Perspective on Radionuclidic Purity Methods

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Mirion Connect 2025

Radiopharmaceutical lifecycle

Radioisotope production facility

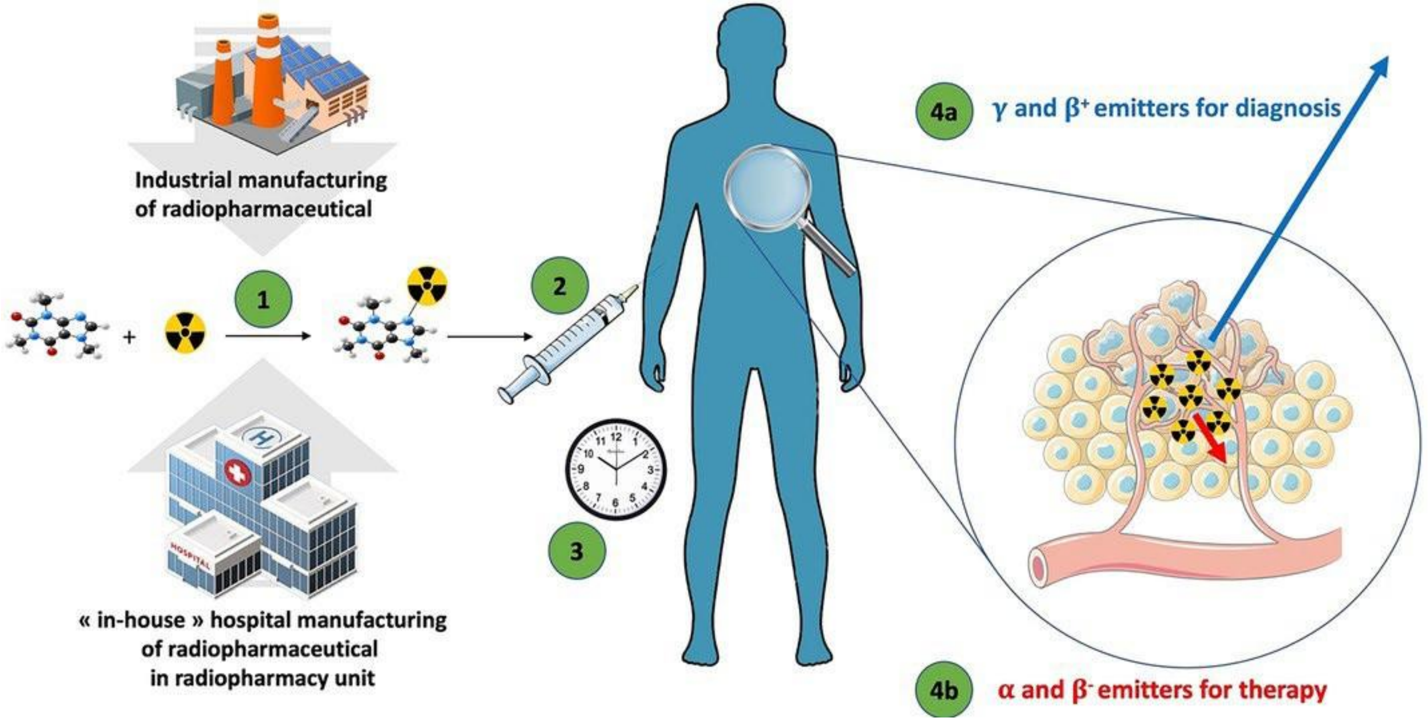


Figure from *Front. Nucl. Med. 2:990330. doi: 10.3389/fnume.2022.990330*

55 acre Campus Designed with a Purpose

NorthStar is the first and only U.S. company housing commercial-scale, multi-radioisotope production and radiopharmaceutical development services on the same campus, enabling collaborator companies to realize logistical, regulatory, and cost benefits

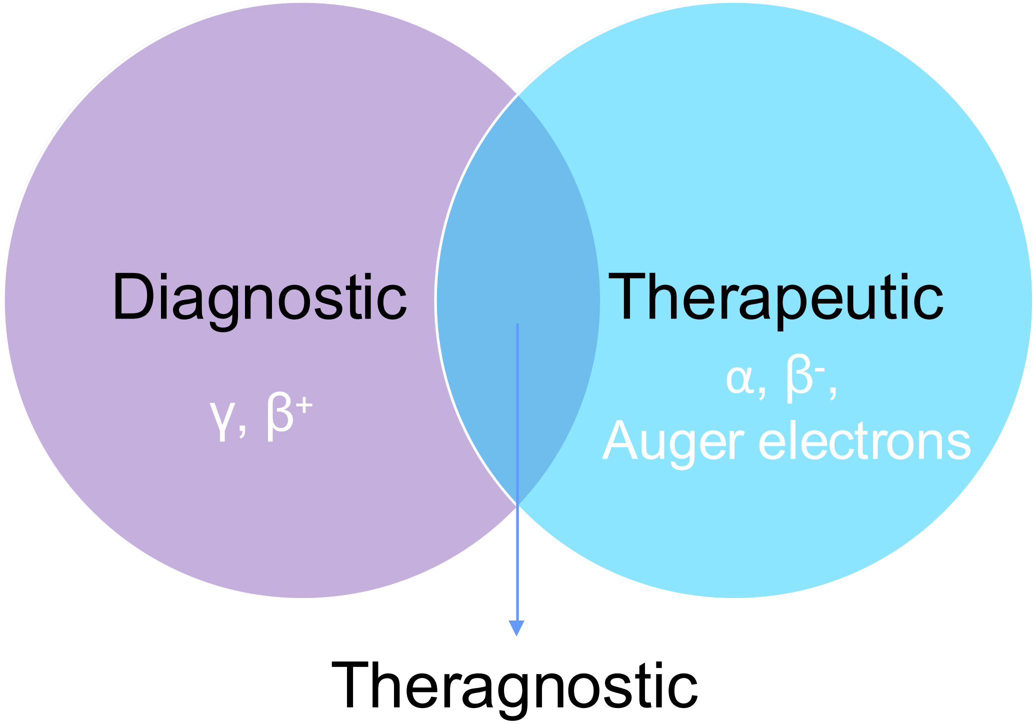
Living our Mission to Provide Patients Global Access to Game-Changing Radiopharmaceuticals

