U.S. DEPARTMENT OF ENERGY

OFFICE OF SCIENCE

DOE Isotope Program Production of Radioisotopes for Medical Applications
October 14, 2020

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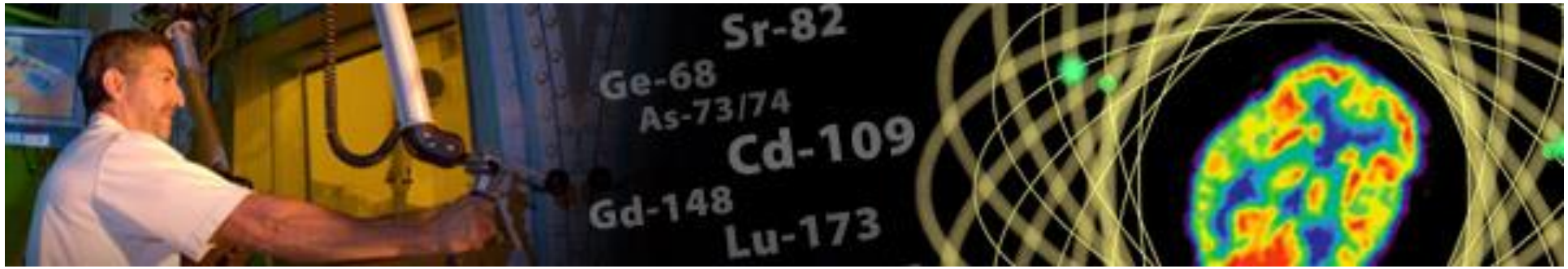
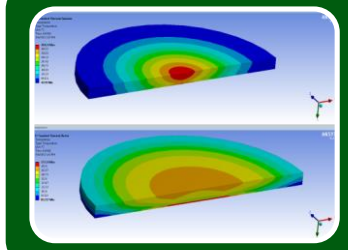
Office of Isotope R&D and Production, Office of Science, U.S. Department of Energy



DOE Isotope Program Mission

Produce and/or distribute radioactive and stable isotopes that are in short supply; includes by-products, surplus materials and related isotope services

Maintain the infrastructure required to produce and supply priority isotope products and related service



Conduct R&D on new and improved isotope production and processing techniques which can make available priority isotopes for research and application. Develop workforce.

Reduce U.S. dependency on foreign supply

Isotope Program
U.S. Department of Energy

Isotope Program Authority, Resources, Goals

- Isotope Program in DOE has sole authority to produce isotopes for sale and distribution – labs may not embark on isotope production on their own.

- Public Law 101-101 (1990), as modified by Public Law 103-316 (1995) created the Isotope Production and Distribution Program Fund (called a revolving fund) and allows prices charged to be based on costs of production, market value, U.S. research needs and other factors.
  - **Commercial isotopes at full-cost recovery; research isotopes at reduced prices.**

- Anticipate isotope demand for federal missions, research and U.S. industry
  - **Increase availability of isotopes in short supply**
  - **Mitigate potential shortages**
  - **Develop new production and processing techniques of isotopes currently unavailable**
  - **Reduce U.S. dependencies on foreign supply**

- **DOE IP not responsible for Mo-99 (NNSA), Pu-238 (NE) and SNM for weapons (NNSA)**

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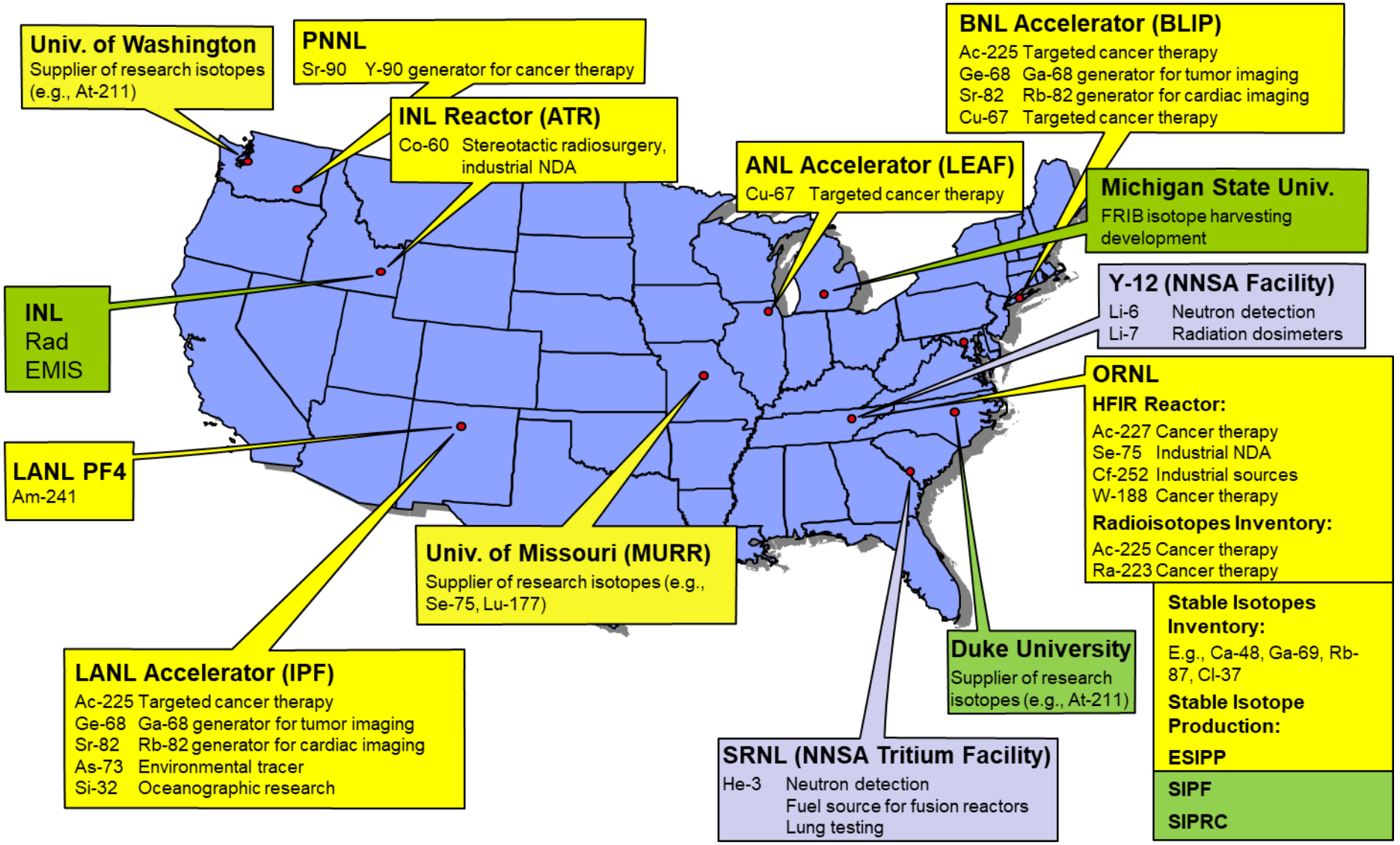
DOE Isotope Program Production Sites



National Isotope Development Center

- The Department of Energy NIDC (includes the Isotope Business Office located at Oak Ridge National Laboratory) coordinates the distribution of all DOE isotope products and services available from DOE facilities.
- All contractual discussions with customers.
- Responsibilities in transportation, QA, public relations (website, newsletter, booth), cross-cutting technical topics, marketing strategy and assessments.
- Customers maintain technical discussions with sites.
- **www.isotopes.gov**

- Quality Assurance and Regulatory Affairs Manager: Jennifer Cross

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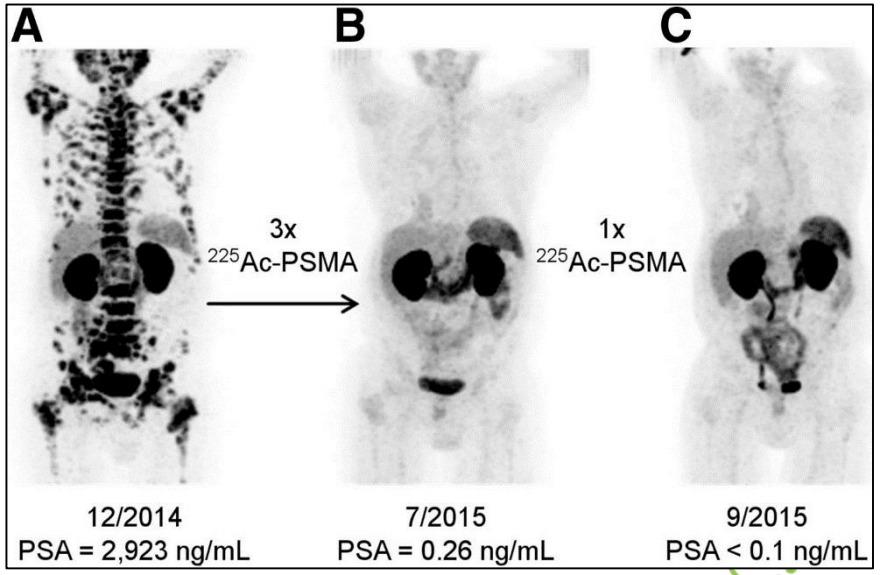
Alpha Emitters of Interest for Therapy

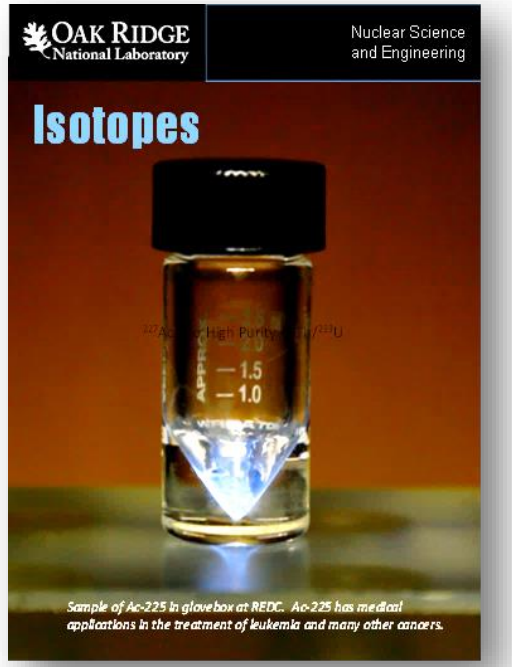
Radionuclide	Half-life
^{225}Ac	10 d
^{211}At	7.2 h
^{212}Bi	60 m
^{213}Bi	46 m
^{212}Pb	10.6 h
^{223}Ra	11.43 d
^{226}Th	31 m
^{227}Th	18.7 d

- For the past ten years, alpha emitters have been the highest priority for the DOE Isotope Program.
- The DOE Isotope Program is producing or developing production of all of these isotopes.

Actinium-225 Production Summary

- High priority for NIH for decades
- Since 2009, DOE IP is world leader in R&D
- ORNL extracts Ac-225 from Th-229 recovered from U-233: 1,200 mCi per year - entire U.S. supply and more than half the worldwide supply.
- Supply cannot support adequate clinical trials or therapy
- IP has developed accelerator production route- full scale production can meet clinical and therapy demands
- Accelerator production started 2017





- Completed Stage 1: 5-50 mCi/batch
- Stage 2: 10-100mCi/B ; already 150 mCi/batch
- Stage 3: 100-1000 mCi/batch
- IP strategy includes other production routes- reactor production of Th-229, extraction of Th-229 from legacy U-233, low-energy cyclotron production, and electron accelerator production demand.
- PRODUCT AVAILABLE NOW

^{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**

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

Various $^{225}Ac/^{229}Th$ Production Routes

Facility	Nuclear Reaction
Reactor (thermal neutrons)	$^{226}Ra(3n,g)^{229}Ra \rightarrow ^{229}Ac \rightarrow ^{229}Th$ (plus ^{228}Ra target)
Accelerator (electrons)	$^{226}Ra(g,n)^{225}Ra \rightarrow ^{225}Ac$
Accelerator (low energy particles)	$^{226}Ra(p,2n)^{225}Ac$ $^{226}Ra(a,n)^{229}Th$ $^{226}Ra(p,pn)^{225}Ra$ $^{232}Th(p,x)^{229}Th$
Accelerator (high energy particles)	**$^{232}Th(p,x)^{225}Ac$** $^{232}Th(p,x)^{225}Ra \rightarrow ^{225}Ac$
Accelerator (high energy neutrons)	$^{226}Ra(n,2n)^{225}Ra$
Hot Cell Facility (^{233}U processing)	^{229}Th decay to ^{225}Ac

Accelerator Production via $^{232}Th(p,x)^{225}Ac$

Initial R&D Promised Significant Impact

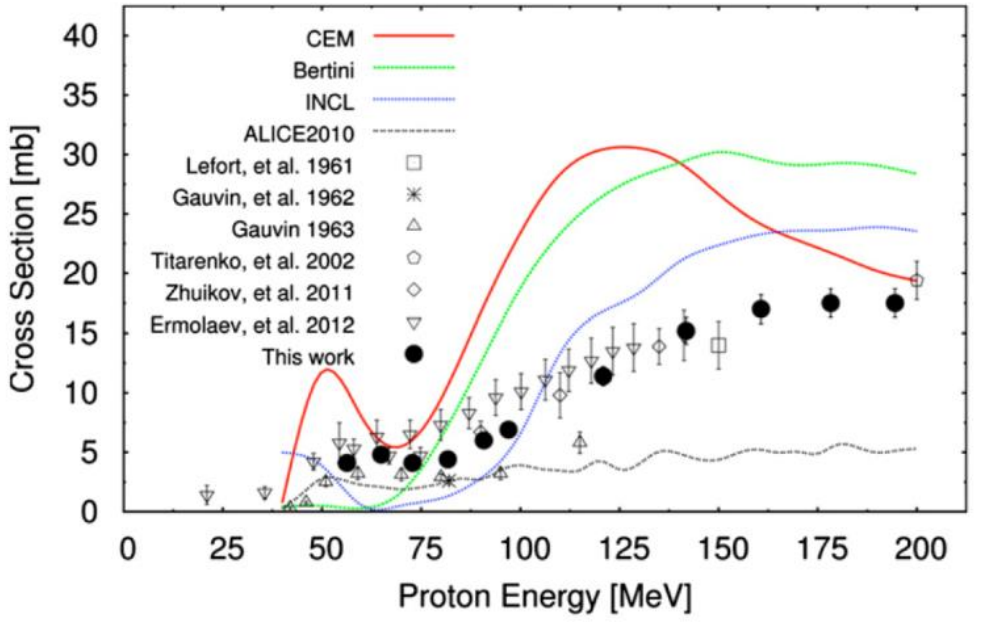


Fig. 1. Experimental and theoretical cumulative cross sections for the formation of ^{225}Ac by the proton bombardment of thorium.

