Product Quality Considerations in Actinium-225 Radiopharmaceuticals

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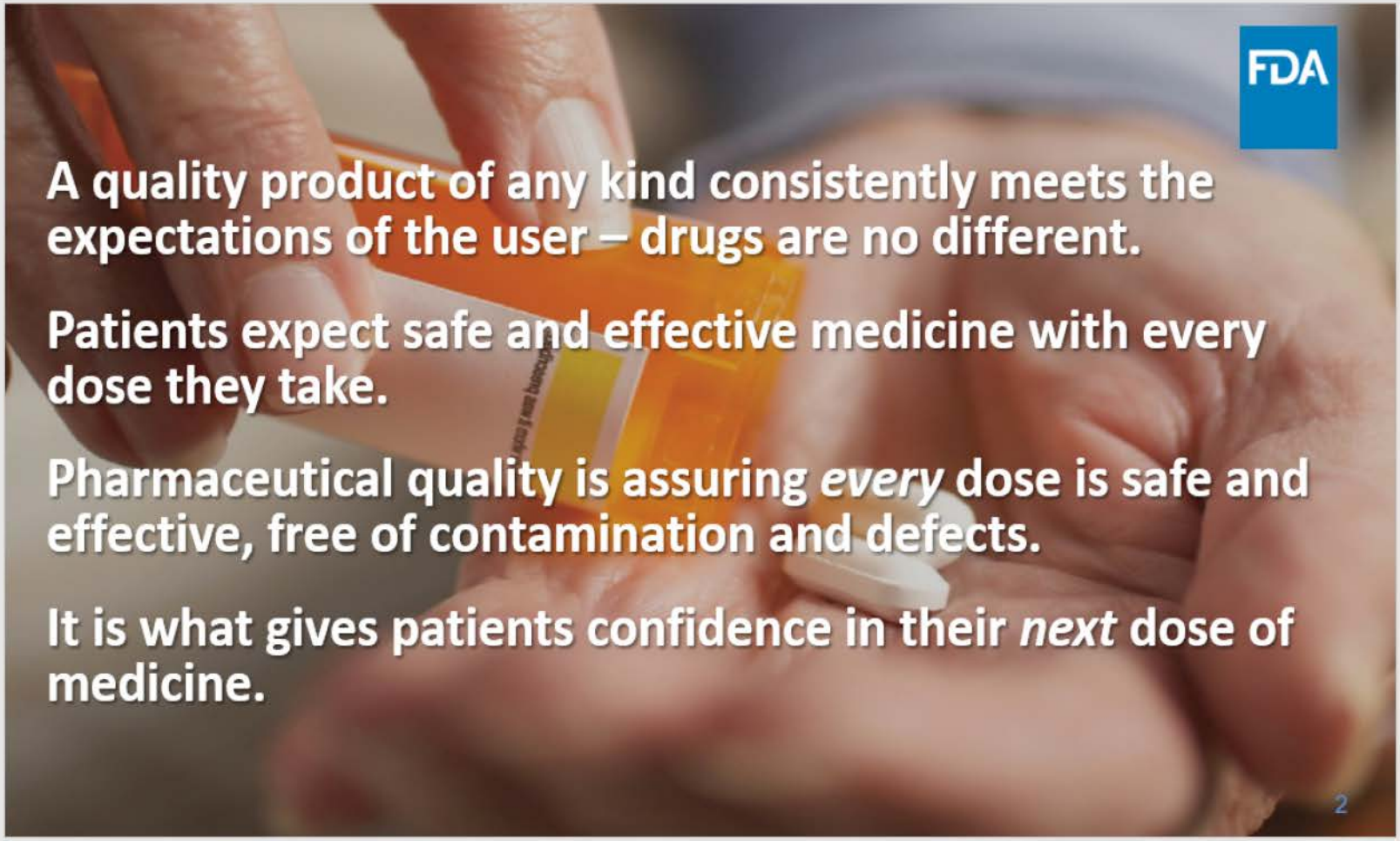
FDA
A quality product of any kind consistently meets the expectations of the user – drugs are no different.
Patients expect safe and effective medicine with every dose they take.
Pharmaceutical quality is assuring *every* dose is safe and effective, free of contamination and defects.
It is what gives patients confidence in their *next* dose of medicine.
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Outline

- Submission of chemistry, manufacturing and controls (CMC) information
- Acceptance specifications for the Actiniun-225 (Ac-225) radiochemical
- Controlling and reporting of radionuclidic impurities
- Changing generator produced Ac-225 to accelerator produced Ac-225
- Manufacture and quality control of Ac-225 radiopharmaceuticals
- Qualification of Ac-225 radiolabeling process
- Radioactive drug and radionuclide reference standard considerations