Photo taken May 2025

Agenda

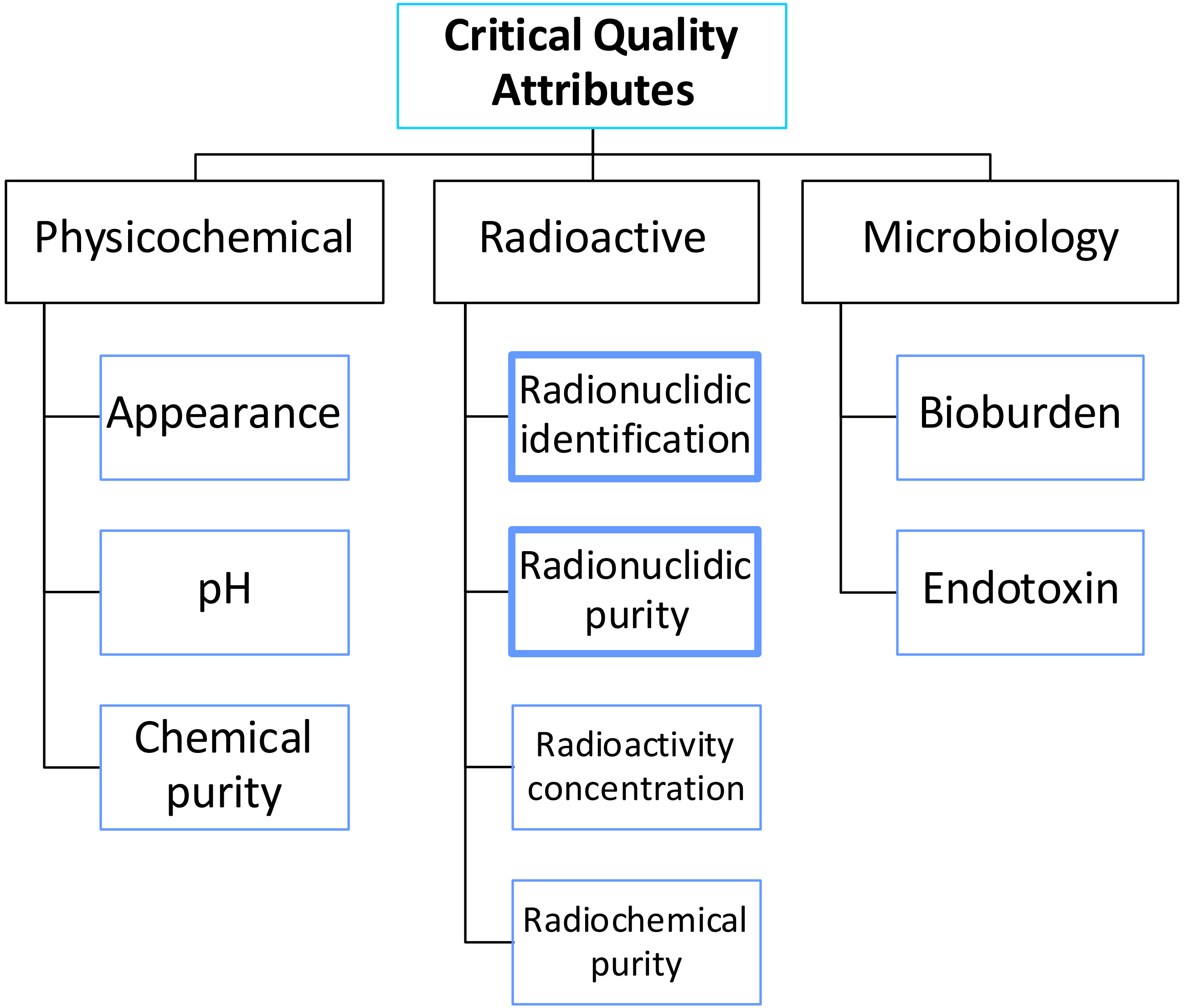
- Radionuclide Production
- Quality Target Product Profile
- Radionuclidic Identification and Purity Methods
- Challenges and Opportunities

Radionuclide Production



- Radionuclide production
  - > Fission
  - > Neutron activation
  - > Charged-particle induced reactions
  - > Generators
- Radionuclide separation and purification
  - > Physical processes
  - > Chemical processes

Quality Target Product Profile



Radionuclidic Identification Methods

Comparison with radioisotope spectrum having a known purity (<3% of radionuclidic impurities*) using the same instrument and configuration

- Challenging with short-lived radioisotopes

Measure nuclear decay scheme parameters (half-life, photopeak energy, and abundance of emissions) within ± 10% of reported value*

