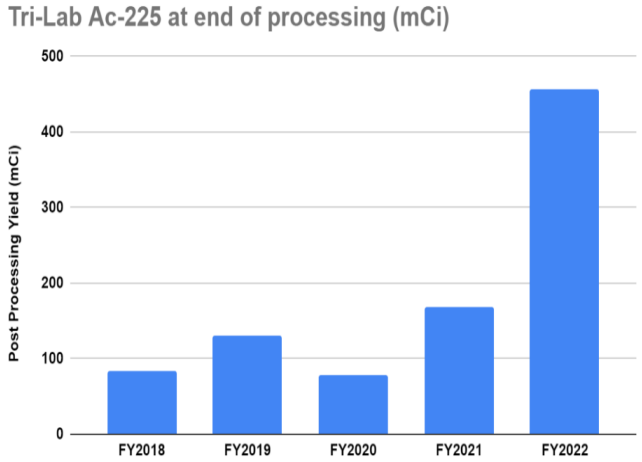
Ac-225 Tri-Lab Effort (Accelerator Production)

BNL the Brookhaven Linac Isotope Producer (BLIP); 66-202 MeV incident energy range at 165 mA for routine production

LANL Isotope Production Facility (IPF) at LANSCE; 100 MeV incident energy up to 275 mA for routine production

ORNL - Approximately 25 years of experience in the isolation of ^{225}Ac from fissile ^{233}U via ^{229}Th



Status and Update

- Effort initiated 2014
- First "batches" processed in 2018
- Reliably producing about 50mCi/batch after processing since FY22
- Up to 600 mCi present in current target design at End of Bombardment
- Amount of Ac-225 available is currently limited by:
  - Processing capabilities
  - Transit time between irradiation sites (BNL & LANL) and the processing site (ORNL)

Process is scalable by:

- Increasing target size
- Increasing frequency of irradiations (every 4 weeks → 3 weeks)

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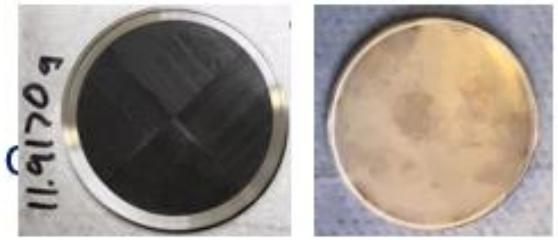
Workflow of Ac-225 production campaign at BNL

- Thorium material machined and cut into 5 pieces at LANL.
- Pieces shipped to BNL, assembled and EB welded at EB industries (Farmingdale, NY)
  - 0.3 mm (0.015 in) thick (~11g) Th foil
  - Inconel Capsule
- BLIP irradiation
  - 160 or 200 MeV for up to 12 days, up to 165 μA
- After irradiation target transferred to RRPL opened and packaged for shipment, or processed

- Chemical processing and dispensing of Ac-225 (50 mCi/batch now and plans to increase)



Processing Facilities at BNL: New as of March 2023

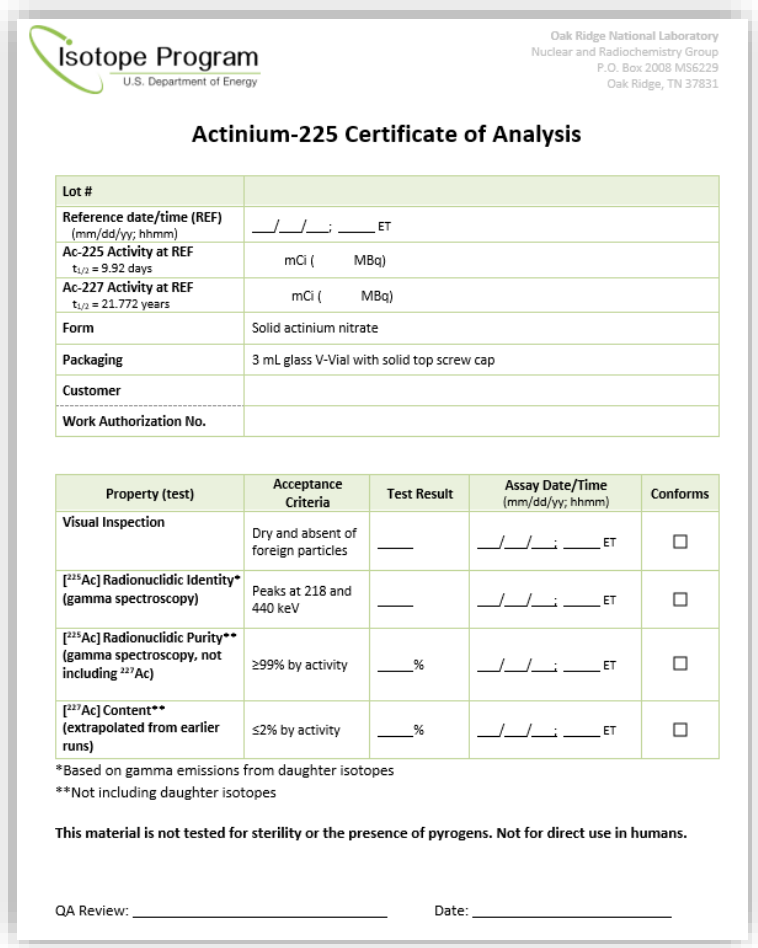
- Refurbished hot cells at BNL
- Completed Commissioning activities
- Received approval to start operations
- Processed Ac-225 and sent out to customers
- DOE IP now has two processing sites: ORNL and BNL
- Consist of three hot cells, two ready rooms, special storage unit, special ventilation, acid scrubber system, clamshell for target introduction to reduce dose to operators.