Organization of CMC Information

- Format for submitting information in an application, including CMC, is the Common Technical Document(CTD)
  - Drug Substance section (3.2.S) for biomolecule (e.g., MoAb)
  - Drug Substance section (3.2.S) for bulk chelate containing molecule (e.g., DOTA-Linker-MoAb or small molecule))
  - Drug Substance section (3.2.S) for Ac-225 radiochemical (e.g., $^{225}AcNO_3$)
  - Drug Substance section (3.2.S) for Ac-225 radioactive drug (e.g., to describe the nomenclature, structure, general properties, structure characterization, reference standard, other relevant information)
    - A radioactive drug (radiopharmaceutical) is the entire molecule, including the radionuclide
  - Drug Product section (3.2.P) for vialed chelate containing product, if any
  - Drug Product section for (3.2.P) for radioactive drug product

(As appropriate, the information may be referenced to other NDA, BLA or a type-II DMF. When referencing, LOA should be provided)

Actinium-225 Production

- $^{229}Th/^{225}Ac$ generator
  - Advantage - Free of other Ac-isotopes (may have other radionuclidic impurities)
  - Disadvantage - Limited Th-229; Limited Ac-225
- Accelerator produced Ac-225
  - Advantage – Can produce large amount of Ac-225
  - Disadvantage - Contains Ac-227 ($t_{1/2}$ = 21.8 yrs.) isotopic impurity (may have other Ac-isotopes and other radionuclidic impurities)
- CMC information for Ac-225
  - Submitted in a type-II DMF, which the radiopharmaceutical manufacturer should reference
  - Include Letter of Authorization (LOA) in the application

Acceptance Specifications for Ac-225 Raw Material

- Specifications should include
  - Appearance (e.g., material is received without apparent defects)
  - Identity of radiochemical
  - Radiochemical purity
  - Radionuclidic identity
  - Radionuclidic purity
  - Impurities
    - Specific radionuclidic / radioisotopic impurities (e.g., Ac-227, others)
    - Other nonradioactive elemental impurities
- The results for the lot may be accepted from qualified supplier's COA
- Need your own analytical methods for each test attribute

(Specification includes test attribute, acceptance criteria and test procedure)

Considerations for Control of Accelerator Produced Ac-225

- Long lived radionuclidic impurity → Ac-227 ($t_{1/2}$ = 21.8 yrs.)
  - Content increases during the shelf life of the ^{225}Ac- radiopharmaceutical drug product
- Ac-227 is an undesired impurity and the amount should be kept as low as reasonably possible
  - Explore all possible approaches to reducing the impurity content in the administered dose (e.g., rapid production methods, reducing hold times, limiting to clinically necessary shelf life)
- For Ac-225 radiochemical (e.g., $^{225}Ac(NO_3)_3$)
  - Establish specifications, including acceptable limit for Ac-227 impurity as material acceptance criteria
  - Establish Ac-227 content limit at the time of use (in-process acceptance criteria)
  - Establish use period - to assure that Ac-227 content will be below an established amount before its use and in the Ac-225 drug product

Control of Actinium-227 Containing Impurities in Radioactive Drug Product

- Ac-227 containing impurity issues must be considered
  - When accelerator produced Ac-225 is used
  - When generator produced Ac-225 is changed to accelerator produced Ac-225
- Establish justified limits.
  - Drug product batch must meet this criterion through expiry
- In establishing limits, consider:
  - Ac-227 containing impurities, at proposed limit, will not be retained in the body on long term basis.
    - Mass balance study
    - In vitro stability study using physiological conditions
  - Ac-227 impurities, at proposed limit, will not significantly adversely affect dosimetry of the intended Ac-225 product.
- Provide justification for impurities and radionuclidic purity
- Introduction of a new radionuclidic impurity may require revalidation of the drug product radionuclide impurity quantitation method(s), or implementation of a new analytical method that can quantitate Ac-227 in the drug product.

(A radiopharmaceutical product may contain other impurities (or degradation products), such as drug molecule related impurities or process related impurities (e.g., residual solvents, elemental impurities). These chemical impurities should be controlled as specified, each unspecified and total impurities, as appropriate)

Steps to Take to Change of Generator Produced Ac-225 to Accelerator Produced Ac-225

- Submit IND amendment, with necessary changes, when changing from generator Ac-225 to accelerator Ac-225
- Consider the following when changing Ac-225 process
  - Change in raw material (e.g., $^{225}Ac(NO_3)_3$) specifications
  - Establish use period for $^{225}Ac(NO_3)_3$ radiochemical, establish validated hold periods
  - Qualify the manufacturing process using accelerator produced Ac-225
  - Revise drug product specifications to include new rdionuclidic / radioisotopic impurities
  - Change the affected analytical methods, as appropriate
  - Provide data on verification batches
  - Assess impact of change on drug product stability

Manufacture of Ac-225 Radiopharmaceuticals

- Finished drug product should be manufactured at a CGMP manufacturing facility and be sent to the clinical site / user of the drug product as a ready to use product.
- The applicable CGMP regulations are in 21 CFR 211.