Facility	Anticipated Single Target Ac-225 Yields (10 day irradiation)
LANL (100 MeV, 250-450 μA)	1.3-2.3* Ci
BNL (200 MeV, 165 μA)	2.2 Ci

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

*J.W. Weidner et al. Appl. Radiat. Isot. 70 (**2012**) 2602*
*J.W. Engle et. al. Phys. Rev. C. 88 (**2013**) 014604*
*J.W. Engle et. al. Radiochim. Acta 102 (**2014**) 569*
*J.R. Griswold et. al. Appl. Radiat. Isot. 118 (**2016**) 366*

Facility investments at IPF and BLIP have increased our projected production capacity

Actinium-225 Production 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 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

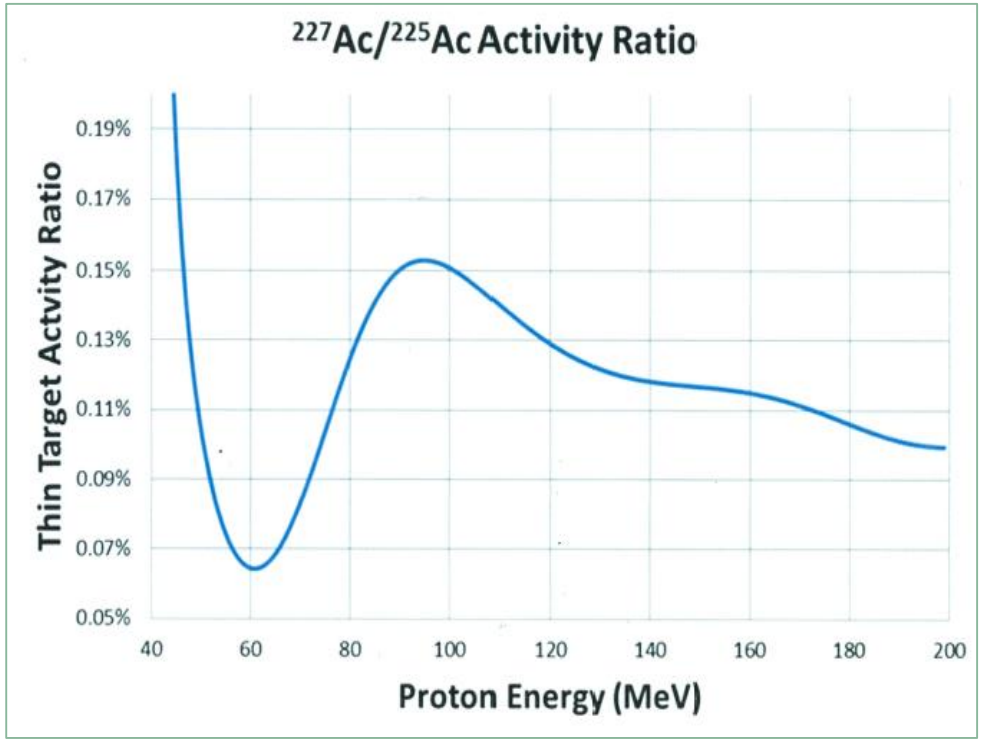
Accelerator Product and ^{227}Ac

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 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.

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)

Actinium-225 DMF/FDA Updates

- Drug Master File was submitted in December 2019 for the accelerator Ac-225
- DMF filings are anticipated for:
  - CY2020 (^{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 helping address issues associated with their use

New Radionuclide Development General Issues

- Licensing
  - Financial assurance requirements for isotopes with half-lives >120 days
  - NRC Petition for Rulemaking NRC-2017-0159 (Naturally-Occurring and Accelerator-Produced Radioactive Materials) seeks to update 10 CFR 30 Appendix B table of nuclides
- Patient waste/Disposal pathways
  - Drug developer concerns on whether these will be large hurdles for products, what the requirements/options are, etc.
- Impurities
  - How will long-lived impurities be treated by FDA/NRC? What levels will be deemed acceptable? Who is responsible for determining this? What preclinical testing is needed to assess effects of long-lived impurities?
- cGMP
  - When is a 'GMP' radionuclide or generator required? Is a graded approach to GMP expected during trials for radionuclides? At what point does the FDA recommend submitting a DMF? What/how much information should be provided to IND holders before that point?
- DOE IP is working with FDA and NRC to address these issues and will join drug developers in discussions with FDA and NRC if requested to address drug-specific issues

Long-lived nuclides not listed in 10 CFR 30 Appendix B listed in docket comments

Actinium-227
Aluminum-26
Cadmium-109
Cobalt-57
Germanium-68
Lutetium-177m
Rhenium-184m
Silicon-32
Sodium-22
Strontium-90 (this was not called out specifically; Y-90 was mentioned)
Thorium-228
Titanium-44

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 325 mCi of accelerator produced ^{225}Ac to evaluators
  - We are working with companies and research hospitals in preparation to support Phase I trials - DMF will be submitted late this calendar year
  - ^{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
- DOE IP is working with FDA and NRC to facilitate the use of novel radioisotopes and will join drug developers in discussions with FDA and NRC on drug-specific issues
  - E.g., dosimetry, toxicology, biodistribution must be addressed on a drug-by-drug basis and discussions with the FDA must be initiated by the drug developers

Development of Physical Standards for Novel Radionuclides: Experience with Alpha-Emitters

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Nuclear Medicine Project, Radiation Physics Laboratory

denis.bergeron@nist.gov

14 October 2020

National Institute of Standards and Technology
U.S. Department of Commerce

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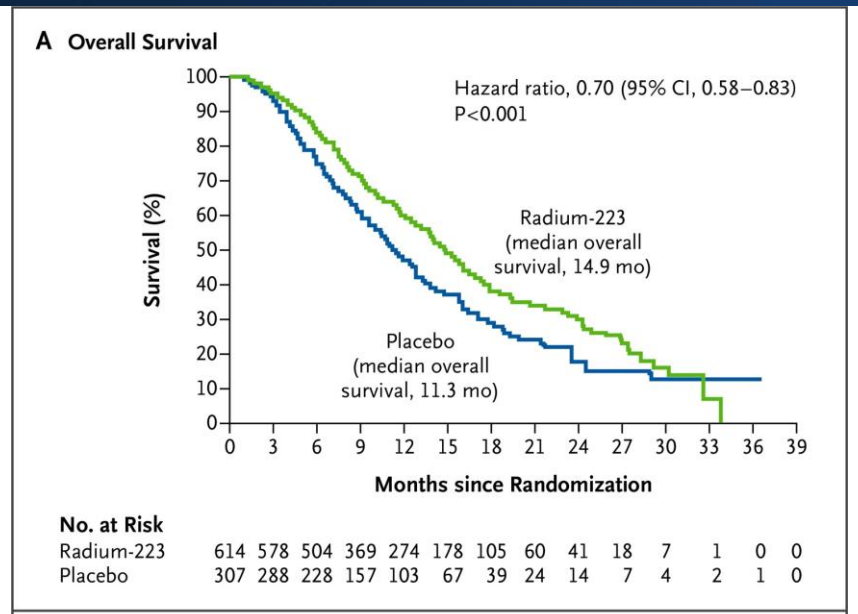
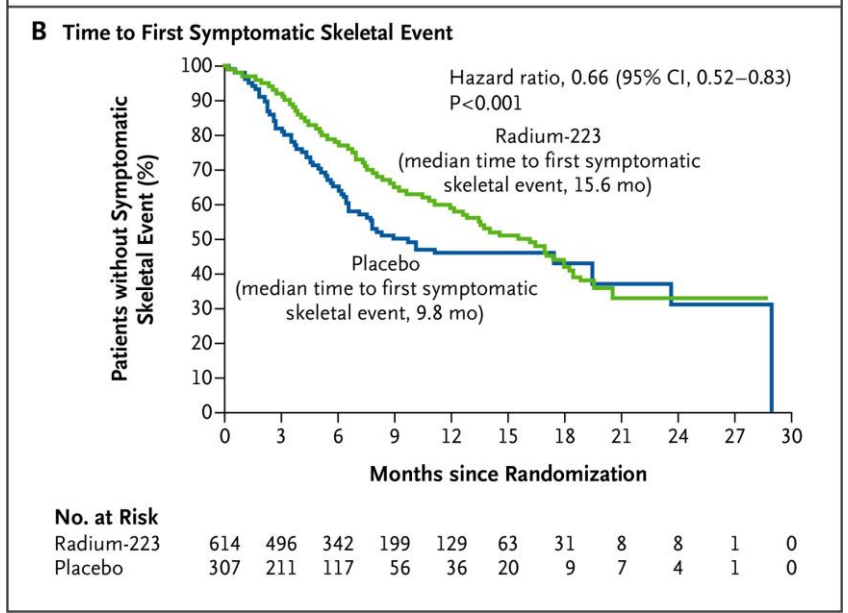
PHYSICAL MEASUREMENT LABORATORY

NIST role in the ^{223}Ra story





Everyone knows $^{223}RaCl_2$ as a "first-in-class" alpha-therapeutic

Algeta approached NIST in 2005, at the direction of FDA, to develop measurement standards

NIST developed a calibration capability and reported settings for radionuclide calibrators

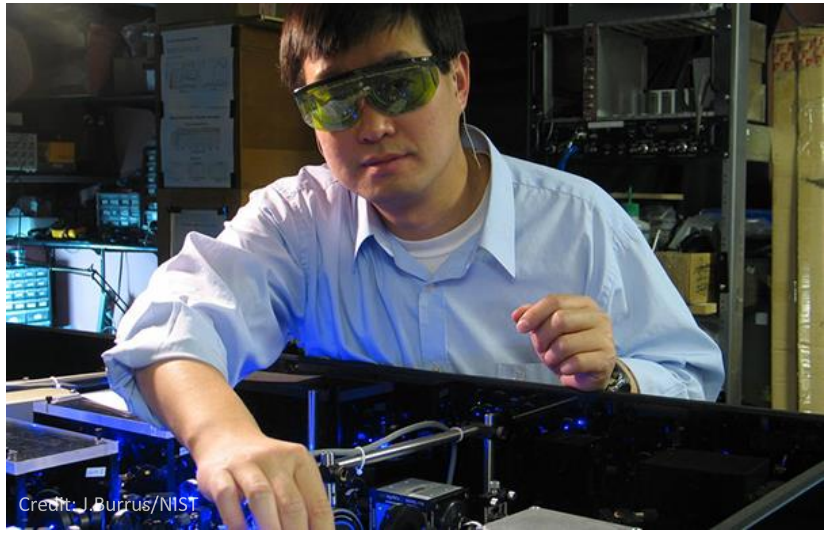
Bayer participates in the NIST Measurement Assurance Program and shipments of Xofigo to new sites include a NIST-traceable calibration source

NIST does not recommend or endorse commercial products.

Parker et al., NEJM 369, 213 (2013).

NIST Mission

To promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology in ways that enhance economic security and improve our quality of life

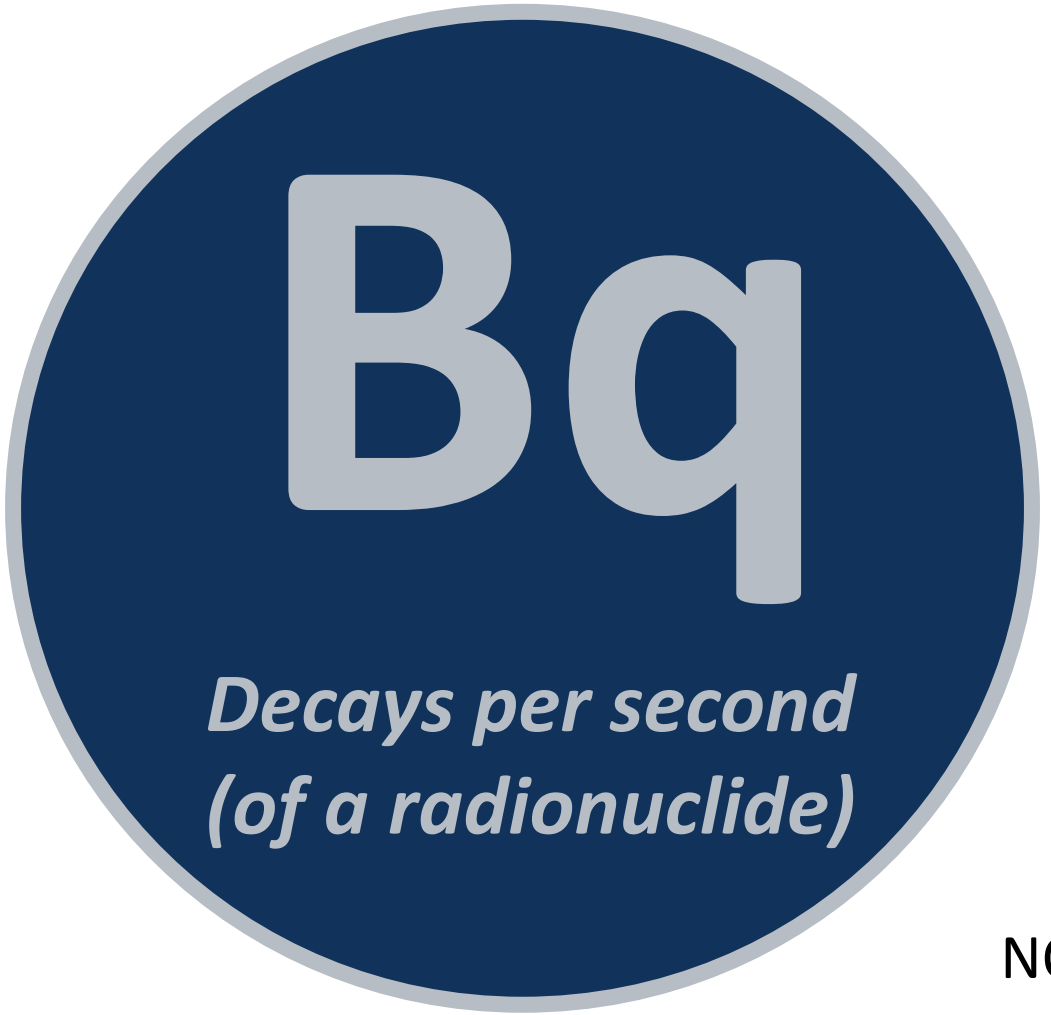


Measurements essential to commerce, trade, and innovation

Federal role established in the U.S. Constitution

Article I, section 8 gives Congress the power to “fix the **standard** of weights and **measurement**.”