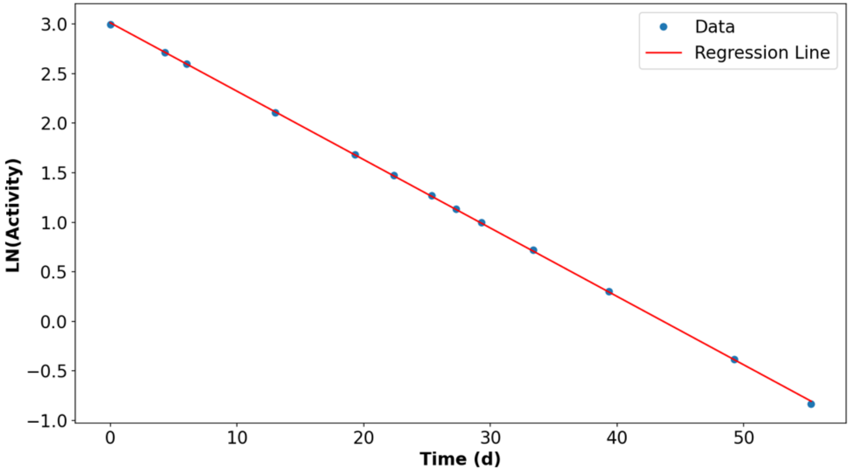
- Commonly used in radioisotope production
  - Agreement of 2 or more parameters

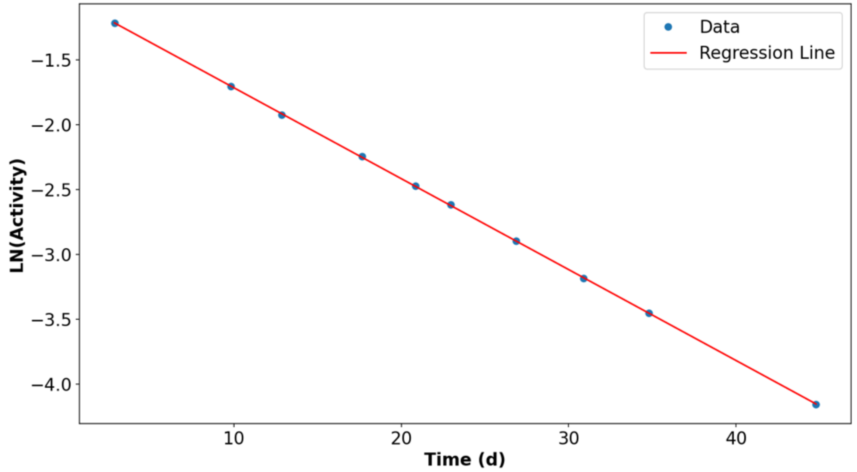
*USP — ⟨821⟩ Radioactivity

Radionuclidic Identification Methods

Half-life — successive counting of radioisotope over a period that is long enough compared to its half-life

Measuring ^{225}Ac half-life based on ^{213}Bi 440 keV photopeak within ± 10% of reported value of 9.917 d



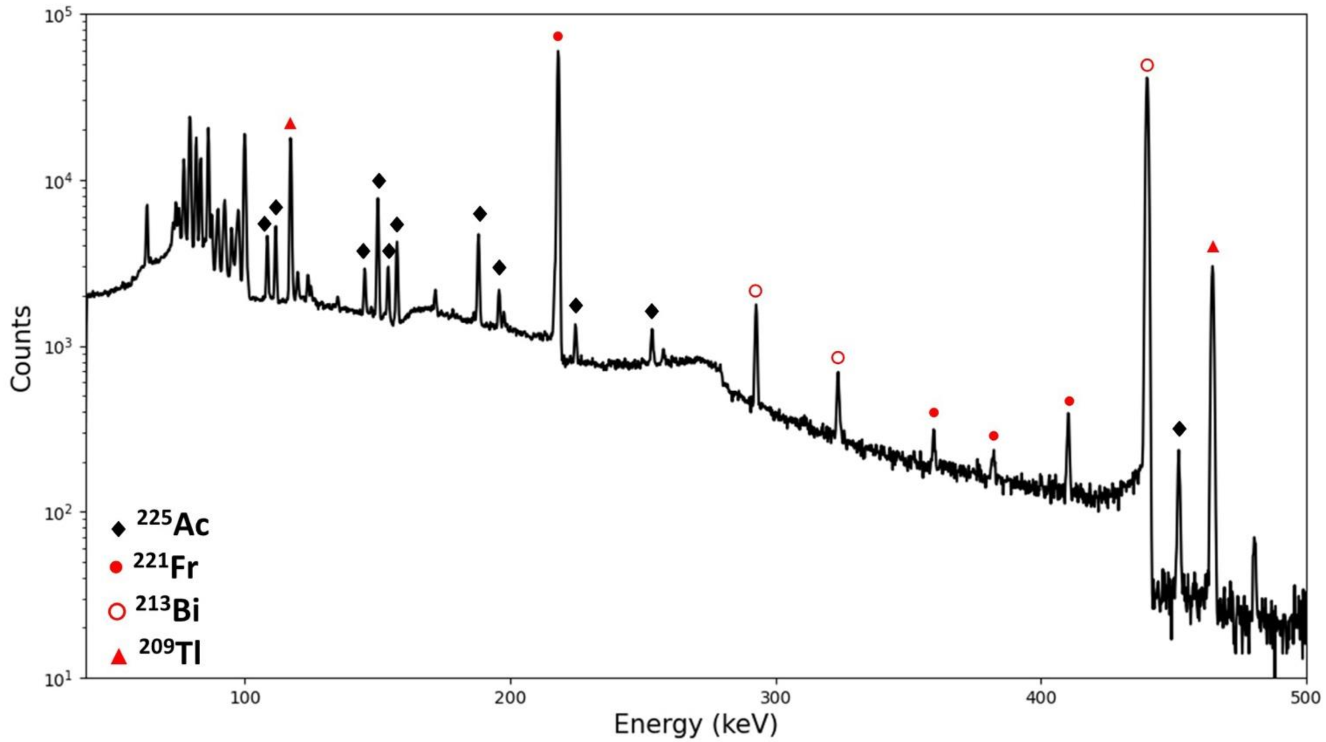


Radionuclide	^{213}Bi
A_0 (μCi)	20.35
Half-life (d)	10.04
Unc Half-life	0.028
%Error	1.24