Identity of Ac-225 Radiopharmaceutical

- Radionuclidic identity – confirms intended isotope
- Radiochemical identity – confirms that the Ac-225 is in the desired chemical / biological form
- Radiochemical identity must be unambiguously established as part of structure characterization of radioactive drug substance
  - Assess possibility of establishing a non-radioactive reference standard using an element that has similar chemistry as Ac-225 (surrogate standard, e.g., Lanthanum etc.)
- Structure characterization – use a minimum of two orthogonal methods
- Batch release method – must be appropriately validated, including for specificity

Radiochemical Purity

- Percentage of Ac-225 activity in the desired chemical form
- Method that simply separates unbound Ac-225 from bound Ac-225 can not be assumed to be valid radiochemical purity determination method
- Besides unbound Ac-225, the method must be capable of separating ligand (e.g., peptide) related radioactive impurities
  - Ligand degradation should be evaluated during the stress stability studies
  - Consider using a surrogate reference standard (with fully characterized structure) to establish the chromatographic profile of the drug molecule.
- Recommend using a HPLC based method, or a combination of HPLC and TLC methods

Radionuclidic Impurities in Ac-225 Radiopharmaceuticals (Finish Drug Product)

- Include specifications for radionuclic purity
  - Acceptance criteria to at least one decimal point (e.g., NLT 99.5%)
  - Provide justification for the proposed limit (how was it derived?)
- Include limits for specified radionuclidic (radioisotopic) impurities
  - E.g., Ac-227
  - Each other radionuclide (based on production methods, as appropriate)
- Include validated analytical method(s)
  - Must be capable of quantitating the desired radionuclide and the undesired radionuclidic contaminants.

Analytical Methods – Detection of Ac-225

- Based on detection of gamma emission from Ac-225 decay products (primarily from Fr-221 and from Bi-213)
- For accurate results, Ac-225 and its decay products must be in a secular equilibrium, so that the gamma emission information can be extrapolated to Ac-225 activity
- Method description in submissions must include the hold periods (including how they were determined) for the drug product samples and during analysis
- Describe the method used for extrapolation of gamma emission data to the Ac-225 activity in analytical methods

Analytical Methods – Radioactivity Assay

- Must have test for assay
- Provide details of the method
- Describe how the accuracy and reliability of radioactive dose is assured
- Dose calibrator detects gamma emissions from Ac-225 decay products
  - How is that information translated to Ac-225 activity

Ac-225 – Radiolabeling Qualification

- Radiolabeling process should be validated
  - For generator produced Ac-225
  - For accelerator produced Ac-225
  - Use of highest radioactivity amount to be used during radiolabeling, containing maximum amount of impurity (e.g., Ac-227)
    - Accelerator product – much more Ac-227 atoms than Ac-225 atoms - generator and accelerator stoichiometry (ligand / radioactivity) may be different
  - Use of fresh and aged Ac-225 radiochemical
  - Well defined hold periods for Ac-225 radiochemical and Ac-225 radiolabeled product (as appropriate)
- Provide process qualification and the batch data in the submission

Ac-225 Radionuclide Reference Standard

- Need NIST reference standard
- To establish dose calibrator setting using official standard
  - Must have for commercial products
  - Assures trust that the administered dose is accurately measured
- Recommend - radiopharmaceutical manufacturer coordinate with NIST to develop the *SRM* in a timely manner

SUMMARY

- Submission of CMC information
- Controlling and reporting of Ac-227 radionuclide Impurities
- Quality control considerations for Ac-225 radiopharmaceuticals
- Radiolabeling process qualification
- Reference standard considerations

Thank You

Isotope Program
U.S. Department of Energy

High Energy Accelerator Production of Actinium-225 to meet Clinical Demand

FDA-NRC Workshop: Enhancing Development of Targeted Alpha Emitting Radiopharmaceutical, Special Session on Actinium-225