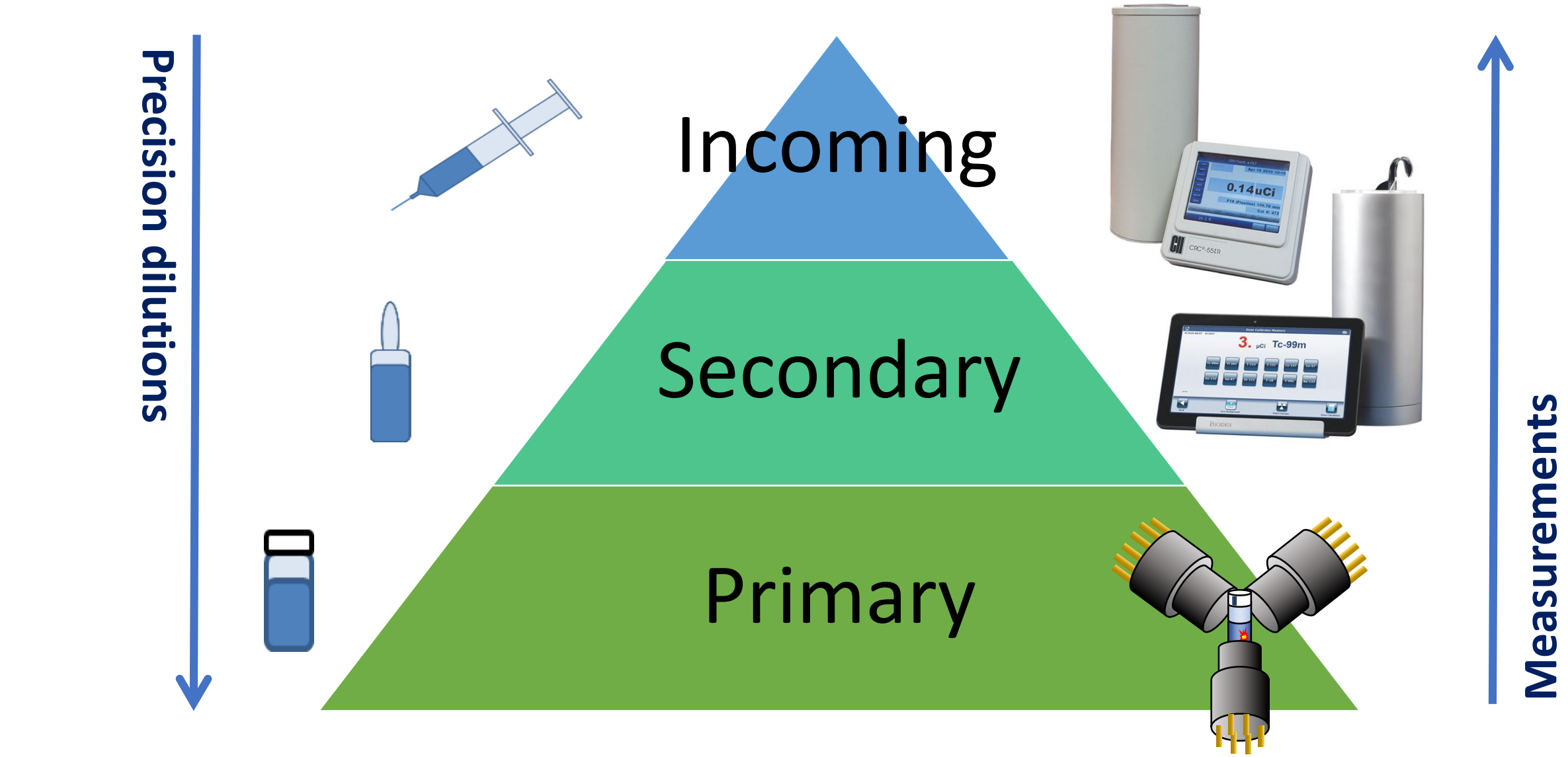
NIST defines the becquerel



- **Physical standards are the basis for activity calibrations**
- **Standardizations are based on measurements with ‘primary’ methods**
  - Primary means internally consistent, self-calibrating

NOTE: 1 mCi = 37 MBq

Calibrations require precise links



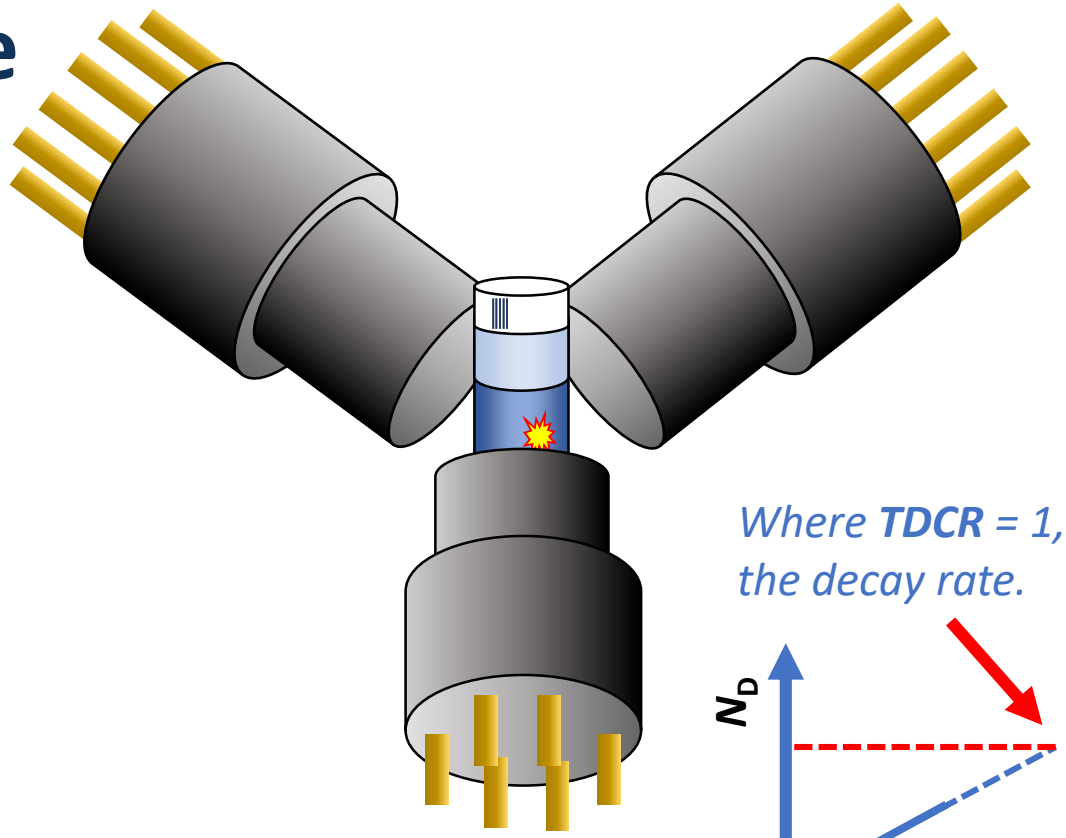
TDCR is well-suited for alpha-emitters

Triple-to-double Coincidence Ratio (TDCR) counting

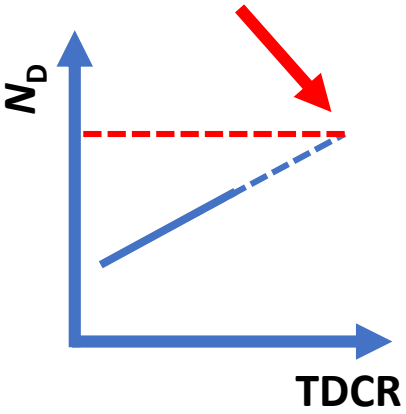
- Liquid scintillation counting
- 3-detector system where double and triple coincidence events are counted

$$TDCR = N_T/N_D = \varepsilon_T/\varepsilon_D$$

- Vary efficiency
- **As $\varepsilon_T/\varepsilon_D \rightarrow 1$, N_D (and N_T) $\rightarrow N$**
  - In practice, a bit more complicated, but we have good models!



*Where **TDCR** = 1, N_D is the decay rate.*



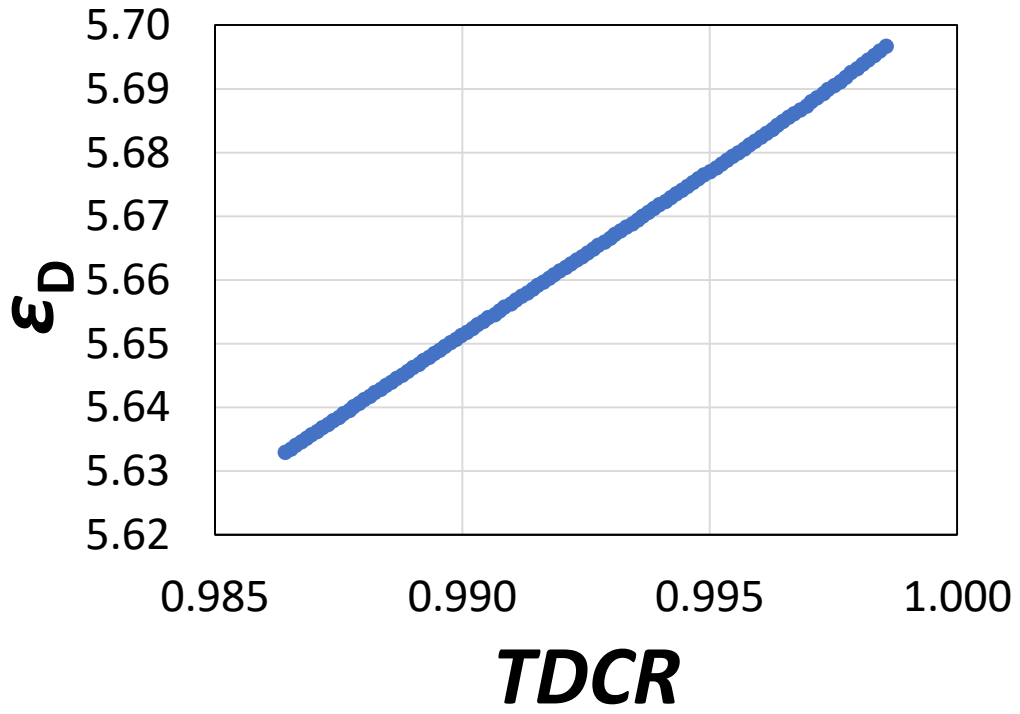
LS counting efficiencies from decay data

Triple-to-double Coincidence Ratio (TDCR) counting

$$TDCR = N_T/N_D = \varepsilon_T/\varepsilon_D$$

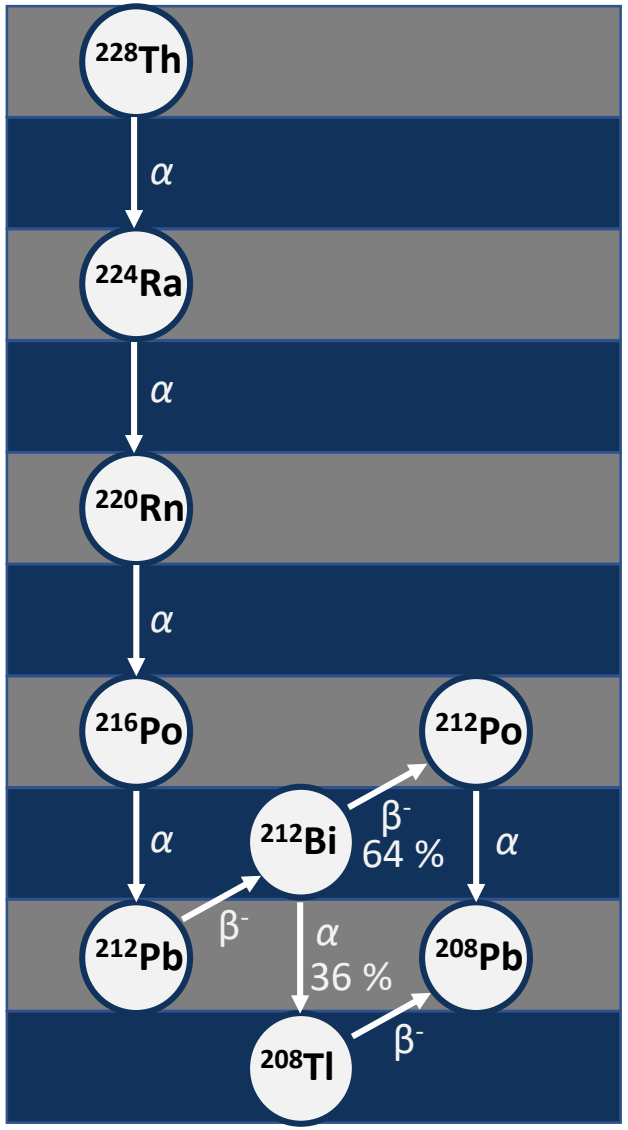
The MICELLE2 model* uses a Monte Carlo approach to calculate ε_T and ε_D for β^- decay branches

We get about 5.65 counts per ^{224}Ra decay



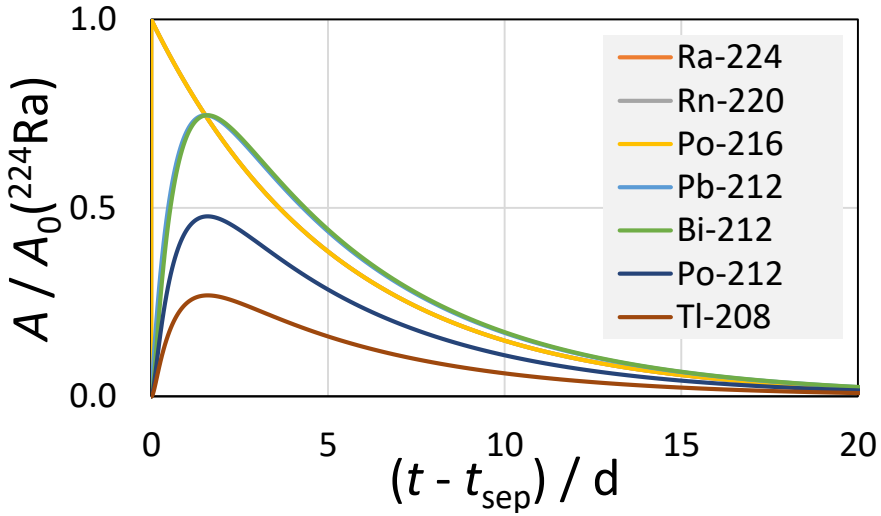
*Kossert & Grau Carles, Appl. Radiat. Isotop. 68, 1482-1488 (2010).