Radionuclide	^{213}Bi
A_0 (μCi)	0.36
Half-life (d)	9.90
Unc Half-life	0.022
%Error	-0.225

Radionuclidic Identification Methods

Nuclear emissions (energy and abundance) — transition energies match those in decay scheme, whereas the area under each photopeak is proportional to the abundance after correction for detector system efficiency



Representative spectrum of ^{225}Ac in secular equilibrium with its daughters

Some of the ^{225}Ac used in this research was supplied by the U.S. Department of Energy Isotope Program managed by the Office of Isotope R&D and Production

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Radionuclidic Purity Methods

"Fraction of radioactivity attributable to the desired radionuclide in the total radioactivity measured"

$$RP = \frac{A_x}{A_x + A_i} \times 100$$

Lower radionuclidic purity can:

- Cause deviations in the prescribed radioactivity concentration
- Increase the dose delivered to healthy organs (i.e., side effects)
- Influence quality control
- Impact regulatory compliance

Radionuclidic Purity Methods

- Influenced by production route
  - > Target material
  - > Competing reactions
- Influenced by separation and purification scheme
- For radionuclide generators can be defined as breakthrough of parent radionuclide
- Must meet compendial standards (e.g., USP; Ph. Eur.; international monographs)

Radionuclidic Purity Methods
Case study #1

^{225}Ac from ^{229}Th generator

^{229}Th (A_{imp} $T_{1/2}$ = *7907 y*) → α emissions (4.8-4.9 MeV)

↓ α

γ emissions (88.5 keV, 23.9%; 193.5 keV, 4.4%)

^{225}Ra (A_{imp} $T_{1/2}$ = *14.8 d*) → β^- emissions (E_{max} = 316 keV, 68.8%; E_{max} = 356 keV, 31.2%)

↓ β^-

γ emissions (40 keV, 30.0%)

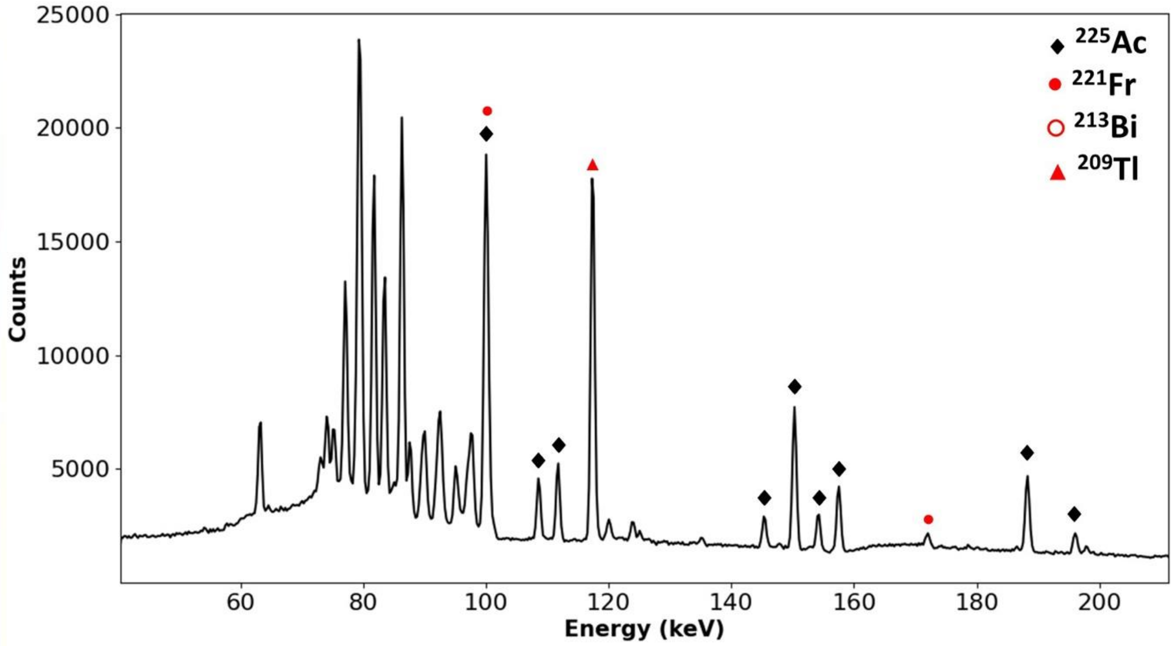
^{225}Ac (A_x $T_{1/2}$ = *9.917 d*) → alpha emissions (5.9 MeV, 52.4%)

γ emissions (150.0 keV, 0.8%; 187.9 keV, 0.58%)

^{221}Fr (A_x $T_{1/2}$ = *4.9 min*) → γ emission (218.1 keV, 15.6%)

^{213}Bi (A_x $T_{1/2}$ = *45.6 min*) → γ emission (440.4 keV, 30.8%)