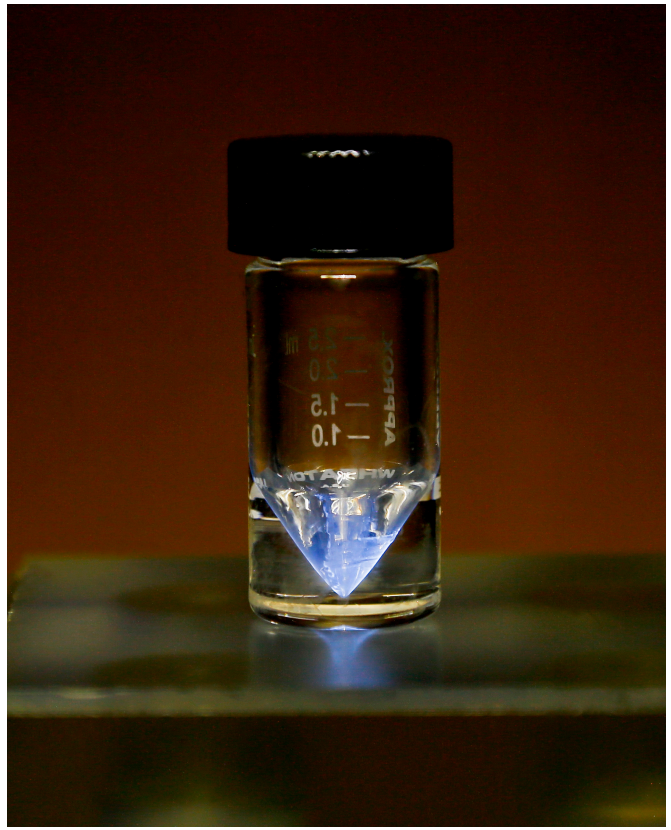
Cathy S. Cutler, Brookhaven National Laboratory

Dan Stracener, Oak Ridge National Laboratory, Project Manager, U.S. DOE Tri-Lab

Brookhaven National Laboratory
OAK RIDGE National Laboratory
Los Alamos NATIONAL LABORATORY
NIDC NATIONAL ISOTOPE DEVELOPMENT CENTER
MANAGED BY THE U.S. DEPARTMENT OF ENERGY ISOTOPE PROGRAM
U.S. DEPARTMENT OF ENERGY

Agenda

- A brief perspective on supply/demand for ^{225}Ac
- High-energy accelerator production of ^{225}Ac (with ^{227}Ac co-product) for a robust consistent supply
- Status of Drug Master File development, FDA interactions and licensing issues
- Improvements and alternate production routes being pursued



ORNL ^{225}Ac Finished Product

Alpha Therapeutic Agents

- Alpha Emitters
  - Ability to deliver target-specific radiation dose due to short & well-defined track length (<100 µm)
  - High linear energy transfer (LET) properties of alpha can be therapeutically effective in cells with low sensitivity to low-LET radiation (Quality factor = 5)
  - Also effective against dormant tumor cells in G_o phase
  - Cytotoxicity at both high and low-dose rates
  - Works in hypoxic tissues
  - Overcome required resistance
  - ***Limited use due to availability, complexation chemistry needs development, requires specialized facilities for handling***

Actinium-225 Production

- Th-229/Ac-225 generator
  - Advantage – free of other Ac isotopes
  - Disadvantages- limited Th-229; limited Ac-225
- Accelerator Produced Ac-225
  - Advantage – can produce large amounts reliably year around
  - Disadvantage – contains Ac-227 ($t_{1/2}$ = 21.8 yr) impurity
- Other routes are being pursued

What is required?

- Sufficient year-round supply
- Robust consistent supply
- Established Specifications
- Documented GMP production

^{225}Ac Supply & Demand

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

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

^{225}Ac: 2-5 μCi per patient kg

(160-640 μCi/patient)

^{213}Bi: 1 mCi per patient kg

(Optimum generator loading estimated at 100-150 mCi ^{225}Ac)

Projection of ^{225}Ac demand assuming multiple, approved ^{225}Ac and ^{213}Bi drugs and robust clinical R&D programs could be in the hundreds of Ci/year*

*International Atomic Energy Agency. Technical Meeting Report "Alpha Emitting Radionuclides and Radiopharmaceuticals for Therapy" IAEA Headquarters Vienna, Austria, June **2013**

And

International Atomic Energy Agency. Technical Meeting Report "Supply of Actinium-225" IAEA Headquarters Vienna, Austria, October **2018**

US DOE Offices of Nuclear Energy and Nuclear Physics "2008 Workshop on The Nation's Needs for Isotopes: Present and Future" Rockville, MD August **2008