DMF/FDA Updates

- A Type II Drug Master File (DMF) was submitted in December 2019 for accelerator produced Ac-225
- A Type II DMF was submitted in December 2020 for the ^{229}Th-derived ^{225}Ac product
- Interaction with the Food and Drug Administration is ongoing in reference to both products
- We are committed to making these products available to our customers/the medical community and are happy to address any further questions

Actinium-225 Specification and DMF Development

- Accelerator-Produced Material:
  - A specification was developed to enable use of the product in Phase I clinical trials
  - Drug master file submission was submitted in 2019
- Thorium-229 Derived Material
  - Drug master file submission submitted in Dec 2020



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Actinium-225 Certificate of Analysis

Lot #	
Reference date/time (REF) (mm/dd/yy; hhmm)	__/__/__; ____ ET
Ac-225 Activity at REF $t_{1/2}$ = 9.92 days	mCi (MBq)
Ac-227 Activity at REF $t_{1/2}$ = 21.772 years	mCi (MBq)
Form	Solid actinium nitrate
Packaging	3 mL glass V-Vial with solid top screw cap
Customer	
Work Authorization No.	

Property (test)	Acceptance Criteria	Test Result	Assay Date/Time (mm/dd/yy; hhmm)	Conforms
Visual Inspection	Dry and absent of foreign particles	____	__/__/__; ____ ET	☐
[^{225}Ac] Radionuclidic Identity* (gamma spectroscopy)	Peaks at 218 and 440 keV	____	__/__/__; ____ ET	☐
[^{225}Ac] Radionuclidic Purity (gamma spectroscopy, not including ^{227}Ac)**	≥99% by activity	____%	__/__/__; ____ ET	☐
[^{227}Ac] Content (extrapolated from earlier runs)**	≤2% by activity	____%	__/__/__; ____ ET	☐

*Based on gamma emissions from daughter isotopes
**Not including daughter isotopes