Radionuclidic Purity Methods
Case study #1



Representative spectrum of ^{225}Ac in secular equilibrium with its daughters

Some of the ^{225}Ac used in this research was supplied by the U.S. Department of Energy Isotope Program managed by the Office of Isotope R&D and Production

Equipment: a conventional coaxial germanium detector with energy range from 40 keV to >10 MeV and a integrated alpha spectrometer

- Identify 100, 193.5, and 210.9 keV ^{229}Th peaks
  - Minimum detectable activity in the presence of nCi to µCi levels of ^{225}Ac
- Identify low energy (4.8-4.9 MeV) α particle emissions
  - Quantitative measurement of ^{229}Th

Is there consensus between ^{225}Ac producers from ^{229}Th generators?
>99.9% vs. >99.7%

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Radionuclidic Purity Methods
Case study #2

Typically requires decommissioning plan, environmental monitoring, and emergency planning in accordance to regulatory authorities

Main radionuclidic impurity: ^{227}Ac ($T_{1/2}$ = 21.7 y)

The % impurity of ^{227}Ac increases with time due to difference in half-lives

21.7 y vs. 9.9 d

^{225}Ac from spallation

$^{232}Th(p, spall)^{225}Ac$

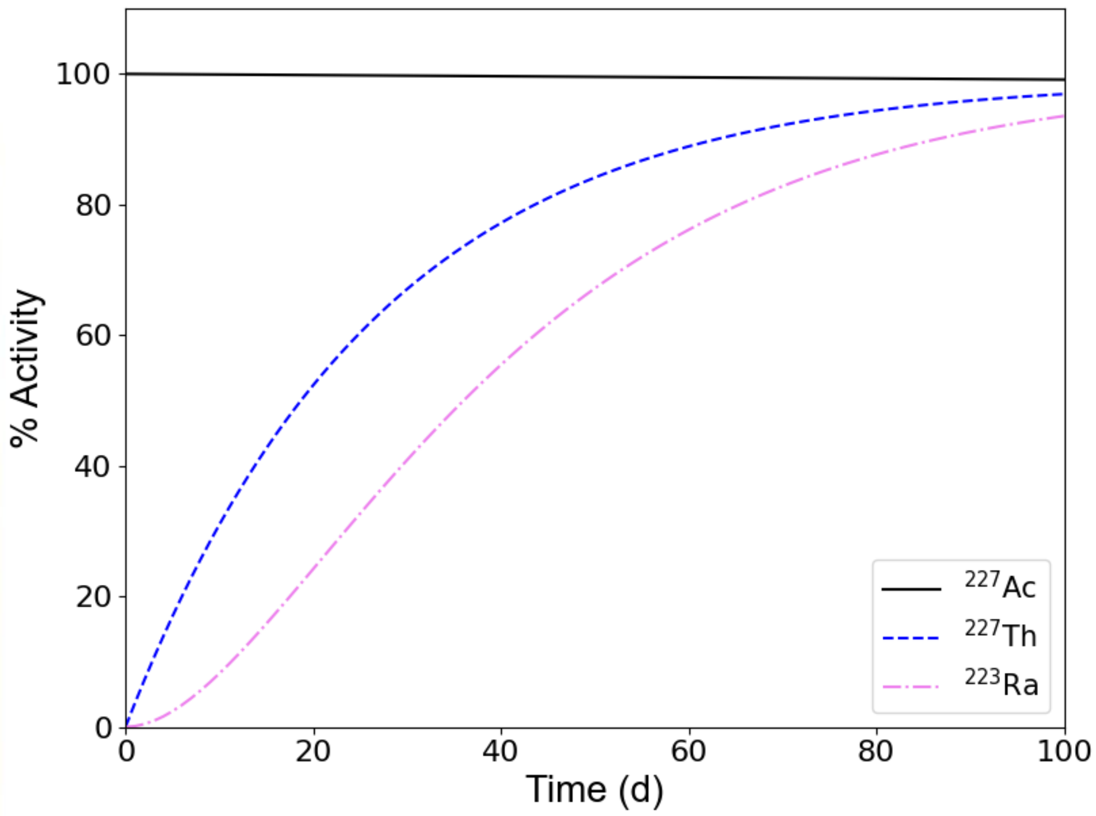
^{227}Ac has gamma emissions with relatively low emission probability (i.e., gamma silent)

Direct measurement based on <2% alpha decay chain or low beta emission

Indirect measurement through decay daughters

Other radionuclidic impurities:
^{225}Ra, radiolanthanides, light nuclides (spallation products)

Radionuclidic Purity Methods
Case study #2



In growth of ^{227}Ac daughters with time

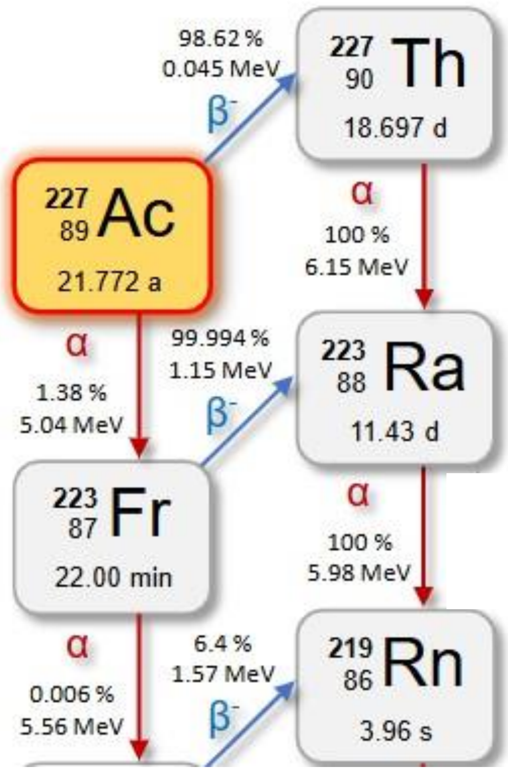
Indirect measurement through decay daughters