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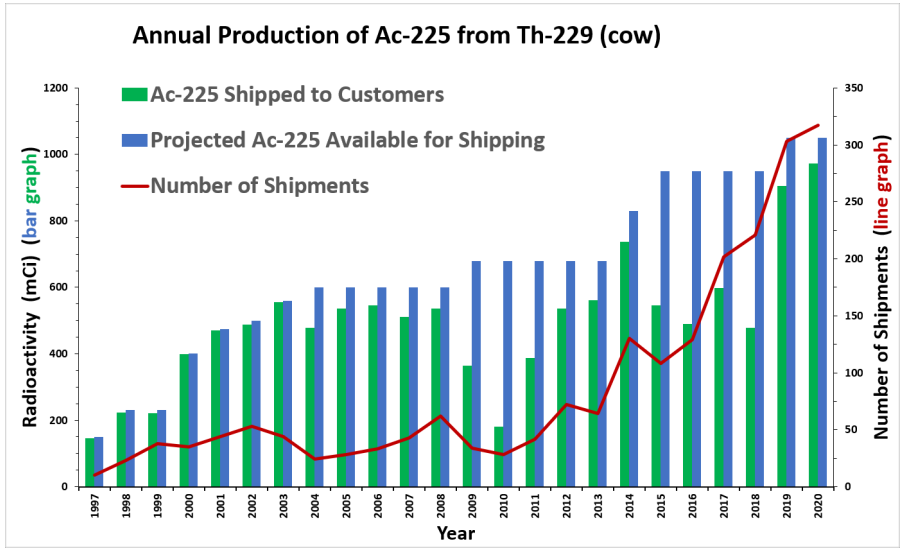
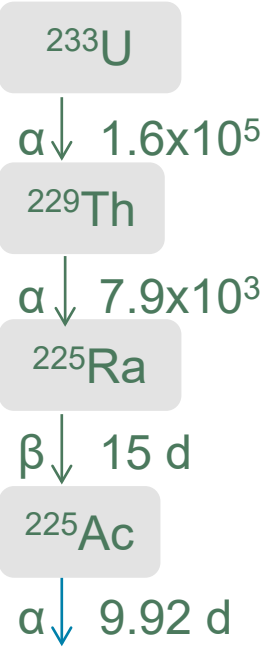
Actinium-225 Production at ORNL

- 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 campaigns are performed per year, with weekly customer shipments

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





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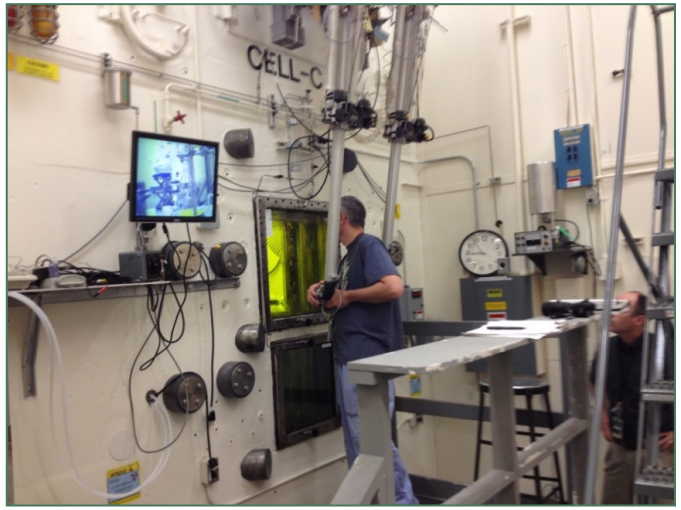
Basis of the Tri-Lab Effort:

Leveraging Unique Isotope Program Facilities, Capabilities, and Expertise to Address ^{225}Ac Supply



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

LANL Isotope Production Facility (IPF) at LANSCE; 100 MeV incident energy up to 275 μA 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