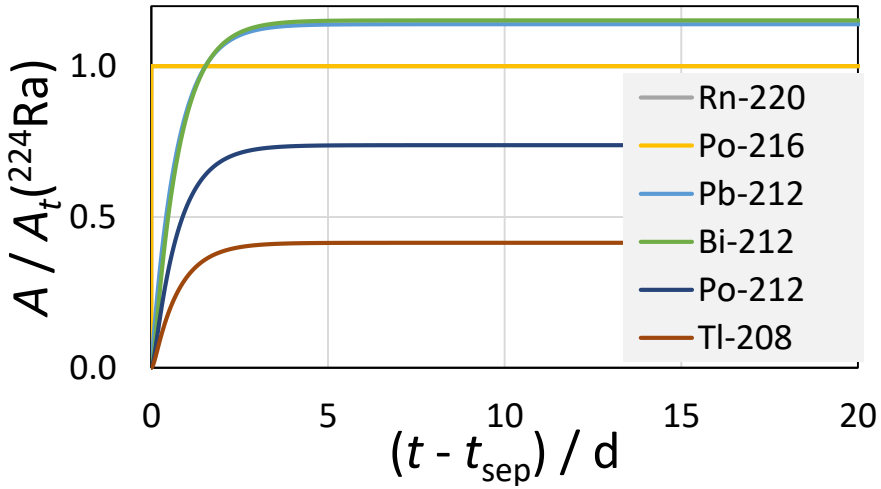
Decay chain requires attention



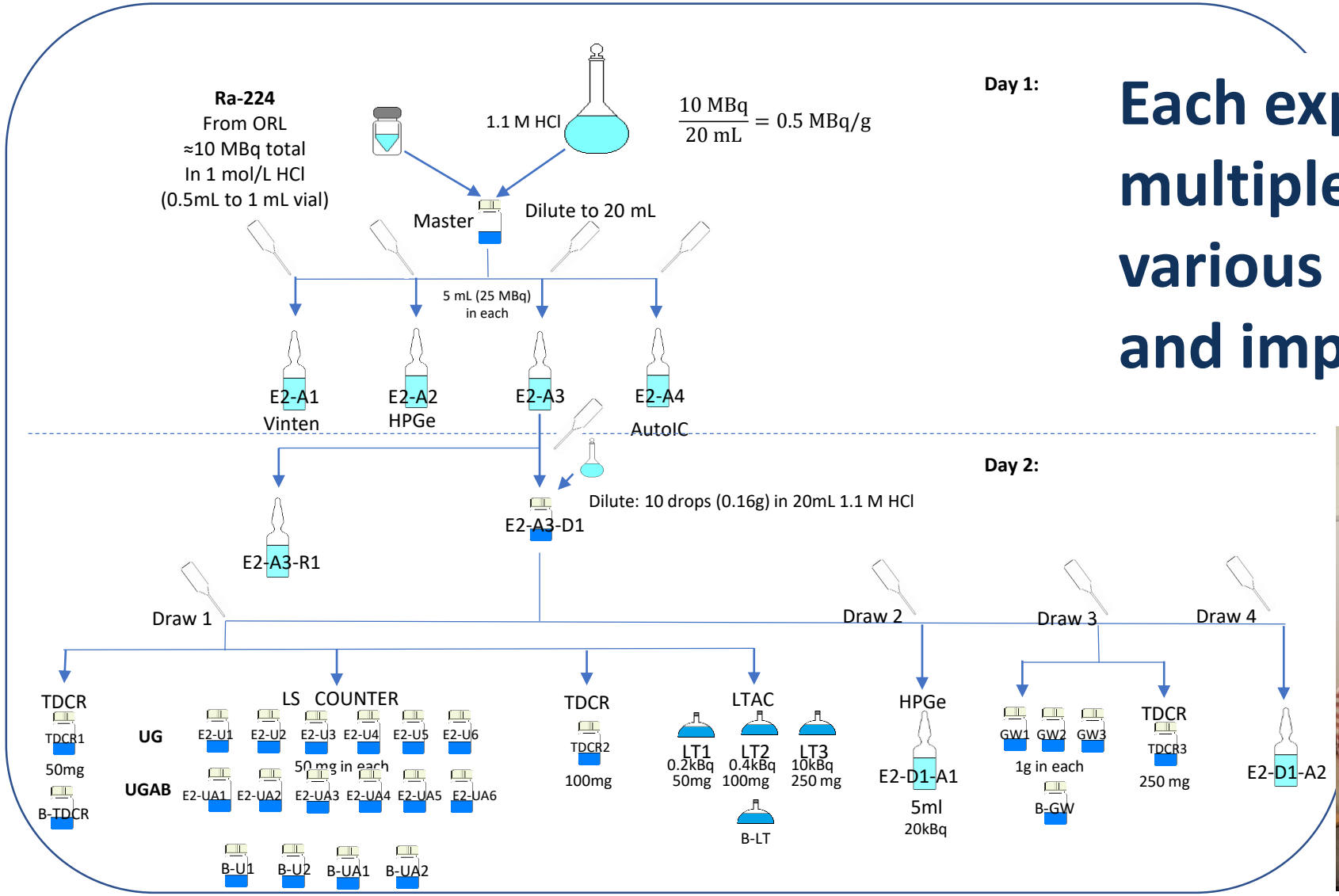
	$T_{1/2}$	$A/A_{Ra\text{-}224}$
^{224}Ra	3.631(2) d	1
^{220}Rn	55.8(3) s	1.000178(1)
^{216}Po	0.148(4) s	1.000178(1)
^{212}Pb	10.64(1) h	1.13928(15)
^{212}Bi	60.54(6) min	1.15263(15)
^{212}Po	300(2) ns	0.7385(11)
^{208}Tl	3.058(6) min	0.4144(20)

Complex decay chain requires about 6 d to reach equilibrium.

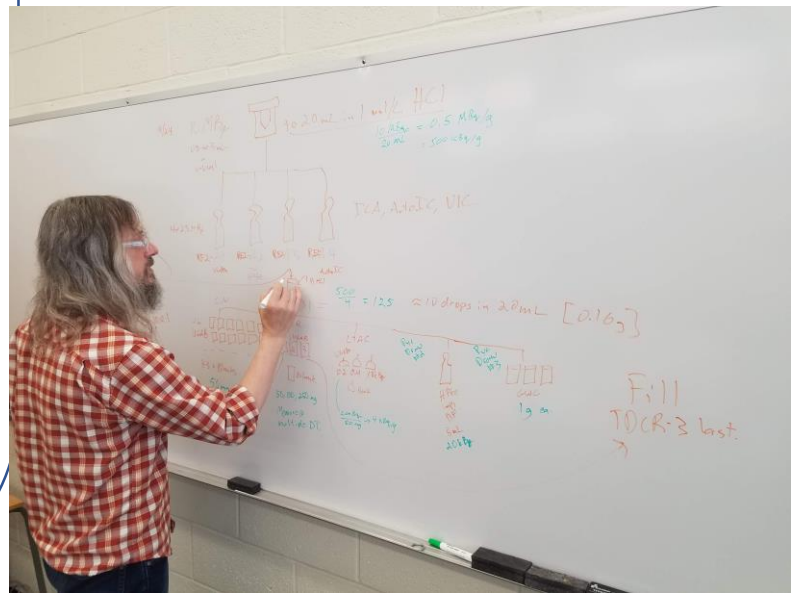




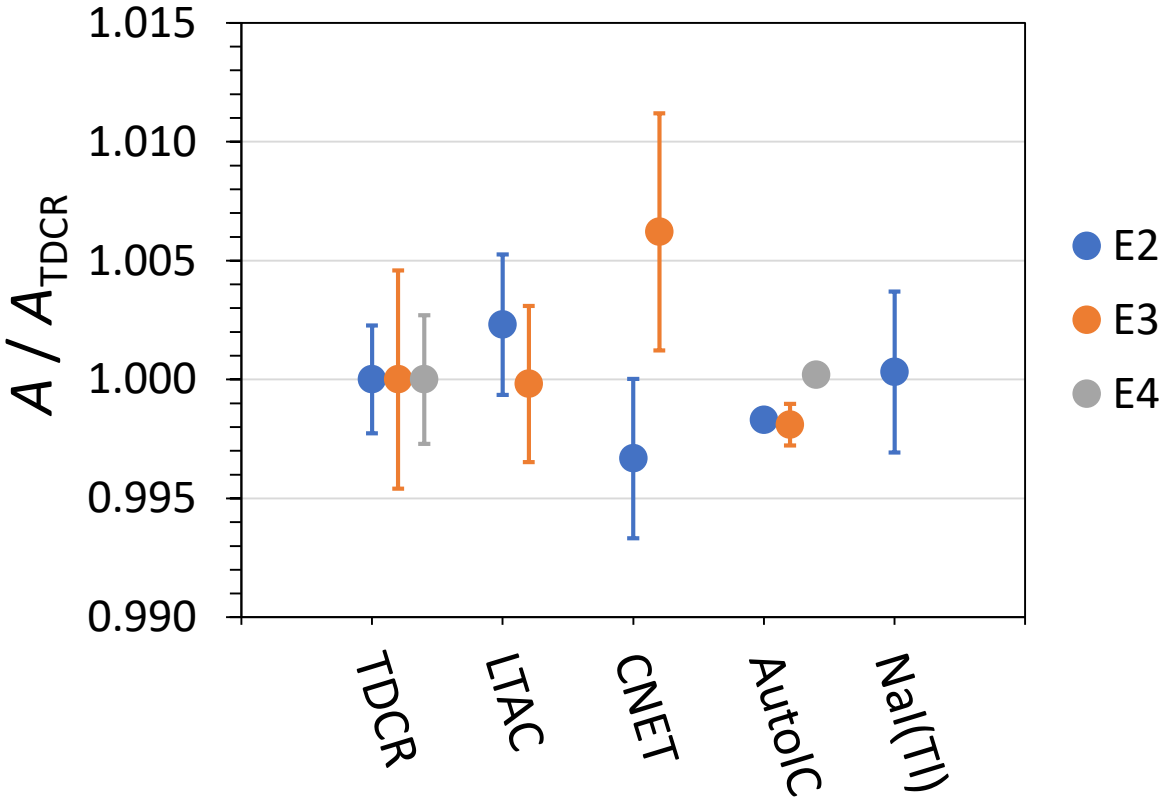
The TDCR-based ^{224}Ra activity standard



Each experiment involves multiple dilutions and various measurements and impurity checks



The ^{224}Ra activity standard



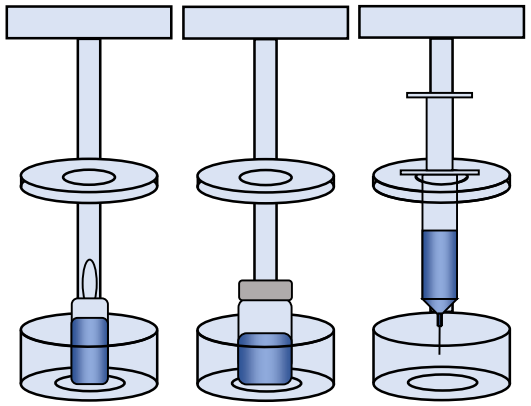
HPGe measurements showed a consistent bias of -4 %. It appears the $\gamma_{1,0}$(Rn) emission probability requires revision.

The activity standard carries a relative combined standard uncertainty < 0.5 %

Dissemination via ionization chamber factors & nuclear data

Napoli et al., Appl. Radiat. Isotop. 155, 108933 (2020); 164, 109265 (2020).

What does an activity standard look like?



- **Delivery of NIST-calibrated reference source**
- **Guidance on clinical calibrations**
  - Benchmark calibrator settings
  - Geometry/composition-dependence
- **Published results, including review/update of decay data**

An attempt at quantifying ‘typical’

Latestcalendar.weebly.com

How long?

If a standard exists, calibrations can be completed in a week or two*

Development of a new primary activity standard takes longer. In two recent cases, standardization campaigns spanned 6 months to 10 months*

****Once work starts. Lead times can be long.***

https://aronssolomon.com/articles/can-my-ex-spouse-empty-our-joint-checking-account-during-divorce/attachment/broken-piggy-bank

How much?

NIST is required to recover costs. In a few recent standardizations, customers have paid ~ $60k to $150k

NIST Nuclear Medicine Project Team

Brian E. Zimmerman (lead), Jeffrey T. Cessna
Ryan Fitzgerald, Leticia Pibida, Lizbeth Laureano-Pérez, Ron Collé

Questions?

Contact: denis.bergeron@nist.gov

National Institute of Standards and Technology
U.S. Department of Commerce

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Backup slides

NIST AT A GLANCE

Industry's National Laboratory

3,400+
FEDERAL EMPLOYEES

5
NOBEL PRIZES

2 CAMPUSES
GAITHERSBURG, MD [HQ]
BOULDER, CO

3,500+
ASSOCIATES

10
COLLABORATIVE INSTITUTES

400+
BUSINESSES USING NIST FACILITIES

ManufacturingUSA

14
NATL OFFICE FOR MANUFACTURING INSTITUTES

51
MANUFACTURING EXTENSION PARTNERSHIP CENTERS

U.S. BALDRIGE PERFORMANCE EXCELLENCE PROGRAM

Calibration Services

https://www.nist.gov/calibrations

Contact: jeffrey.cessna@nist.gov

NRMAP Program

The NIST Radioactivity Measurment Assurance Program (NRMAP)

https://www.us-rma.org

Month	Isotope	Low Level	High Level	Estimated Unc.
January	I-131	5 MBq	750 MBq	<1%
February	Mo-99	5 MBq	1 GBq	<1%
March	OPEN MONTH			
April	Tl-201	5 MBq	500 MBq	<1%
May	Ga-67	5 MBq	500 MBq	<1%
June	OPEN MONTH			
July	In-111	5 MBq	500 MBq	<1%
August	Tc-99m	N/A	1 GBq	<1%
September	OPEN MONTH			
October	Y-90	5 MBq	100 MBq	<1%
November	I-125	5 MBq	5 MBq	<1%
December	OPEN MONTH			

NRMAP Program

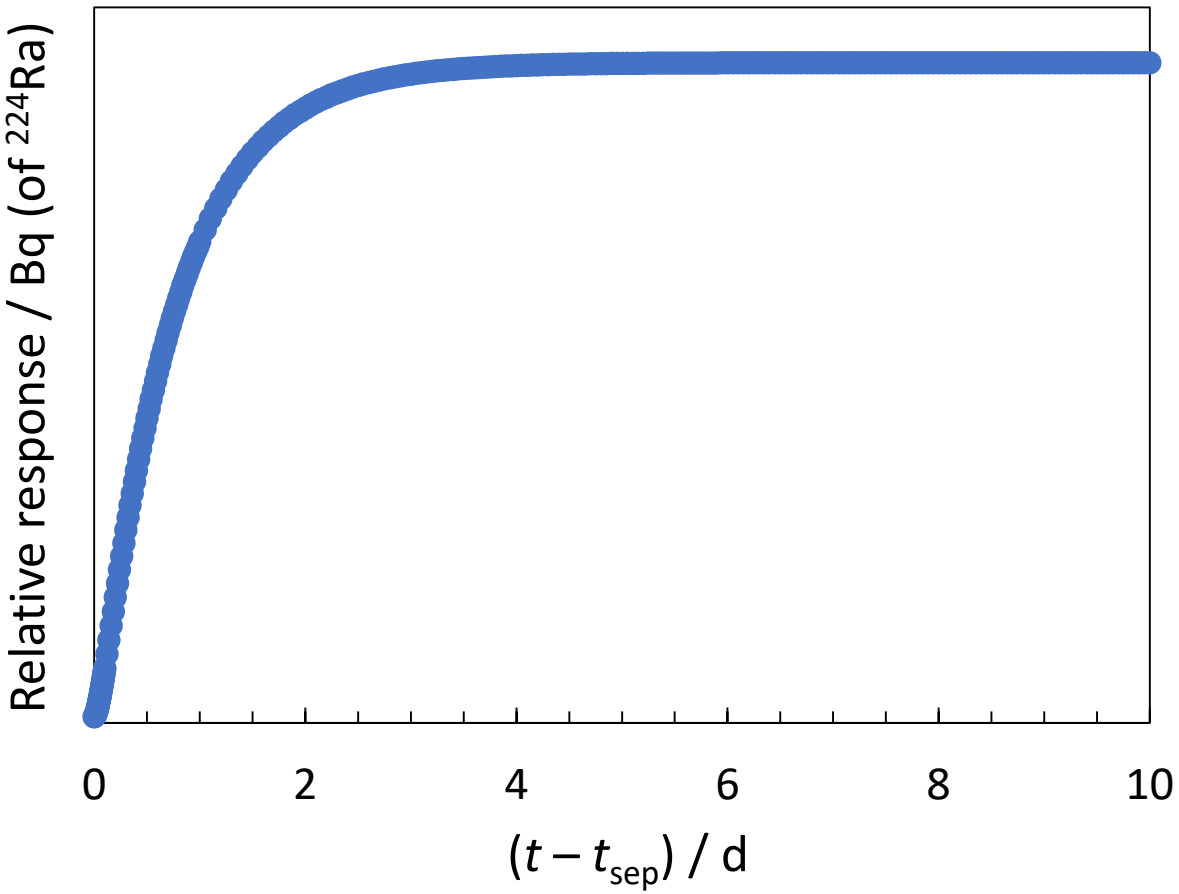
The NIST Radioactivity Measurment Assurance Program (NRMAP)

https://www.us-rma.org

Membership in NRMAP demonstrates compliance with:

- NRC Reg Guide 4.15, Quality Assurance for Radiological Monitoring Programs;
- NUREG 1576, Multi-Agency Radiological Laboratory Analytical Protocols Manual; and
- ANSI N42.22-1995, American National Standard Traceability of Radioactive Sources to NIST and Associated Instrument Quality Control.

