U.S. DOE Tri-Lab Production Effort to Provide Accelerator-Produced $^{225}$Ac for Radiotherapy

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Current worldwide supply of $^{225}\text{Ac}$ from $^{229}\text{Th}/^{225}\text{Ac}$ generators is estimated at 1200-1700 mCi/yr*

Patient doses, as informed by clinical trials, are estimated at:

$^{225}\text{Ac}$: 2-8 $\mu$Ci per patient kg  
(160-640 $\mu$Ci/patient)

$^{213}\text{Bi}$: 1 mCi per patient kg  
(Optimum generator loading estimated at 100-150 mCi $^{225}\text{Ac}$)


### Addressing the Supply Chain: Various $^{225}\text{Ac}/^{229}\text{Th}$ Production Routes

<table>
<thead>
<tr>
<th>Facility</th>
<th>Nuclear Reaction</th>
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</thead>
<tbody>
<tr>
<td>Reactor (thermal neutrons)</td>
<td>$^{226}\text{Ra}(3n,\gamma)^{229}\text{Ra} \rightarrow ^{229}\text{Ac} \rightarrow ^{229}\text{Th}$ (plus $^{228}\text{Ra}$ target)</td>
</tr>
<tr>
<td>Accelerator (electrons)</td>
<td>$^{226}\text{Ra}(\gamma,\text{n})^{225}\text{Ra} \rightarrow ^{225}\text{Ac}$</td>
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<tr>
<td>Accelerator (low energy particles)</td>
<td>$^{226}\text{Ra}(\text{p,2n})^{225}\text{Ac}$ $^{226}\text{Ra}(\alpha,\text{n})^{229}\text{Th}$ $^{226}\text{Ra}(\text{p, pn})^{225}\text{Ra}$ $^{232}\text{Th}(\text{p,x})^{229}\text{Th}$</td>
</tr>
<tr>
<td>Accelerator (high energy protons)</td>
<td>$^{232}\text{Th}(\text{p,x})^{225}\text{Ac}$ $^{232}\text{Th}(\text{p,x})^{225}\text{Ra} \rightarrow ^{225}\text{Ac}$</td>
</tr>
<tr>
<td>Accelerator (high energy neutrons)</td>
<td>$^{226}\text{Ra}(\text{n,2n})^{225}\text{Ra}$</td>
</tr>
<tr>
<td>Hot Cell Facility ($^{233}\text{U}$ processing)</td>
<td>$^{229}\text{Th}$ decay to $^{225}\text{Ac}$</td>
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Accelerator Production via $^{232}$Th(p,x)$^{225}$Ac – Initial R&D Promised Significant Impact

Facility Anticipated Single Target Ac-225 Yields (10 day irradiation)

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<th>Anticipated Single Target Ac-225 Yields (10 day irradiation)</th>
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<tbody>
<tr>
<td>LANL (100 MeV, 250-450 µA)</td>
<td>1.3-2.3* Ci</td>
</tr>
<tr>
<td>BNL (200 MeV, 165 µA)</td>
<td>2.2 Ci</td>
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</table>

* Theoretical maximum value assumed for production with 450 µA on target resulting from recent facility investments.


Facility investments at IPF and BLIP have increased our projected production capacity
Basis of the Tri-Lab Effort: Leveraging Unique Isotope Program Facilities, Capabilities and Expertise to Address $^{225}$Ac Supply

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

BNL Linac at the Brookhaven Linac Isotope Producer (BLIP) 165 µA intensity to targets at incident energies ranging from 66-202 MeV

ORNL - Approximately 25 years of experience in the isolation of $^{225}$Ac from fissile $^{233}$U via $^{229}$Th
Past DOE Tri-Lab Stage 1 Effort Focused on Research with Emphasis on Technical Feasibility and Logistics

Significant technical progress related to target design experience and chemical process optimization

Stage 1 irradiations have provided us with invaluable logistical experience and delivered a means to supply $^{225}\text{Ac}$ material for materials evaluation campaigns and bio-distribution, dosimetry, toxicity studies.
Current and Future Effort Focused on Scaled-Up Production and GMP Implementation