Methods:

- Alpha and/or gamma spectroscopy of ^{227}Th and ^{223}Ra
  - Slow ingrowth of ^{227}Th and ^{223}Ra
  - Activity of ^{225}Ac
  - Quantification of low activity levels in the presence of ^{225}Ac

Performed on validation batches, not for routine production and/or release

Radionuclidic Purity Methods
Case study #2



Decay scheme of ^{227}Ac

Image from https://www.chemlin.org/isotope/actinium-227

Direct measurement based on <2% alpha decay chain or low beta emission

Methods:

- Alpha spectroscopy of 5.02 MeV (I% 0.55) and 5.04 MeV (I% 0.66) from ^{227}Ac
  - Potential interferences: 5.0 MeV (I% <0.0015) from ^{225}Ac
- Gamma spectroscopy of 50 keV (I% 33) and 234.7 keV (I% 2.7)
  - What is the minimum detectable activity in the presence of ^{225}Ac?
    - Low contribution to gamma spectrum

Radionuclidic Purity Methods
Case study #3

^{225}Ac from ^{226}Ra*

$^{226}Ra(p, 2n)^{225}Ac$

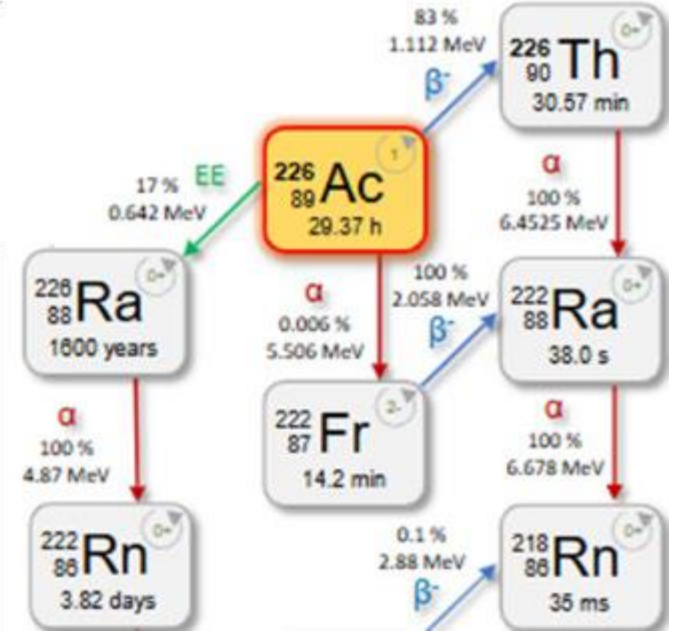
$^{226}Ra(\gamma, n)^{225}Ra \rightarrow {}^{225}Ac$

- Direct ^{225}Ac production from ^{226}Ra
  - Potential radionuclidic impurities*
    - ^{226}Ac and ^{226}Ra
- Indirect ^{225}Ac production by a ^{225}Ra/^{225}Ac generator
  - Potential radionuclidic impurities*
    - ^{227}Ac
    - ^{226}Ra and ^{225}Ra (i.e., Ra breakthrough)

*M. Tosato, et al., Alpha Atlas: Mapping global production of α-emitting radionuclides for targeted alpha therapy, Nuclear Medicine and Biology (2024), DOI

Radionuclidic Purity Methods
Case study #3

- Direct ^{225}Ac production from ^{226}Ra



Decay scheme of ^{226}Ac

Image from https://www.chemlin.org/isotope/actinium-226

Target allowed to decay for at least 3 d, leading to significant decay of ^{225}Ac (~20% of activity loss)*

Gamma spectroscopy:

^{226}Ac (β^-) → 158 keV (I% 17.5), 230 keV (I% 26.9)

^{226}Ac (EC) → 185 keV (I% 4.8), 253 keV (I% 5.7)

^{226}Ra (α) → 186 keV (I% 3.6%)

- ^{226}Ra > 1 µCi requires general licensing according to 10 CFR 31.12(a)(2)
- ^{226}Ra is a bone seeker radionuclide
- Presence of ^{226}Ac in ^{225}Ac API, what is the limit?

*M. Tosato, et al., Alpha Atlas: Mapping global production of α-emitting radionuclides for targeted alpha therapy, Nuclear Medicine and Biology (2024), DOI