Measuring before equilibrium is tricky



Ionization chamber response increases rapidly after separation as progeny grow in, meaning that any uncertainty on difference between t_{sep} and t_{meas} results in a very large uncertainty on the activity

Product Quality Considerations: FDA Perspective on Diagnostic and Therapeutic Radiopharmaceuticals

Danae Christodoulou, Ph.D.
Branch Chief
Office of New Drug Products - OPQ
FDA/CDER

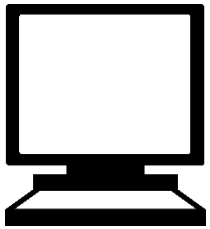
Introduction

- FDA is committed to ensuring availability of safe, effective and high quality medical isotopes and imaging drugs

- Mission Statement:
  - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.
- Websites:
  - FDA Homepage: http://www.fda.gov/
  - About the FDA: http://www.fda.gov/opacom/hpview.html

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.



Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


FDA
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.

Outline

- NDA submissions of radiopharmaceuticals, CMC section
- Quality of radiopharmaceutical drug products from clinic to market:
  - Establishing identity
  - Bridging formulation
  -Production of radionuclides
  - Supporting product labeling with quality data
  - Theranostic pair FDA approved, NRC licensed
- GMP compliance of manufacturing facilities

Quality from Clinic to Market

- Drug substance is the entire chemical entity that contains the radionuclide and pharmacophore (precursor)
- Drug substance is prepared *in situ, not isolated* and formulated to the drug product
- Commercial product/process(es) representative of what was used in the clinic
- The identity, purity, potency and reproducibility of the product must be established
- Patients dosed at different health centers, on different days are receiving the same drug

Quality from Clinic to Market

A. Reference Standard – Establish Identity

- Establish identity of the radioactive drug substance by comparison to an authentic "cold" reference standard containing the natural isotope, e.g., Ga 68 DOTATATE to ^{nat} Ga DOTATATE
- Identity needs to be established for the radioactive drug substance used in the clinic and the radioactive drug substance intended for marketing
- Characterization by two orthogonal analytical methods: Mass Spectroscopy, fully interpreted NMR spectra, HPLC with UV, SEC and RAD detectors (product)

A. Reference standard – Examples

- Radiotracers have evolved to sophisticated molecules - a rigorous physicochemical characterization is appropriate
- Metal complexes may exhibit stereoisomers, resolved by a suitable HPLC assay. A mixture of isomers may be qualified - isomeric ratio is determined
- We encourage physicochemical characterization of the reference standard, and a routine acceptance testing
- In an NDA, a designated batch of high purity, fully characterized ^{nat}X-radiotracer
- Reference standard: authentic and stable

B. Formulation development

- Drug product composition: Ideally, the proposed commercial formulation has been used in the clinic. In a multicenter trial, the same formulation (quantitative composition) used in all centers

- Drug product composition not tested in the clinic: A side-by-side comparison of the product(s) with justification and supporting data demonstrating that any differences in active and inactive ingredients do not contribute to differences *in vivo* performance and the physicochemical characteristics e.g., solubility profile, pH, osmolality/tonicity, viscosity would not alter safety or efficacy of the drug product.

  21 CFR 314.94(a)(9)(iii)

B. Formulation Development

Component/Final composition	Commercial Product	Clinical Product (IND or literature study)
Radiotracer, e.g., peptide (mass)	X µg	Y µg
Radiolabeled , radioactivity	Z MBq, mCi	W MBq, mCi
Radiolabeled , mass	H µg	---
Volume	≤ A mL	≤ B mL
Specific Activity (GBq/Total peptide)	C GBq/µmol or µg	D GBq/µmol or µg
Radioconcentration	E MBq/mL	F MBq/mL
<u>Other Excipients, e.g.,</u> Ascorbic acid Gentisic acid Formic acid EDTA Buffer Water for Injection	<u>mg/vial</u> G I J	Buffer or saline Water for Injection (WFI)

Production of radionuclides

Technologies: Cyclotron, high energy accelerator, nuclear reactor, generator

Target → Radionuclide

- Include in the NDA application, or cross-reference a Type II Drug Master File for complete CMC information and supporting data.
  - Nuclear reaction describing the formation of daughter radionuclide from its parent
  - Decay modes, principal radiation emission and half-lives of the parent and daughter radionuclides.
  - Chemical form and composition of parent radionuclide - specifications.

Production of radionuclides – targets

Targets, e.g., U 235, Mo 98, Zn 68, Ni 64

- Fabrication of target, target composition, and specifications-target impurity controls.
- Irradiation parameters, irradiation facilities.

After irradiation

- Processing and purification methods including control of materials.
- Assessment of impurities present including radionuclidic, radiochemical or chemical and their potential for contamination.

Department of Energy (DOE) Isotope Program, Office of Nuclear Physics (NP) provides target materials with opportunities for technology transfer
http://science.energy.gov/np

CMC data supporting the FDA label

In "*Highlights of Prescribing Information*" of the PI

- Proprietary name, established name, dosage form, route of administration
- Dosage Forms and Strengths

In "Full Prescribing Information" of the PI

- 2 Dosage and Administration – Radiolabeling procedure
- 3 Dosage form and strengths
- 11 Description
- 16 How Supplied
- 17 Patients Counseling

In additional "*User Manuals*" for any system manipulations to ensure safe use for the operator and delivery of accurate dose to the patient

In "*Container Labels*" for components of the drug (kits), radiolabeled drug for radiopharmacy, and shielding (pig)

Strength: Radioconcentration

- Radioactive concentration, e.g., mCi/ml or MBq/ml at the time of calibration (TOC), generally at the end of synthesis (EOS)
- For a multi dose vial at EOS
- For a unit dose vial strength calibrated to a particular time

"FDA Oversight of PET Drug Products, Q&A" 2012
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances

Reconstitution or radiolabeling

CMC data supporting "*Dosage and Administration*"

- In the NDA application, include stepwise instructions of the radiolabeling procedure, accompanied with diagram, conditions, calculations, radiolabeling efficiency and release testing with acceptance criteria for the end user (radiopharmacy), e.g., in the form of a executed batch record
- The diagram accompanied with stepwise instructions may be included in the PI
- If the radionuclide is obtained from a generator, the generator type and acceptance criteria for the generator eluate may be included in the PI

User Manuals

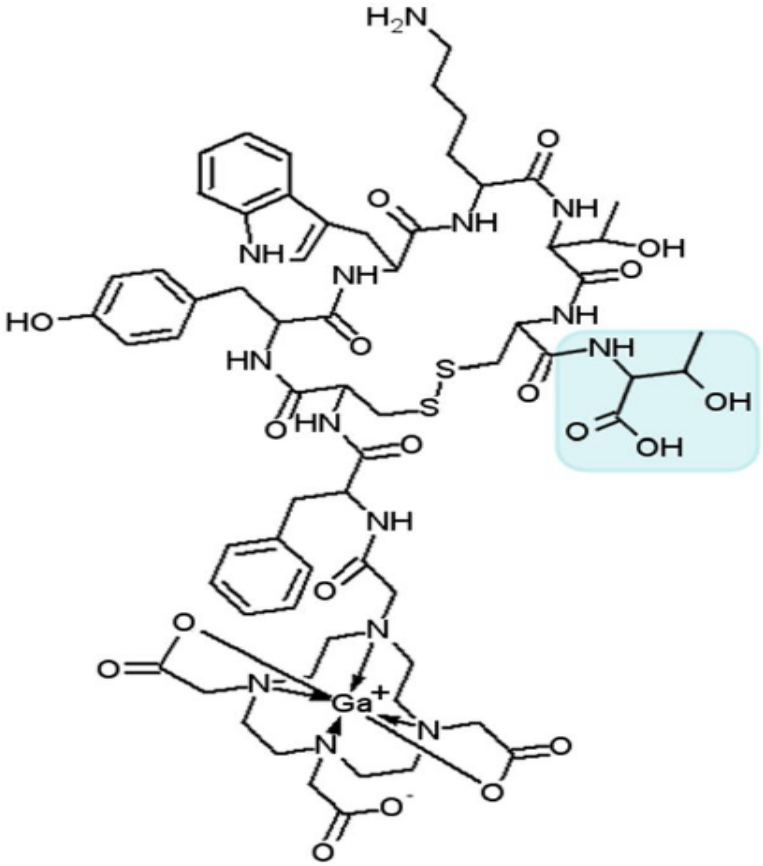
- New technologies may include complex instructions for the end user. Safe use and delivery of the accurate dose consistent with clinical practice are critical
- Human Factors Studies account for end user ability to consistently and safely perform system manipulations according to labeling to deliver the drug
- Training and certification of end users may be necessary for complex technologies
- Interdisciplinary review of User Manuals for complex systems and Novel Technologies

NETSPOT and LUTATHERA

- The pharmacophore ligand is the same (DOTATATE) in these two products
  - DOTATATE is a somatostatin (SST) analog linked to DOTA, a metal chelator (strongly chelates Ga-68 and Lu-177 respectively)
  - Selective to the SST Receptor-2
  - These receptors are highly expressed in neuroendocrine tumors

(DOTA = 1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid)

Structure of ^{68}Ga-DOTATATE



Generator Produced Ga-68

- The Ge-68 (parent) radionuclide for generator derived Ga-68 (daughter)
- Ge-68 ($t_{1/2}$ 270.8 days); Ga-68 ($t_{1/2}$ 68 minutes)
  - Ge-68 is absorbed on a solid support and decay to Ga-68
  - Ga-68 is eluted from the generator with HCl solution
  - Ge-68 breakthrough limit ≤0.001% (*Ph. Eur.*)
- cGMP generators (for NDA submissions)
  - Generator(s) is qualified with the proposed kit
  - DMF preferred (Type II DMF or Complete CMC in NDA)
- Non-GMP generators are permitted for INDs
  - DMF or certificate of analysis (COA) is adequate

NETSPOT (Ga-68 DOTATATE)

2.3 Drug Preparation

The NETSPOT kit is supplied as 2 vials *[see Dosage Forms and Strengths (3)]* which allows for direct preparation of Ga 68 dotatate injection with the eluate from one of the following generators (see below for specific instructions for use with each generator):

- Eckert & Ziegler GalliaPharm Germanium 68/Gallium 68 (Ge 68/Ga 68) generator
- IRE ELiT Galli Eo Germanium 68/Gallium 68 (Ge 68/Ga 68) generator

The Ge 68/Ga 68 generators are not supplied with the NETSPOT kit.

c. Test periodically (weekly) the Ga 68 chloride eluate for Ge 68 breakthrough by suitable method. Ge 68 breakthrough and other gamma emitting radionuclides should be $\leq 0.001\%$.

Production of Lu-177

- Lu-177; $T_{1/2}$ = 6.67days; β^--and γ-emitter
- There are two established methods for production of the radionuclide in a reactor
  - Direct method: thermal neutron bombardment of enriched Lu-176 to generate Lu-177 (carrier added)
    - Control of Lu-177m radionuclidic impurity
  - Indirect method: thermal neutron bombardment of enriched Yb-176 to produce Yb-177 which in turn decays to Lu-177 (no carrier)
  - Filed supporting DMFs if available with letter of authorization

(*Ref: Dash. A, et al. 2015*)

Conclusions

- FDA is committed to timely reviews of safe, effective and high quality medical isotopes and radiopharmaceuticals
- FDA encourages innovation and engages with stakeholders and sister agencies through interagency collaboration to make available new technologies to patients
- When data in IND studies are leveraged for NDA submission, sufficient CMC information such as chemical characterization of new pharmacophores, radionuclides and radiolabeled drug substances are needed to establish the identity, purity, potency and reproducibility of new drugs
- CMC data support product quality and drug labeling.

Thank You

Questions

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA
10903 New Hampshire Ave
Silver Spring, Maryland 20993


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Special Quality Considerations for Gallium and Technetium Generators

John K. Amartey, Ph.D.

FDA/CDER

Office of Pharmaceutical Quality

Office of New Drug Products

Introduction

- The utility of the Mo-99/Tc-99m generator is well established in Nuclear Medicine practice and is used in >80% diagnostic procedures by SPECT globally.
- Although the Ge-68/Ga-68 decay was described over half a century ago, it has become prominent in recent years because of molecular imaging by PET and the concept of theranostics. The Ge-68/Ga-68 generator has been qualified through FDA approvals of Ga-68 diagnostics since 2016.

Outline

- Components of these generators
- Eluates and radionuclides quality and reactivity
- Stability and sterility issues
- Conclusions

General Elements of a Generator

- Column material (glass or plastic)
- Absorbent (solid matrix with high selectivity for the parent)
- Eluant (solution to wash out the radioactivity)
- Eluate (the solution containing the radioactivity)

Ga-68 and Tc-99m Generators

- The Ge-68 is the parent radionuclide for generator derived Ga-68 (daughter)
- Ge-68 ($t_{1/2}$ 270.8 days); Ga-68 ($t_{1/2}$ 68 minutes)
- The Mo-99 is the parent radionuclide for generator derived Tc-99m (daughter)
- Mo-99 ($t_{1/2}$ 66 h); Tc-99m ($t_{1/2}$ 6 h)

Production of radionuclides

Technologies: Cyclotron, high energy accelerator, nuclear reactor.

Target → Radionuclide

- Include in the NDA application, or cross-reference a Type II Drug Master File for complete CMC information and supporting data.
  - Nuclear reaction describing the formation of daughter radionuclide from its parent
  - Decay modes, principal radiation emission and half-lives of the parent and daughter radionuclides.
  - Chemical form and composition of parent radionuclide - specifications.