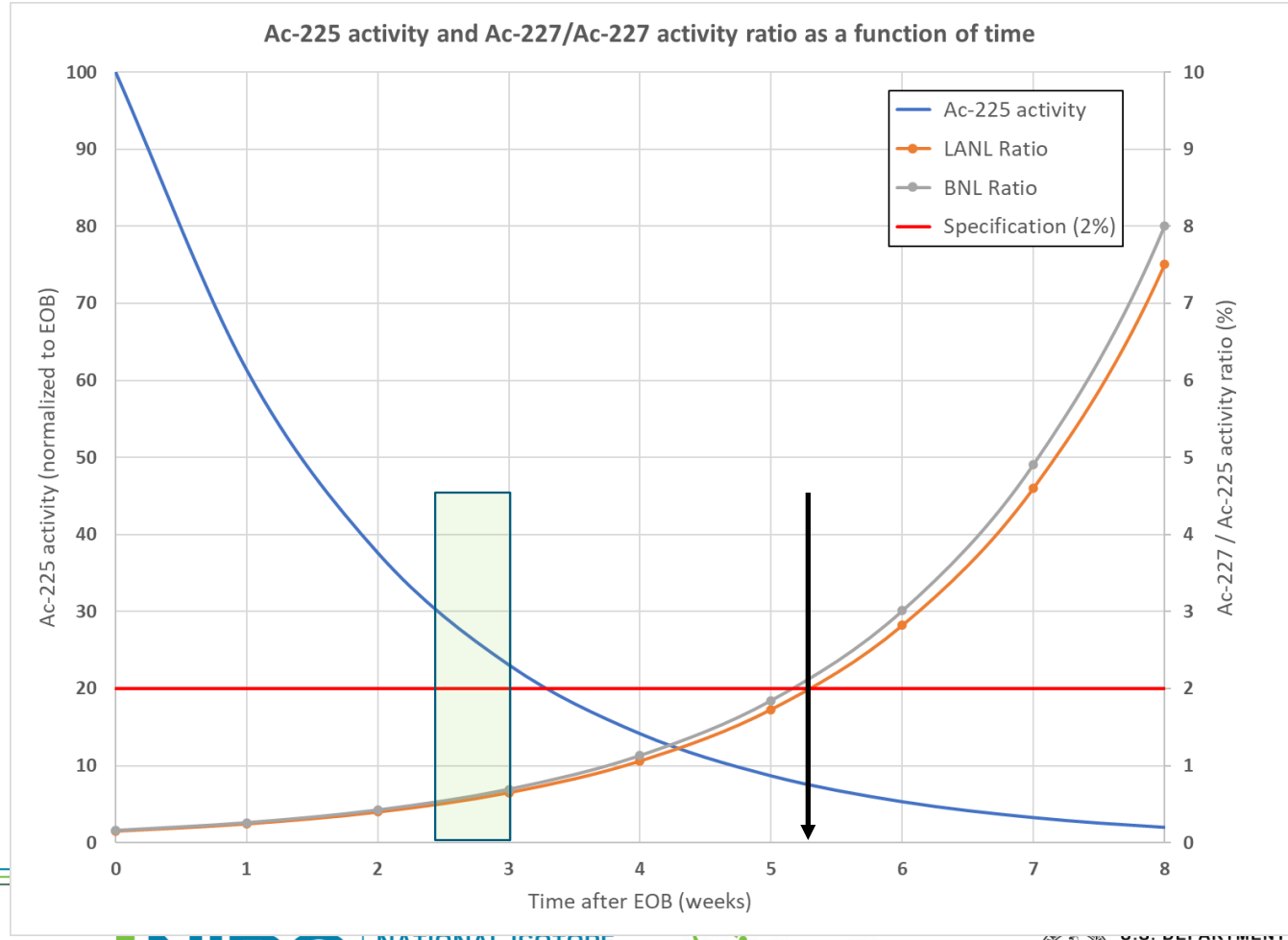
This material is not tested for sterility or the presence of pyrogens. Not for direct use in humans.

QA Review: _____ Date: _____

Current CoA for Accelerator Material

Ac-225 decay and Ac-227/Ac-225 activity ratio

- End-of-bombardment (EOB) is Week 0
- Ac-225 decays with a half-life of 9.92 days
- The relative amount of Ac-227 (21.7 years) increases with time
- The ratio of Ac-227/Ac-225 at EOB is ~0.15 (same for both accelerator labs)
- Specification: Ac-227 activity ratio is <2%
- The Ac-227 activity ratio exceeds 2% ~5 weeks after EOB (black arrow)
- Currently Ac-225 dispensing from ORNL or BNL occurs 2.5 – 3 weeks after EOB (green box)
  - Ac-225 activity is ~25% of activity at EOB
  - Ac-227/Ac-225 ratio is ~0.7%



Continuing Efforts to Increase Availability of 225Ac

- The Tri-Lab effort is routinely producing ^{225}Ac and *product is available* for end users and shipments to multiple users have been completed
- We have distributed over 500 mCi of accelerator produced ^{225}Ac to evaluators
- There are now two processing sites **providing redundancy**
- We are working with companies and research hospitals in preparation to support Phase I trials
- ^{227}Ac content is clinically insignificant from a dosimetry/toxicity perspective K. Dadachova . http://dx.doi.org/10.2174/1874471011666180423120707
- Continuing to scale up availability of this important isotope

Summary

- DOE IP has ramped up its supply of Ac-225 to maximize domestic availability
- DOE has upgraded its irradiations facilities and is increasing the processing capability of several DOE IP sites (CARP at BNL, API at LANL, RPF at ORNL)
- Has a history in meeting cGMP and has been audited by the FDA and customers
- Has submitted a DMF for Ac-225 and written letters of authorization

Thank You!

For more information: **https://isotopes.gov/**

https://www.isotopes.gov/information/actinium-225

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