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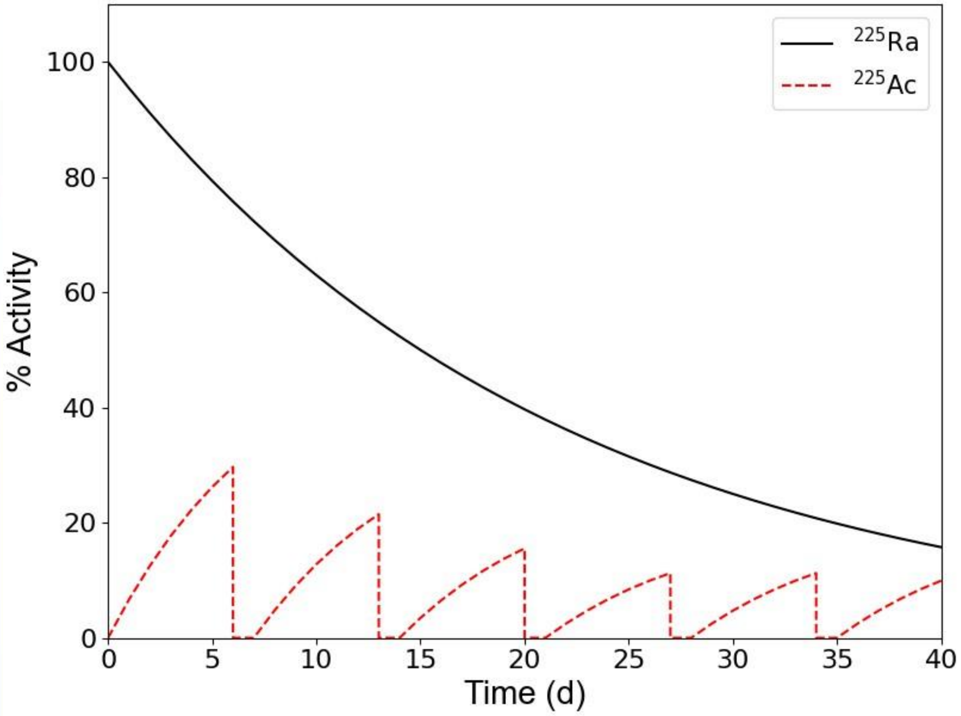
Radionuclidic Purity Methods
Case study #3

^{225}Ac from ^{226}Ra

$^{226}Ra(\gamma, n)^{225}Ra \longrightarrow {}^{225}Ac$

- Indirect ^{225}Ac production by a $^{225}Ra/^{225}Ac$ generator



In growth and elution of ^{225}Ac from ^{225}Ra with a 7-d frequency

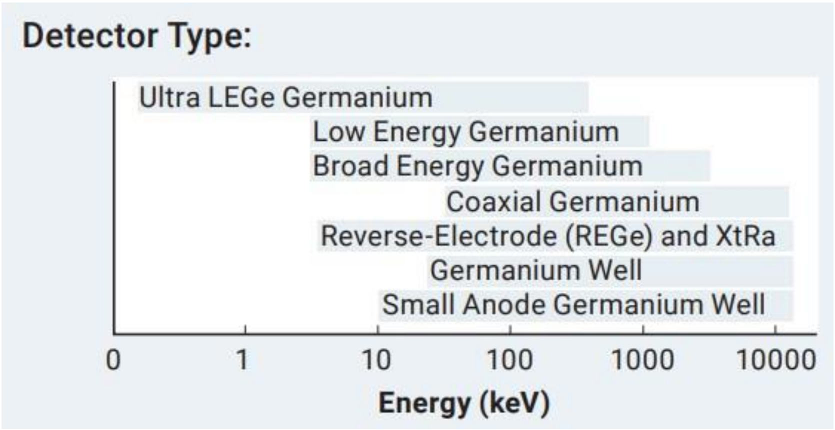
Discard initial $^{225}Ac/^{227}Ac$ fraction*

Gamma spectroscopy:

^{225}Ra (β^-) → 40 keV (I% 30), 230 keV (I% 26.9)

^{226}Ra (α) → 186 keV (I% 3.6%)

Mirion Technologies Germanium Detectors



*M. Tosato, et al., Alpha Atlas: Mapping global production of α-emitting radionuclides for targeted alpha therapy, Nuclear Medicine and Biology (2024), DOI

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Challenges and Opportunities

- Emission properties of trace contaminants in the presence of an overwhelming field of X radioisotope