Production of Ge-68*

- Parent radionuclide for the manufacture of Ge-68/Ga-68 generators
  - Proton irradiation of target in a cyclotron
    - Pure gallium as the target material
      - Purity should be controlled
    - An alloy (such as of gallium and nickel)
      - Composition should be specified and controlled
  - High quality target material required
  - There are limited number of suppliers of the radionuclide

*(*Roesch F and Filosofov DV, in International Atomic Energy Agency, Tech. Doc. Series 2, 2010)*

Special Quality Considerations

- Stable absorbent (e.g. TiO_2) no degradation in the high radiation field
- High quality target material (Ga metal or an alloy) to produce Ge-68
- The $^{68}GeCl_4$ solution for loading the generator processed under GMPs.
- Elution efficiency
- Eluate quality and reactivity (trace metal levels)
- Control of potential breakthrough materials
- Sterility assurance over shelf-life

Special Quality Considerations

- High quality target material (source of Mo-99)
- Stable absorbent (Alumina)
- Elution efficiency should be high and reproducible
- Eluate quality and reactivity
- Control of potential breakthrough materials (alumina and Mo-99)
- Assurance of sterility over shelf-life

Ga-68 Regulatory Considerations

- Relevant radionuclidic impurities should be justified for safety and controlled
- Equivalency of the generator and novel technologies produced Ga-68 chloride solution should be established
  - Successfully and consistently label approved kit(s) with acceptable specifications for the drug product
- European pharmacopeia monograph for generator produced Ga-68 (*and a draft monograph for the cyclotron product*)
- New Ga-68 sources to an approved product are added through prior approval supplement

Generator Produced Ga-68

- Generators processed under cGMP (for NDA submissions)
  - Generator(s) is qualified with the proposed kit
  - Type II DMF or complete CMC may be provided in the NDA application
- Non-cGMP generators may be used for IND studies
  - DMF or certificate of analysis (COA) is adequate

Conclusions

- Robustness of the generator
  - Stability and selectivity of the solid support
  - Elution efficiency
- Sterility and reactivity of the eluate
  - Ability to label approved radiopharmaceutical kits, labeling efficiency
  - Microbial quality throughout longer shelf-life in Ge-68/Ga-68
- Trace metal levels and radionuclidic impurities controlled

Recent FDA approvals and clinical practice highlighted critical quality and safety attributes for generators. FDA continues engagement with stakeholders and sister agencies to ensure that novel technologies become available to patients.

Thank You

Eckert & Ziegler
Radiopharma

Novel Radiopharmaceuticals:
- Standards Development
- Product Quality Considerations
- Supply & Demand

Product Quality Considerations: Recent Experiences with Radiopharmaceutical Approval & Licensing: GalliaPharm® Ge-68/Ga-68 Generators

Hugh W. Evans,
Eckert & Ziegler Radiopharma, Inc., Wilmington, MA

FDA Experiences When Gaining Approval of GalliaPharm®

Eckert & Ziegler Radiopharma

- Creation & submission of a Type II DMF – “Drug Substance” (Not a Drug Product!)
- First review questions pertained to imaging drug rather than Drug Substance – realigned swiftly via CMC staff
- Ge-68 breakthrough of great interest
  - In EU registration as “Drug Product” (but limited to in-vitro radiolabeling) and monograph available in European Pharmacopea
  - Drug Substance necessarily doesn’t qualify for US Pharmacopea – but EU standard accepted
- Differences between EU & FDA classification results in:
  - EU: possibility of approving the generator as stand alone for radiolabeling carrier molecules specifically developed and authorized for Ga-68
  - USA requirement that each NDA (e.g. NETSpot®) is specifically approved for use with the generator
  - NO “GENERIC” GENERATOR APPROVAL

FDA Experiences When Gaining Approval of GalliaPharm®

Eckert & Ziegler Radiopharma

- Great focus on Ge-68 production & targetry
  - Even discussion on geographic source of ores used in production of metal targets
- Lifetime sterility determination – initial approval for max # of elutions or 1 year shelf-life
  - Later amendment to increase max # of elutions after further data submission
  - EMA registration imposed no limitation on the number of elutions
- Even with creation of a Ge-68 "feedstock" specification and resultant eluate specification together with stability data, DMF amendments required for each and every additional Ge-68 feedstock supplier used
- Also, NDA "owner" required to conduct 3 drug radiolabeling runs using Ga-68 eluate from GalliaPharm® and submit supplement to their NDA
- Questions from NDA owners as to necessity for such a regulatory process when a new Ge-68 supplier's feedstock is chemically and radiochemically equivalent to that already approved
- Feedstock Ge-68 of cGMP and quality required for use in GalliaPharm® is a rare commodity !
  - We have experienced supply shortages that required prompt approval of a new alternative supplier – an administratively burdensome task for time & effort

NRC Experiences When Gaining Approval of GalliaPharm®

Eckert & Ziegler Radiopharma

- **Archaic and incorrect Ge-68 rating for DFP requirement eventually amended and exemption granted via assistance from ACMUI and OAS – significant administrative and financial relief**
- **Updated regulations generated and specific guidelines for licensing issued by NRC for GalliaPharm®**
- **However:**
  - **Even after direct liaison with NRC staff to create a legally binding requirement that Eckert & Ziegler Radiopharma GmbH would accept GalliaPharm® returns at the end of the useful life of the generator, users are still mandated to secure financial assurance per 10CFR 30.35(b)**
  - **$1,125,000 for licensees who possess more than 2 generators but less than 20 (>100 to 1000mCi)**

  or

  - **$225,000 in financial assurance for licensees possessing 1 or 2 generators (50 to 100mCi)**
- **As radiolabeling with Ge-68/Ga-68 generators typically occurs in licensed radiopharmacies that already have significant financial assurance bonds for their general operations, it is still a significant financial burden which is considered out-of-step with the fact that the manufacturer has legally committed to accepting the generator at the end of its useful life**

Mo-99/Tc-99m Generators: Recent Experience with Approval and Licensing

FDA-NRC Workshop: Enhancing Development of Emerging Technologies: Radiopharmaceuticals and Radiological Devices

October 14, 2020

James T. Harvey
Chief Science Officer
NorthStar Medical Technologies, LLC

RadioGenix® System (technetium Tc 99m generator) Indication

- The RadioGenix® System is a technetium Tc-99m generator used to produce Sodium Pertechnetate Tc 99m Injection, USP. Sodium Pertechnetate Tc 99m Injection is a radioactive diagnostic agent and can be used in the preparation of FDA-approved diagnostic radiopharmaceuticals.

- Sodium Pertechnetate Tc 99m Injection is also indicated in:
  - Adults for salivary gland imaging and nasolacrimal drainage system imaging (dacryoscintigraphy).
  - Adults and pediatric patients for thyroid imaging and vesicoureteral imaging (direct isotopic cystography) for detection of vesicoureteral reflux.

For RadioGenix® System Full Prescribing Information,
visit https://northstarnm.com/products/northstar-solutions-radiogenix-system/ and
https://northstarnm.com/products/northstar-solutions-radiogenix-system -version-1-2/.

NorthStar

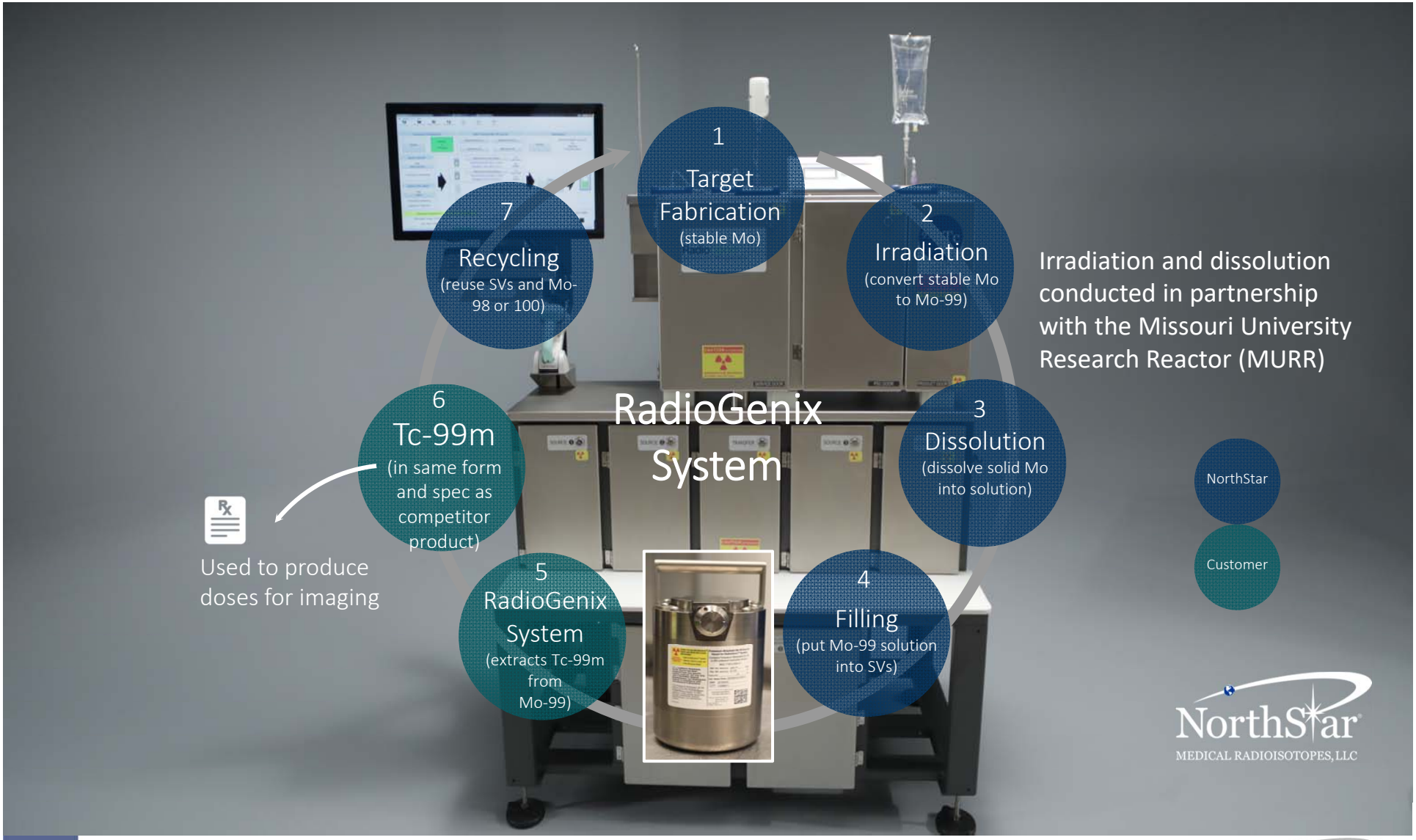
RadioGenix® System (technetium Tc 99m generator) Important Risk Information

- Allergic reactions (skin rash, hives, or itching) including anaphylaxis have been reported following the administration of Sodium Pertechnetate Tc-99m Injection. Monitor all patients for hypersensitivity reactions.
- Radiation risks associated with the use of Sodium Pertechnetate Tc 99m Injection are greater in children than in adults and, in general, the younger the child, the greater the risk owing to greater absorbed radiation doses and longer life expectancy. These greater risks should be taken firmly into account in all benefit-risk assessments involving children. Long-term cumulative radiation exposure may be associated with an increased risk of cancer.
- Unintended Re-186 Exposure: Discard the first eluate from every new Molybdate Mo-99 Source Vessel to minimize the risk of unintended radiation exposure from Rhenium Re-186.
- Temporarily discontinue breastfeeding. A lactating woman should pump and discard breastmilk for 12 to 24 hours after Sodium Pertechnetate Tc-99m Injection administration.
- Sodium Pertechnetate Tc-99m Injection should be given to pregnant women only if the expected benefits to be gained clearly outweigh the potential hazards.
- Follow step-by-step directions for use provided in the RadioGenix® System Operator Guide. Only use potassium molybdate Mo-99, processing reagents, saline and other supplies, including kits, provided by NorthStar Medical Radioisotopes. Do not administer Sodium Pertechnetate Tc 99m Injection after the 0.15 microCi of Mo-99/mCi of Tc-99m limit has been reached or when the 12-hour expiration time from elution is reached, whichever occurs earlier.
- Sodium Pertechnetate Tc 99m Injection contributes to a patient's long-term cumulative radiation exposure. Ensure safe handling to protect patients and health care workers from unintentional radiation exposure. Use the lowest dose of Sodium Pertechnetate Tc 99m Injection necessary for imaging and ensure safe handling and preparation to protect the patient and health care worker from unintentional radiation exposure. Encourage patients to drink fluids and void as frequently as possible after intravenous or intravesicular administration. Advise patients to blow their nose and wash their eyes with water after ophthalmic administration.

For RadioGenix® System Full Prescribing Information,
visit https://northstarnm.com/products/northstar-solutions-radiogenix-system/ and
https://northstarnm.com/products/northstar-solutions-radiogenix-system -version-1-2/.

NorthStar

NorthStar Non-Uranium Domestic Production of Mo-99



NorthStar

Approval and Licensing Timeline

- **FDA**
  - Initial meeting in Oct 2010; many discussions prior to NDA submission in Jan 2013
  - Multiple follow-on meetings with FDA (1) to clarify NorthStar's understanding of FDA concerns during NDA review; and (2) to describe NorthStar's approach to answering those concerns
  - Received initial approval for RadioGenix System and non-uranium Mo-99 in Feb 2018 and multiple subsequent Prior Approval Supplement (PAS) approvals for enhancements/improvements to RadioGenix System and improved production of non-uranium Mo-99
- **OAS/NRC**
  - Began discussions with OAS/NRC in 2013 relative to Guidance Document and Safety Evaluation Report (SER) for regulators and users to refer to for licensing and use of RadioGenix System
  - Guidance Document first issued Feb 2018 with one update released in Jan 2020; SER's issued for each RadioGenix System version released
  - On-going discussions on Guidance Document improvements and implementation

NorthStar

Approval and Licensing Recommendations

- **General**
  - Regulatory bodies should consider the competitive environment into which new technologies will enter and, wherever possible, ensure that the regulatory approach does not create unintended barriers to customer uptake
- **FDA**
  - Continuing interaction with groups either improving current or developing new products that require FDA approval
    - Continued enhancements to RadioGenix System or new novel Mo-99/Tc-99m generator systems
    - Copper-67 therapeutic (DMF?)
    - Actinium-225/Bismuth-213 therapeutic (NDA or DMF?)
      - ✓ Bismuth-213 generator (NDA, DMF or Device?)
  - Continue to provide guidance to clarify and improve required submissions