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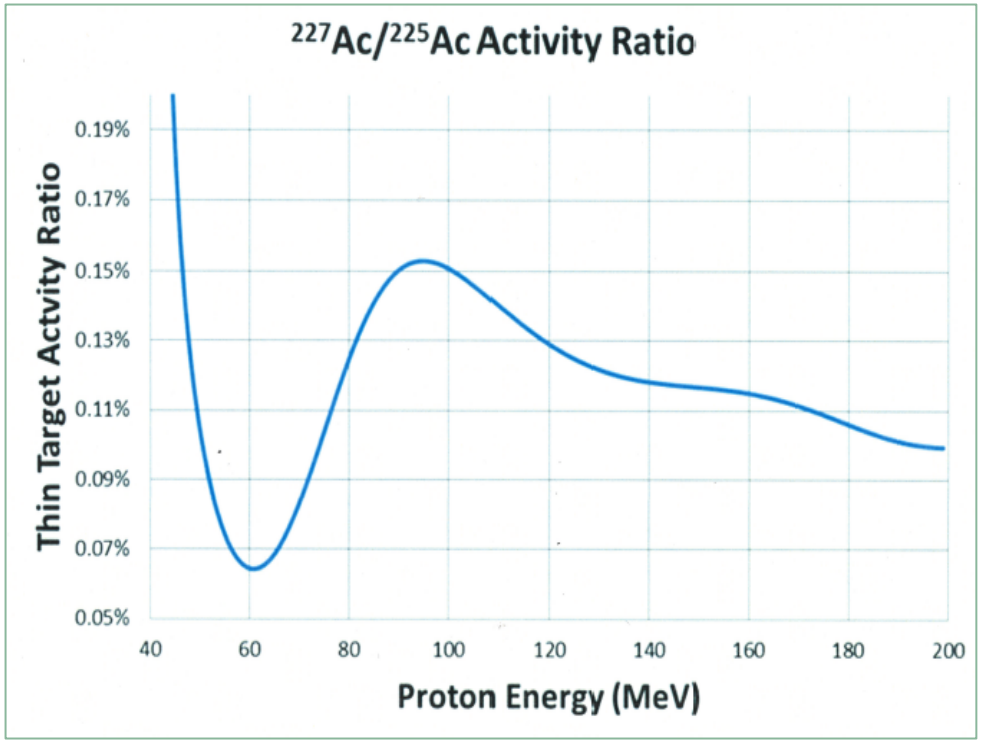
Accelerator Product and ^{227}Ac

Production of ^{225}Ac via high-energy accelerator results in the co-production of ^{227}Ac ($t_{1/2}$ = 21.8 y)

Ratio improves at higher proton energy, but degrades with longer irradiation time – we understand this ratio at an exquisite level of detail

^{227}Ac co-product creates a unique set of challenges – perceptions and facility licensing (NRC), patient waste disposition

These challenges are not unique and have been addressed for other isotope products



Instantaneous activity ratio of ^{227}Ac to ^{225}Ac for a thin Th target as a function of proton beam energy. Note that beam energy range captures current capabilities at BNL's BLIP and LANL's IPF facilities.

Specifications of Accelerator Produced Ac-225

- Long lived radionuclidic impurity →Ac-227 ($t_{½}$ = 21.8 yr)
- Tri-lab effort is well versed in how to keep the Ac-227 to a minimal through control of irradiation parameters
  - Content of Ac-227 remains the same, however the ratio of Ac-227:Ac-225 increases during the shelf life of the 225Ac
- For Ac-225 radiochemical (e.g., $^{225}Ac(NO_3)_3$)
  - Established specifications, including an acceptable limit for Ac-227 impurity of 2%
  - Monitored routinely to ensure levels are maintained and consistent

FDA and End-user Interactions

Accelerator-produced ^{225}Ac for direct labeling and ^{213}Bi generator application viewed by FDA as an Active Pharmaceutical Ingredient (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 prepare their Investigational New Drug Applications (IND)

Accelerator-produced ^{225}Ac Drug Master File submitted at the end of CY19

We will continue to work with IP, NIDC and the ^{225}Ac user community to address issues and concerns

Cathy S. Cutler (BNL) leads a panel discussion at the ^{225}Ac User Meeting hosted by NIDC at the 2019 SNMMI meeting

J. Norenberg
UNM

R. Abergel
LBNL

D. Ludwig
Actinium Pharmaceuticals

R. Hobbs
Johns Hopkins

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Addressing the Perception of ^{227}Ac Content on Dosimetry/Toxicity

Ekaterina Dadachova - Albert Einstein College of Medicine/U. of Saskatchewan Feedback

RESEARCH ARTICLE

***In vivo* Evaluation of Free and Chelated Accelerator-produced Actinium-225 - Radiation Dosimetry and Toxicity Results**

Zewei Jiang[1], Ekaterina Revskaya[1], Darrell R. Fisher[2] and Ekaterina Dadachova[3,*]

[1]Department of Radiology, Albert Einstein College of Medicine, Bronx, NY, 10461 USA; [2]Versant Medical Physics and Radiation Safety, Richland, WA, USA; [3]University of Saskatchewan, Saskatoon, SK, S7N 5E5, Canada

2018 special issue of Current Radiopharmaceuticals

"In conclusion, our data demonstrates that accelerator-produced ^{225}Ac is suitable for the development of pre-clinical and clinical targeted radionuclide therapy"

Jeffrey Norenberg - UNM Feedback – Dosimetry Calculations (injected as acetate)