**STAGE 2**
50-100 mCi

- Continued Production/Processing
- Implement Facility Mods and ES&H/QA Policies
- Receive DOT Type B Container
- Implement Chemistry/Targetry Scale-up

Oct, 2017

**STAGE 3**
100-1000 mCi

- Complete Facility Mods
- Final Prep for Routine Production
- Complete ES&H/QA Documents

Sept, 2020

**Routine, Ci-scale Production**

- Project Complete

April, 2024

**SG-1**

**SG-2**

**SG-3**

**SG-4**

April, 2025

Current and Future Effort Focused on Scaled-Up Production and GMP Implementation

- Current and Future Effort Focused on Scaled-Up Production and GMP Implementation

- Routine, Ci-scale Production

- April, 2024

- April, 2025

- Project Complete

- Current and Future Effort Focused on Scaled-Up Production and GMP Implementation

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Stage 2 Focus

General focus on increasing production frequency and volume in support of clinical R&D and clinical trials

Continued improvements to the design and preparation of thorium targets and radiochemical processing optimization

Continued improvement of shipping capabilities and shipping performance

Submittal of a Drug Master File to inform the FDA - helps our customer base, and protects our process

Starting to execute facility vision with eye toward Stage 3 large scale production

Continued focus on stakeholder and customer interactions.

Clemens Kratochwil, University Hospital Heidelberg – J. Nuc. Med., v57, 2016, pp 1941-1944

$^{225}$Ac-PSMA-617 derived from a $^{229}$Th-cow
FDA and End-User Interactions

Accelerator-produced $^{225}$Ac for direct labeling and $^{213}$Bi generator application will be viewed by FDA as Active Pharmaceutical Ingredients (API)

The Tri-Lab Effort has supported initial dosimetry/toxicity studies aimed at determining impact of $^{227}$Ac content; ultimate determination rests on drug developers as they develop their Investigational New Drug Applications (IND)


Dadachova ER et al.

*TAT11 International Symposium – Dosimetry Session*
Actinium Biokinetics and Dosimetry: What is the Impact of Ac-227 in Accelerator-Produced Ac-225?
Abergel, R et al.

*TAT11 International Symposium – Poster Session*
Pre-Clinical Evaluation of $^{225}$Ac-DOTATOC Pharmacokinetics, Dosimetry, and Histopathology to Enable Phase-1 Clinical Trial in Patients with Neuroendocrine Tumors
Norenberg, JP et al.

FDA has urged us to develop an accelerator-produced $^{225}$Ac Drug Master File
-DMF development is in process and will be submitted this year

We will continue to work with DOE and the $^{225}$Ac user community to address technical and logistical issues
General Accelerator-Produced $^{225}$Ac Product Conclusions

Accelerator-produced $^{225}$Ac performs similar to $^{229}$Th-derived $^{225}$Ac

- direct labeling efficiencies are comparable
- $^{213}$Bi generator performance is the same
- the impact of $^{227}$Ac content on dosimetry has been demonstrated to be negligible

Challenges remain with respect to the logistical considerations associated with the $^{227}$Ac co-product

- facility licensing (decommissioning funding plans)
- discussions ongoing with the NRC to potentially obtain an exemption as previously done for $^{68}$Ge
- patient waste (likely not an issue for an approved drug)
We have positioned ourselves to ensure a strong, reliable supply that meets the quality requirements and quantities needed for clinical application.
The Tri-Lab effort is routinely producing $^{225}\text{Ac}$ and product is available for end users and shipments to multiple users have been completed.

We have distributed over 250 mCi of accelerator produced $^{225}\text{Ac}$ to evaluators.

$^{213}\text{Bi}$ derived from accelerator-produced $^{225}\text{Ac}$ generators exhibits equivalent performance relative to $^{229}\text{Th}$ derived material.

$^{227}\text{Ac}$ content is clinically insignificant from a dosimetry/toxicity perspective – but challenges with perception and regulatory compliance remain; we have a well-defined forward path to address these challenges with DOE.

We are working with companies and research hospitals in preparation to support Phase I trials - DMF development is underway.
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