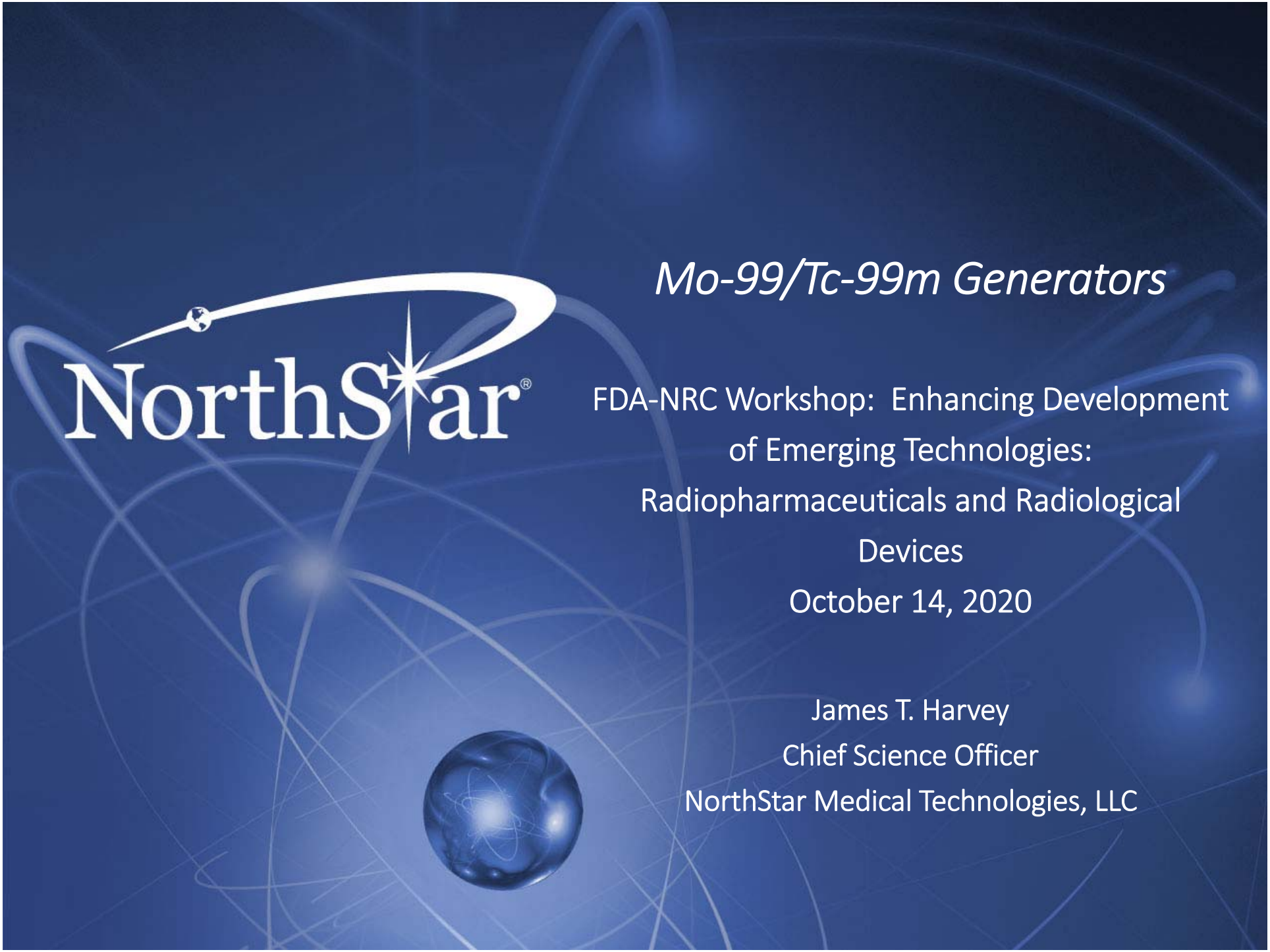
NorthStar

Approval and Licensing Recommendations

- **OAS/NRC**
  - Continuing interaction with groups improving current or developing new products requiring licensing
    - Continued enhancements to RadioGenix System or new novel Mo-99/Tc-99m generator systems (guidance documents, SER's, added training requirements)
    - Copper-67 therapeutic (RAM license, Sales & Distribution license?)
    - Actinium-225/Bismuth-213 therapeutic (RAM license, Sales & Distribution license?)
      - ✓ Bismuth-213 generator (RAM license, Sales & Distribution license, training and/or SER?)
  - Continue to provide guidance to clarify and improve necessary submissions

- ***Regulatory agencies need to be prepared for new and novel approaches in nuclear medicine in the future and be flexible and timely in interactions and responses***

NorthStar



Mo-99/Tc-99m Generators

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Advanced Accelerator Applications

A Novartis Company

Novel Radiopharmaceuticals – Recent experiences: ^{68}Ga-Dotatate, ^{177}Lu-Dotatate

M.F. Mariani MD, PhD, DABT

October 14th, 2020

www.adacap.com

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The views and opinions expressed in this presentation are those of the presenter and do not necessarily reflect the official policy or position of Advanced Accelerator Applications or Novartis.

A brief history of AAA..

2002 — Founded

2010 — Acquired rights to Lu-DOTATATE

2015 — Listed on NASDAQ

Jan 2017 — NETTER-1 publication

July 2017 — CHMP opinion

Jan 2018 — FDA approval

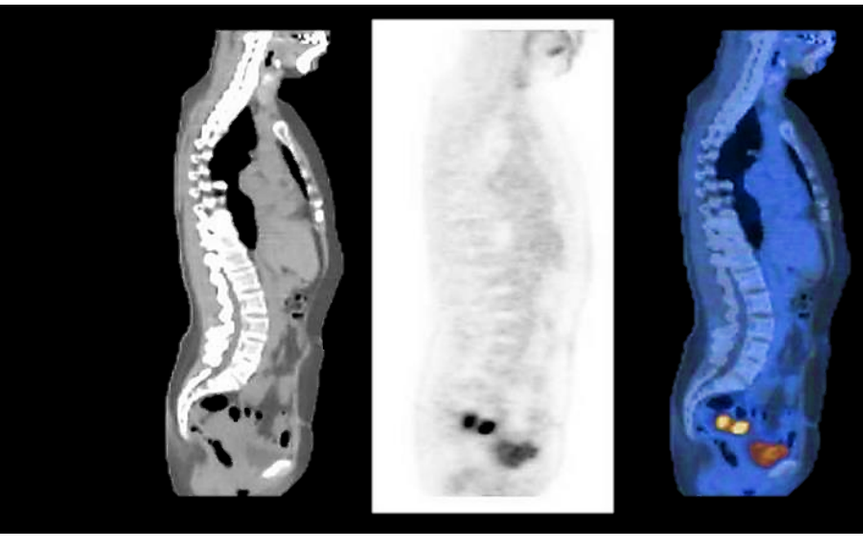
Dec 2018 — Acquired by Novartis

Oct 2019 — Endocyte Acquisition — 831 patients enrolled — VISION

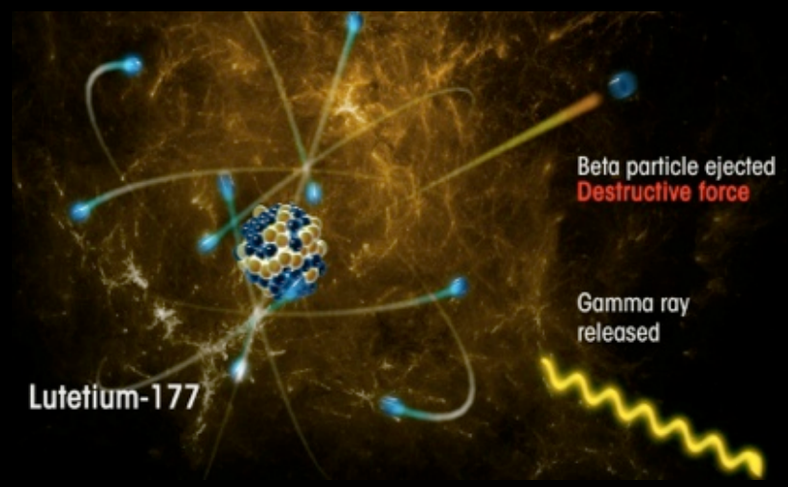
Nuclear medicine

Advanced Accelerator Applications
A Novartis Company

NUCLEAR MEDICINE DIAGNOSTICS



NUCLEAR MEDICINE THERAPEUTICS



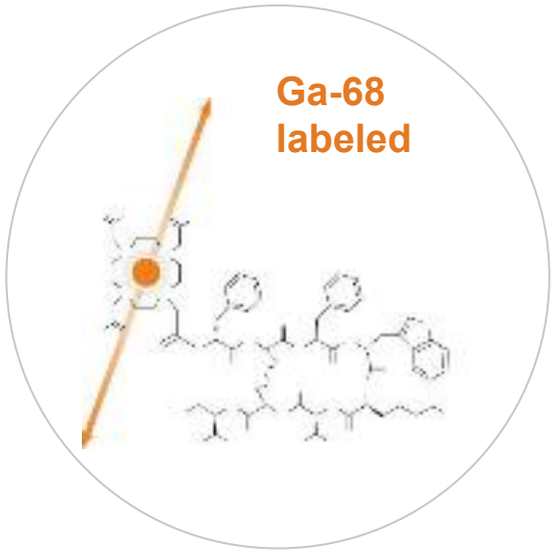
- Accurate diagnosis of complex diseases and cost-effective patient management
- Patients imaged with PET or SPECT cameras
- ~87% of total market in 2017

- Innovative therapeutic modality combining tumor targeting and radiation
- MOA, PK and toxicity are quite simple
- 13% of total market in 2017, expected to represent 60% of NM market by 2030

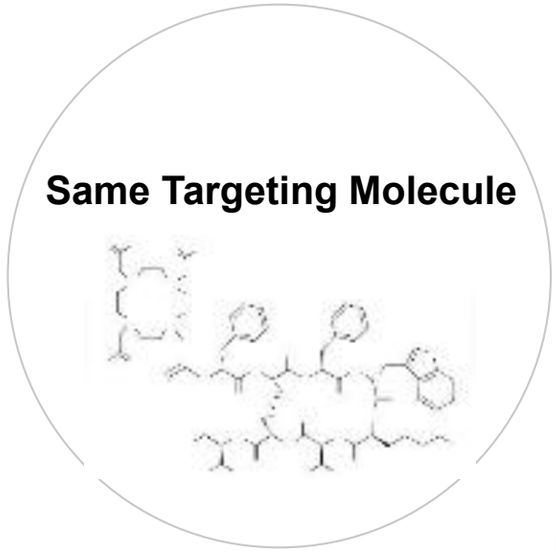
Sources: MEDraysintell 2018 Nuclear Medicine World Market Report & Directory, World Nuclear Association

Theragnostic concept

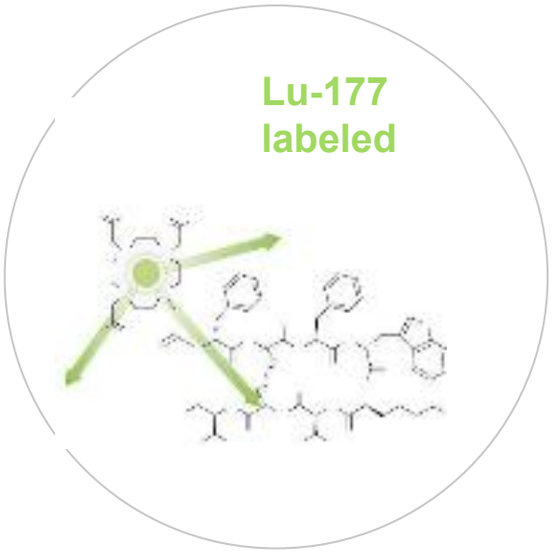
Targeted molecules can be used for Diagnostics and Therapeutics using different labelling isotopes

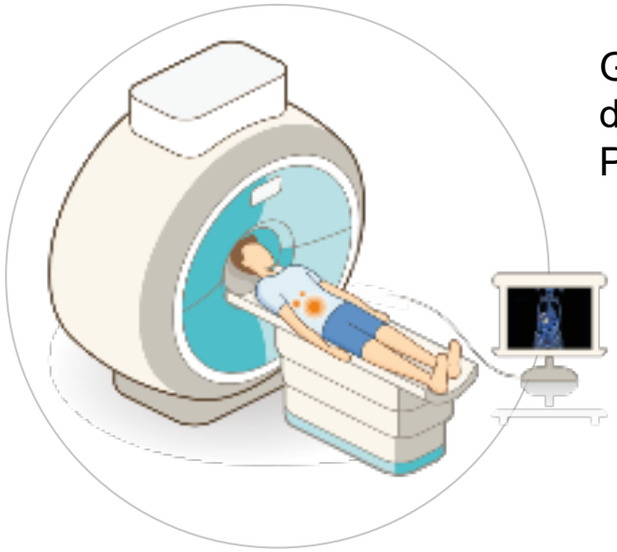


Ga-68 PET
- Diagnosis
- Treatment Selection
- Follow-up



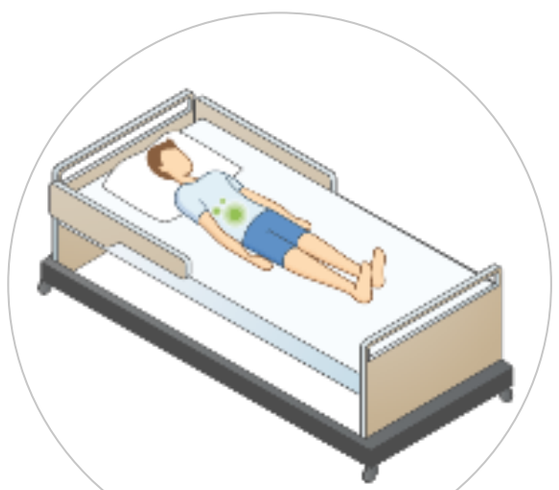
Lu-177 RLT
- Targeted treatment





GAMMA rays detected by PET/CT

BETA radiation treats tumors from within



Therapy and complementary diagnostic

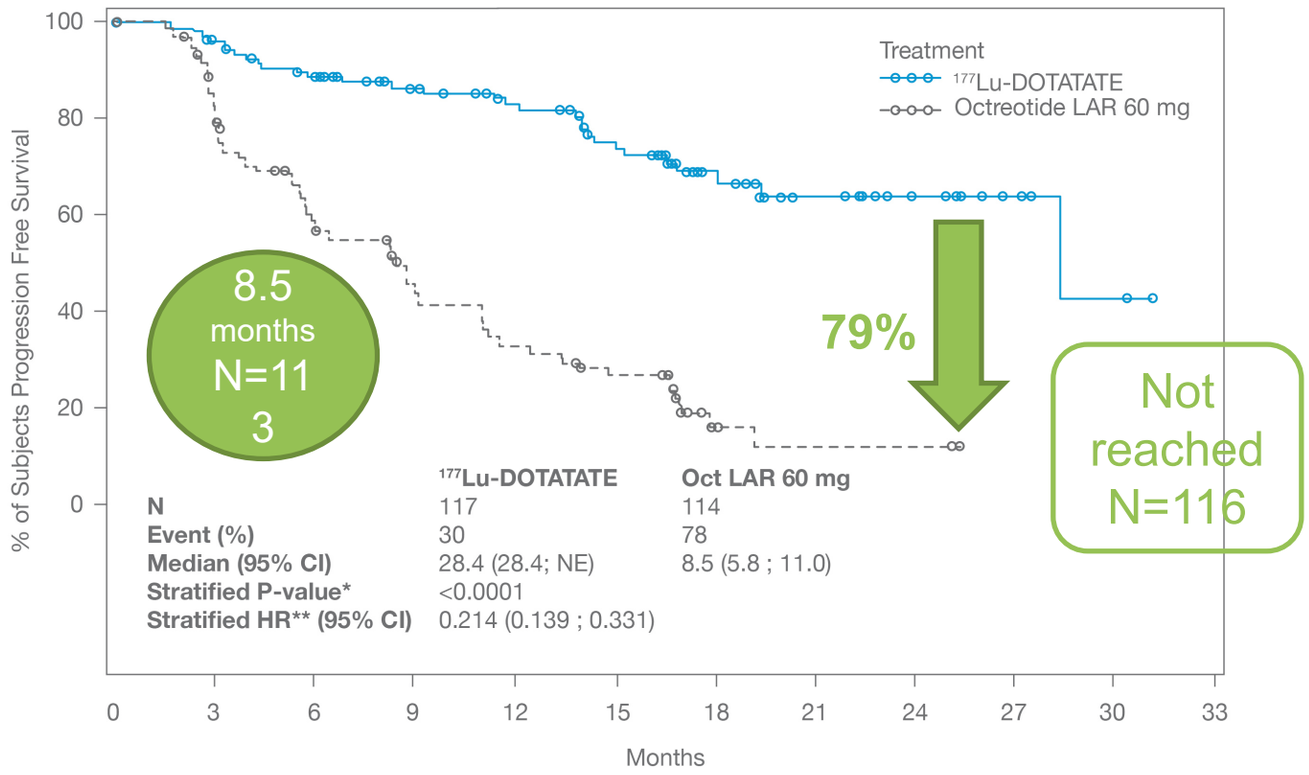
“IF YOU CAN SEE IT YOU CAN TREAT IT”