Region	^{225}Ac (mSv/MBq)	^{227}Ac (mSv/MBq)
Adrenals	1.96E-02	2.21E-03
Brain	9.42E-03	3.72E-03
Breasts	4.14E-03	6.27E-04
Gallbladder Wall	2.56E-02	1.94E-03
LLI Wall	2.92E-01	3.27E-02
Small Intestine	3.63E-01	4.87E-02
Stomach Wall	5.28E-01	8.75E-02
ULI Wall	2.66E-01	2.90E-02
Heart Wall	3.14E+01	8.66E-01
Kidneys	1.74E+02	6.98E+00
Liver	5.21E+02	1.72E+01
Lungs	1.05E-02	1.31E-03
Muscle	4.11E+00	1.10E-01

Region	^{225}Ac (mSv/MBq)	^{227}Ac (mSv/MBq)
Ovaries	7.34E-03	7.42E-04
Pancreas	1.53E+01	4.30E-01
Red Marrow	2.93E+02	4.76E+00
Osteogenic Cells	6.71E+03	5.84E+01
Skin	4.86E-03	1.44E-03
Spleen	8.09E+01	3.57E+00
Testes	7.21E+00	1.55E+00
Thymus	5.41E-03	7.22E-04
Thyroid	6.23E-03	8.09E-04
Urinary Bladder Wall	2.26E+01	1.79E-02
Uterus	5.72E-03	4.09E-04
Total Body	6.13E+01	9.76E+00

***Note**: dosimetry results based on data collected at 100 days after injection*

Region	^{225}Ac (mSv/MBq)	^{227}Ac (mSv/MBq)
Effective Dose	132.00	2.40

The differences between the cow and accelerator materials are "clinically insignificant"

UNM Comprehensive Cancer Center planning for Phase 1 Trial of Intravenous ^{225}Ac/^{213}Bi-DOTATOC for Somatostatin-Receptor Expressing Malignancies using accelerator-produced ^{225}Ac

General Accelerator-Produced ^{225}Ac Product Conclusions

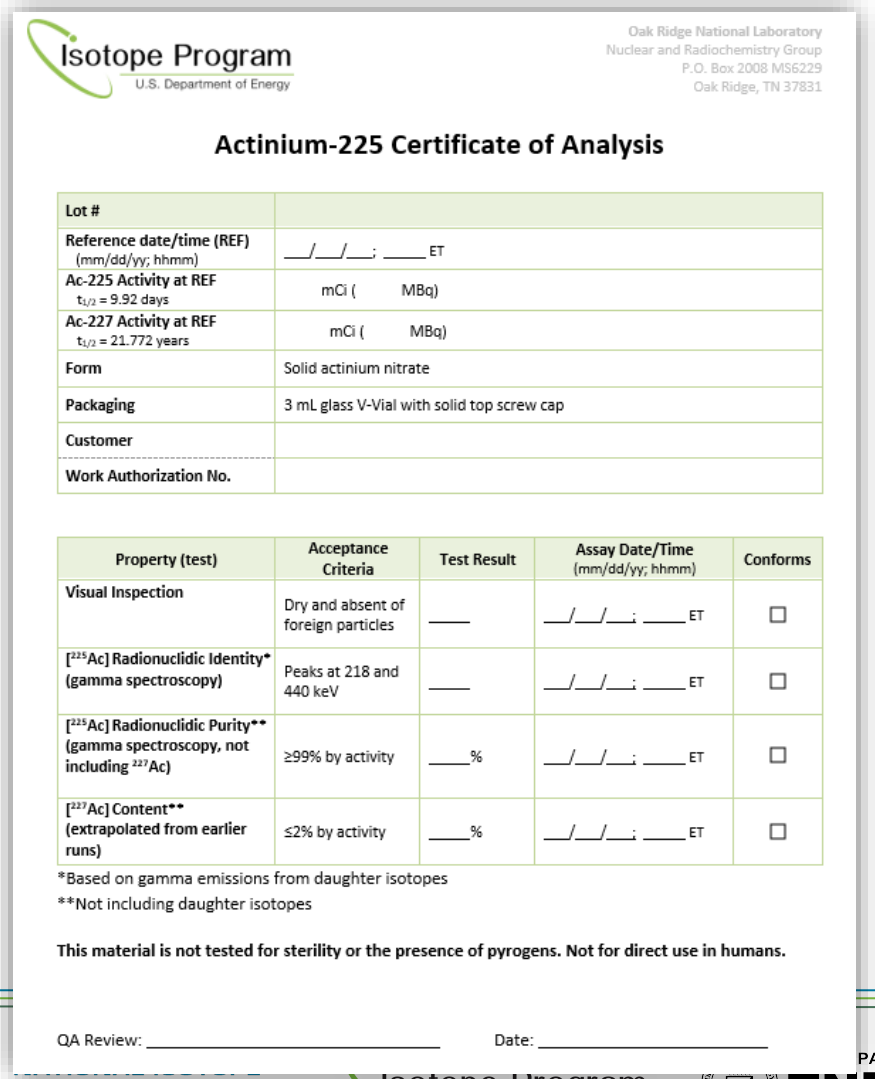
- **Accelerator-produced ^{225}Ac performs similar to ^{229}Th-derived ^{225}Ac**
  - direct labeling efficiencies are comparable
  - ^{213}Bi generator performance is the same
  - the impact of ^{227}Ac content on dosimetry has been demonstrated to be small
- **Challenges remain with respect to the 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)