Results of the NETTER-1 study

First international, multicenter, randomized, controlled study

Evaluate efficacy and safety of ^{177}Lu-DOTATATE + SSAs compared to Octreotide LAR 60mg

Subjects: inoperable, SSTR positive, midgut NET, progressive with Octreotide LAR 30mg



^{177}Lu-DOTATATE was safe and more effective than Octreotide 60 mg:

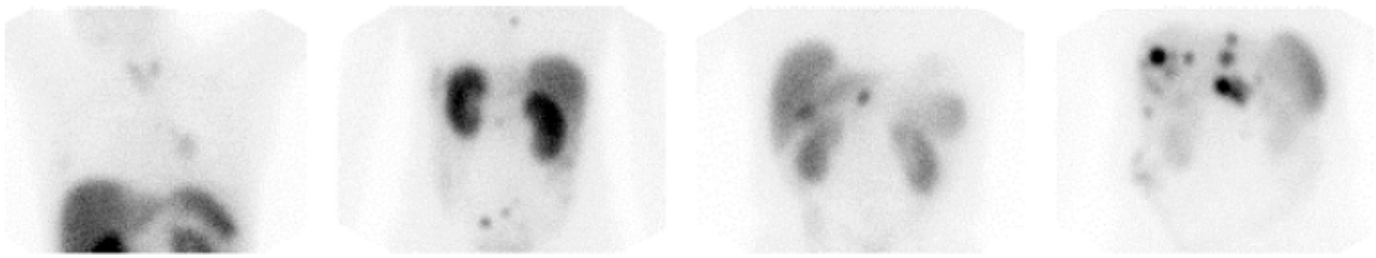
- **PFS** (**Not Reached** vs 8.5 months, p<0.0001)
- **ORR** (13% vs 4%, p=0.0008)
- **OS** (**Not Reached** vs. 27.4 months, interim analysis; p=0.0043)

A Marketing Authorization was granted for this product in Europe and in USA, in September 2017 and January 2018 respectively.

Octeroscan® positivity inclusion criteria in NETTER-1

- Octreoscan® positivity (**≥ normal liver uptake)** was one of the inclusion criteria (Octeroscan = ^{111}In-DTPA-Octreotide)
- **OctreoScan® Tumour Uptake and Extent of Tumour Burden Scales**

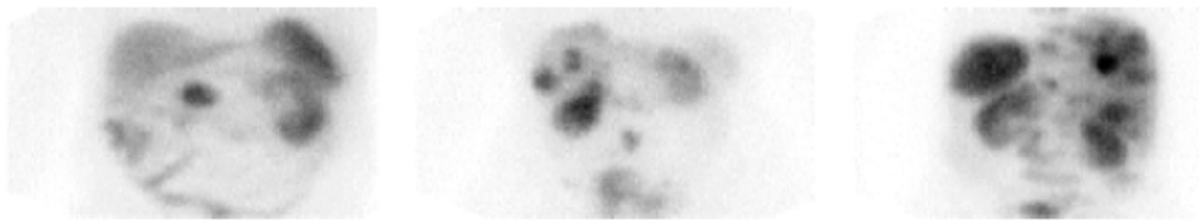
✓ **Tumour Scoring**



Tumor Uptake grade OctreoScan®:

1) < Liver (Excluded) | 2) ≈ Liver | 3) > Liver | 4) Very intense (>>Kidneys, spleen)

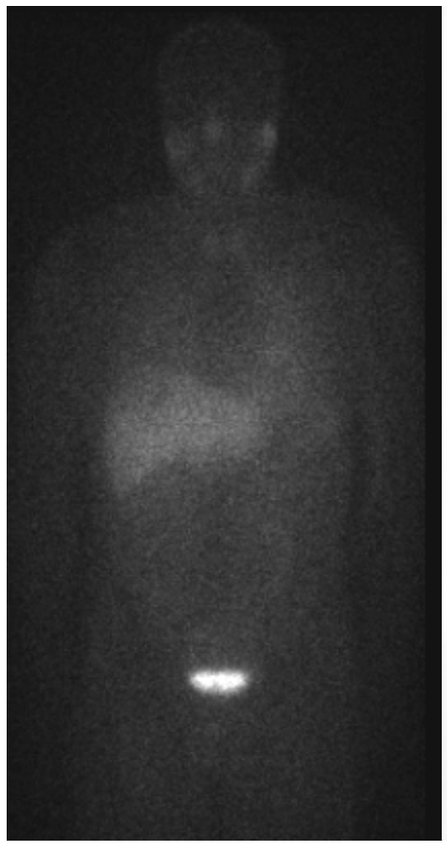
✓ **Extent of Tumor Burden**



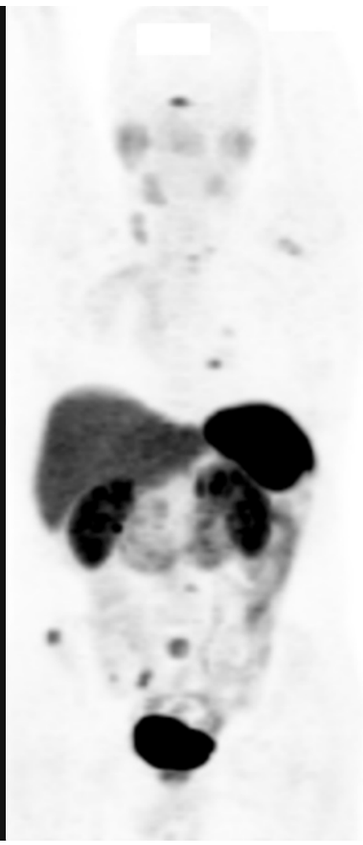
Tumour Burden score OctreoScan®: Limited | Moderate | Extensive

Gallium Ga-68 Dotatate Image vs Octreoscan™

Same Patient



Octreoscan™
SPECT image



Gallium Ga-68
dotatate
PET/CT image

These images may not necessarily be representative. Individual comparisons may vary based on a range of factors

Courtesy of Ron Walker, Vanderbilt University, Nashville TN

Advantages of theranostic approach to therapy

- See what you inject, see if the drug reaches the target
- Improved patient selection, maximizing the possibility of success of the therapy
- Small doses
- Few administrations spaced in time

General features/advantages of the RLT and theranostic approach

- Allows for dosimetric calculations => estimation of the absorbed dose to organs and prediction of possible adverse events/toxicities
- Evaluation of tumor uptake and permanence, tumor-to-blood ratio, tumor-to-target organ ratio

Added values during drug development

Dose selection and Treatment schemes

During our development we leverage on imaging diagnostic for patient enrichement and dosimetric extrapolations to evaluate both tumor and organ radioactive exposure.

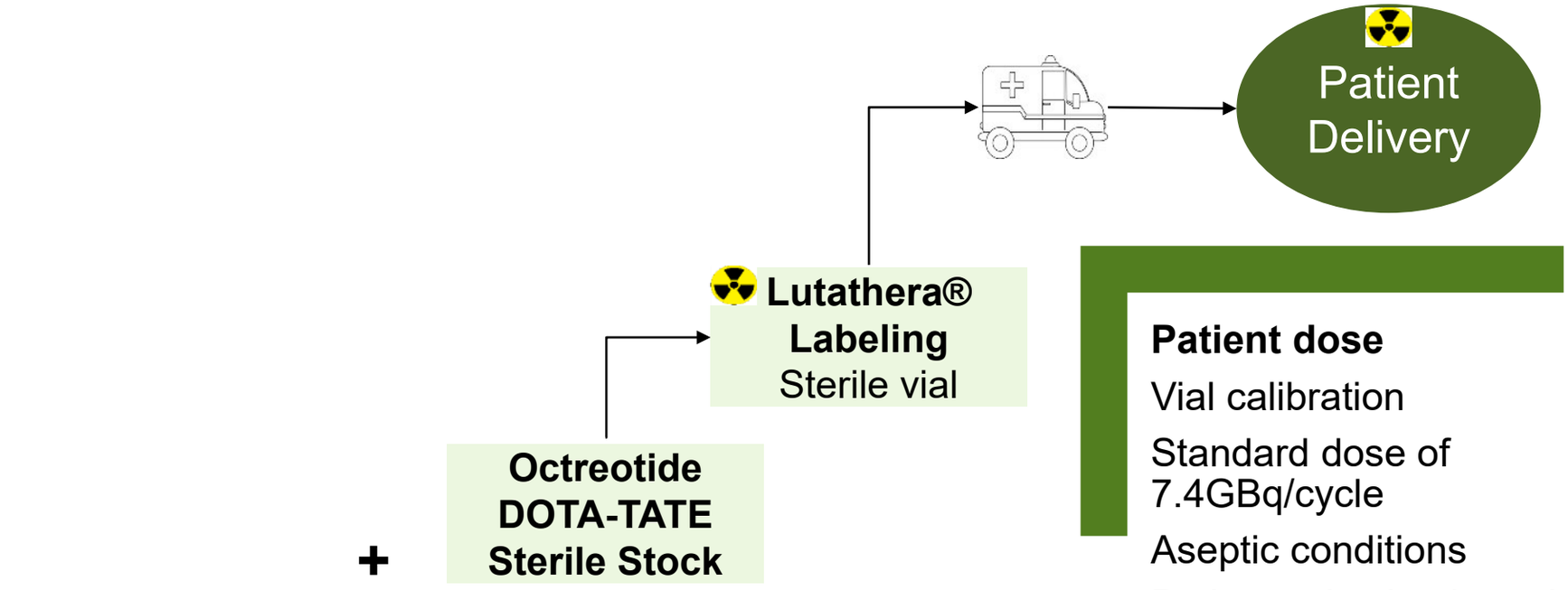
At initial stages of development, dosimetry was used to support the identification of a well-tolerated and efficaceous cumulative dose and therapeutic scheme to be used in Phase III studies.

The **dose** for Phase III studies and for commercialization selected to **maximize the probability of efficacy** in the overall patient population**, while keeping control of the toxicity parameters.**

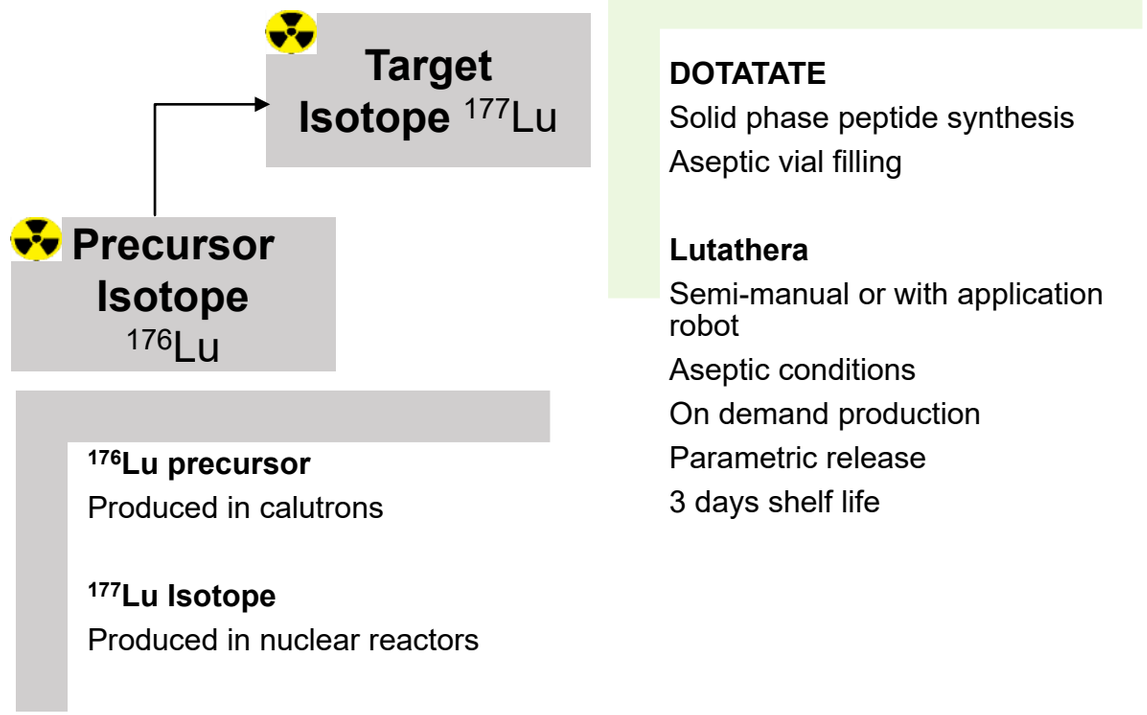
Active monitoring of **clinical, hematological and biochemical assessments** performed at suitable time intervals between treatments, was considered to be **the most reliable tool to monitor potential toxic effects.**

Complex manufacturing and supply chain

Hospital (external)



AAA internal Production



Isotope Supply

^{176}Lu precursor
Produced in calutrons

^{177}Lu Isotope
Produced in nuclear reactors

Conclusions

Targeted molecules can be used for Diagnostic and Therapeutics using different labelling isotopes => **you see what you treat.**

The Theragnostic approach allows **a more effective patient selection**, maximizing the likelihood of therapeutic efficacy**, while keeping control of the toxicity parameters.**

The Theragnostic approach allows for dosimetric calculations => an important tool **at initial stages of development**, to support the identification of the therapeutic scheme to be used in Phase III studies and commercial phase

Complex manufacturing, supply and logistic chain are high barriers for RLT

CDER Postmarketing Safety Reporting

FDA NRC Conference

Product Safety Reporting Requirements

Product or Application type	21 CFR or FD&C Act	Report Type/Timeframe	Type of Information Required
Approved: **NDA** **ANDA** **BLA**	 314.80 314.98 600.80	15-day Alert report;15-day report follow up (calendar days) Reports to applicant instead of FDA/5days Periodic adverse drug experience report/ Quarterly for 3 years from the US approval	Serious and unexpected adverse drug experience. New information from follow up of 15 days Alert report Serious adverse drug experience Individual case safety reports for each adverse drug experience Summary: narrative, analysis and actions taken

What is an Adverse Event?

Any unanticipated experience in human use regardless of causality

Context of use:

- Professional practice
- Overdose (accidental or intentional)
- Abuse
- Withdrawal
- Lack of expected effectiveness

Examples of serious adverse events

- Death
- Life-threatening experience
- Inpatient hospitalization or prolonged
- Disability/incapacity
- Congenital abnormality/birth defect

References

- FAERS https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers
- Adverse event reporting requirements https://www.fda.gov/media/72498/download
- Content of postmarketing safety reports https://www.fda.gov/media/83371/download