Considerations for DMF Content- Accelerator Produced Radioisotope

- Cyclotron/linear accelerator used
- Define starting material – propose adequate controls for the quality of the starting material.
- Target- target fabrication, enrichment, specifications
- Irradiation parameters
- Manufacture – facility and process
- Composition of final radioisotope solution, including the chemical form produced
- Specifications for final product
  - Appearance, radiochemical identity and purity, radionuclidic identity and purity, radionuclide concentration, chemical purity, pH, microbiological attributes, etc.
- Data for three separate irradiation and purifications runs
- Container closure
- Stability

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



Isotope Program
U.S. Department of Energy

Oak Ridge National Laboratory
Nuclear and Radiochemistry Group
P.O. Box 2008 MS6229
Oak Ridge, TN 37831

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: _____

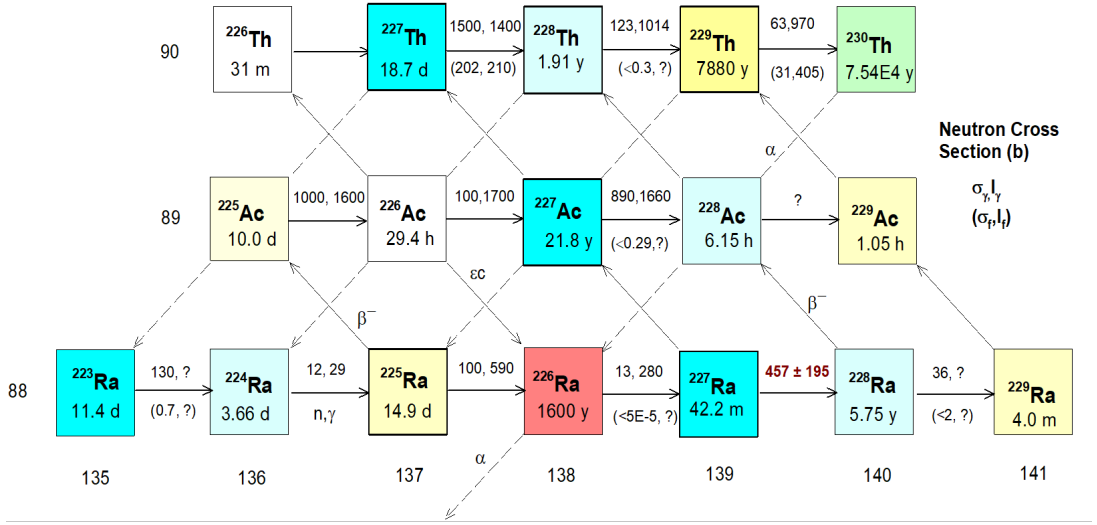
Current CoA for Accelerator Material

Continuing Efforts to Increase Availability of ^{225}Ac

- Increasing frequency and size of batches
- Addressing technical and logistical challenges while ensuring product is consistent and reliable
- Continued improvement of shipping capabilities and performance
- Additional facility investments in progress to enable more frequent and larger batch sizes
- Building in processing capability redundancy to enhance reliability
- Continued focus on stakeholder and customer relations

Alternative Routes of Production Under Investigation

- ANL electron linac production route
  - $^{226}Ra(\gamma,n)^{225}Ra \rightarrow ^{225}Ac$
- BNL low energy cyclotron route
  - $^{226}Ra(p,2n)^{225}Ac$
- ORNL neutron production route
  - $^{226}Ra(3n,\gamma)^{229}Ra \rightarrow ^{229}Ac \rightarrow ^{229}Th$



S. Hogle et al., *Reactor Production of Thorium-229*, Appl. Radiat. Isot. 114, 19 (2016)

Summary

- 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 440 mCi of accelerator produced ^{225}Ac to evaluators
- 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 – but challenges with perception and regulatory compliance remain; we have a well-defined forward path to address these challenges with DOE
- Continuing to scale up availability of this important isotope

Thank You!

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