  Minimum Detectable Activity
  Maximum Potential Percent Impurity

- Lack of or low characteristic emissions

  For example ^{227}Ac in ^{225}Ac API

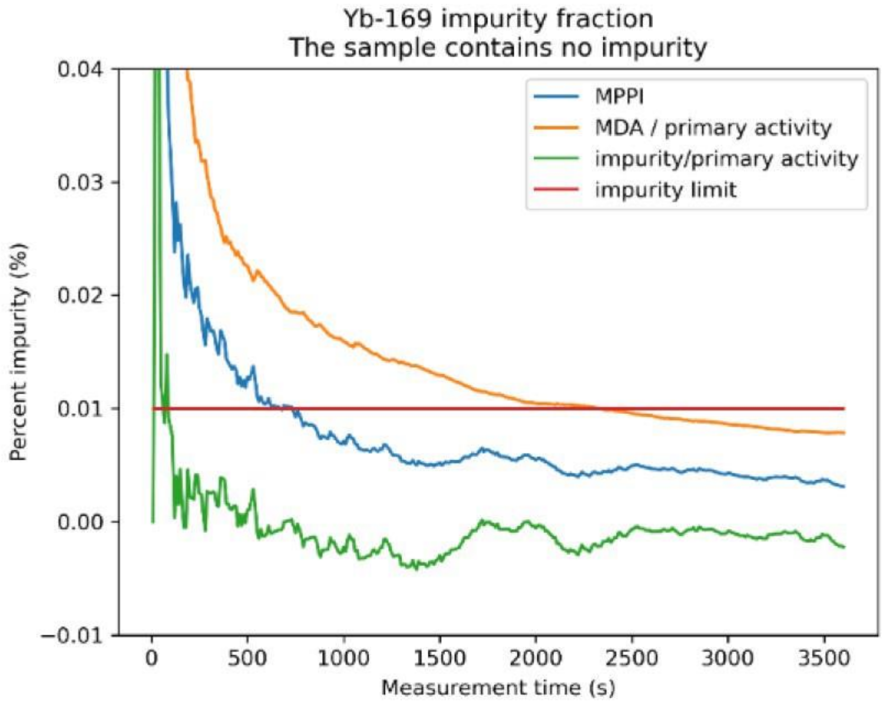

Figure from *Mirion Application Note*

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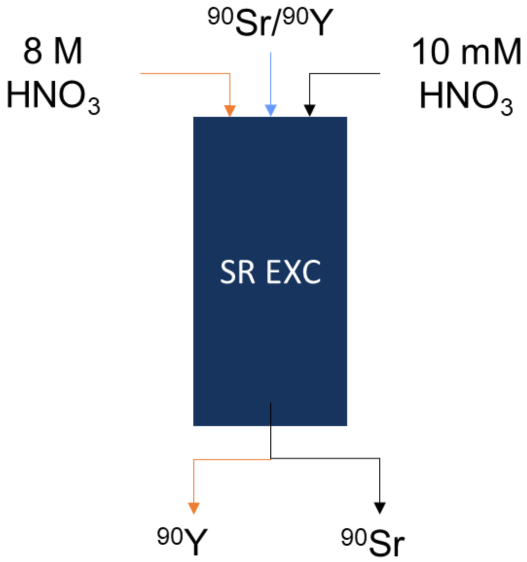
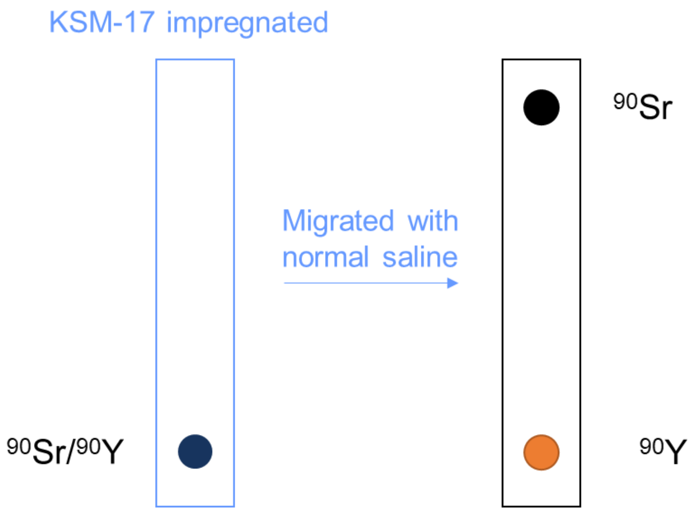
Challenges and Opportunities

- Emission properties of trace contaminants in the presence of an overwhelming field of X radioisotope





Size exclusion and paper chromatography are used to separate trace contaminants from high activities of the desired radionuclide*

*IAEA — Technical Reports Series No. 470

Challenges and Opportunities

- Consideration of half-life for radionuclidic purity—desired radionuclide versus impurities—time sensitive methods

Total of all other gamma-emitting radionuclides 0.5 µCi per 1 mCi ^{99m}Tc at time of administration

No More Than*:

- 0.15 µCi ^{99}Mo ($T_{1/2}$ = 66 h) per 1 mCi ^{99m}Tc ($T_{1/2}$ = 6 h)

- 0.05 µCi ^{131}I ($T_{1/2}$ = 8 d) per 1 mCi ^{99m}Tc ($T_{1/2}$ = 6 h)

- 0.05 µCi ^{103}Ru ($T_{1/2}$ = 39 d) per 1 mCi ^{99m}Tc ($T_{1/2}$ = 6 h)

- 0.0006 µCi ^{89}Sr ($T_{1/2}$ = 52 d) per 1 mCi ^{99m}Tc ($T_{1/2}$ = 6 h)

*USP — Sodium Pertechnetate Tc 99m injection

Challenges and Opportunities

- Isotope specific

^{18}F	
Ph. Eur	99.9%
USP	99.5%

^{99m}Tc	
Ph. Eur	99.88%
USP	99.935%

$^{225}Ac/^{213}Bi$*
>99.9% of ^{213}Bi

$^{90}Sr/^{90}Y$**
>99.998% of ^{90}Y

^{90}Sr is a bone seeker radionuclide
Maximum Permissible Body Burden
2 µCi**

The half-life limits how far the radioisotope can be shipped → ^{90}Y (64 h), ^{18}Fr (110 m), ^{213}Bi (45 min)

- Methods for radionuclidic purity cannot always be adapted to a hospital or pharmacy*

*IAEA-TECDOC-1856 Quality control in the production of radiopharmaceuticals
**IAEA — Technical Reports Series No. 470

Challenges and Opportunities

- General guidelines
  - > The International Pharmacopoeia
    - Recommended procedures and specifications as source material for reference or adaptation of any World Health Organization Member State
    - 26 specific monographs for radiopharmaceuticals
  - > European Directorate for quality of Medicines EDQM
    - Various monographs dealing with radiopharmaceuticals
    - Monographs specify a radionuclidic purity >99.9%*
    - Specific radionuclide precursor monographs (^{18}F, ^{123}I, ^{111}In, ^{177}Lu, ^{90}Y, ^{68}Ga, etc.)
  - > USP Monographs
  - > NRC 10 CFR: 35.204 Permissible molybdenum-99, strontium-82, and strontium-85 concentrations

*Gillings et al. EANM guideline on the validation of analytical methods for radiopharmaceuticals, EJNMMI Radiopharmacy and Chemistry (2020) DOI

Challenges and Opportunities

Radionuclidic methods must be developed and tested for:

Limit of detection

$$LOD = \frac{3 \times \sqrt{B}}{t}$$

Limit of quantification

$$LOQ = \frac{10 \times \sqrt{B}}{t}$$

Minimum detectable activity

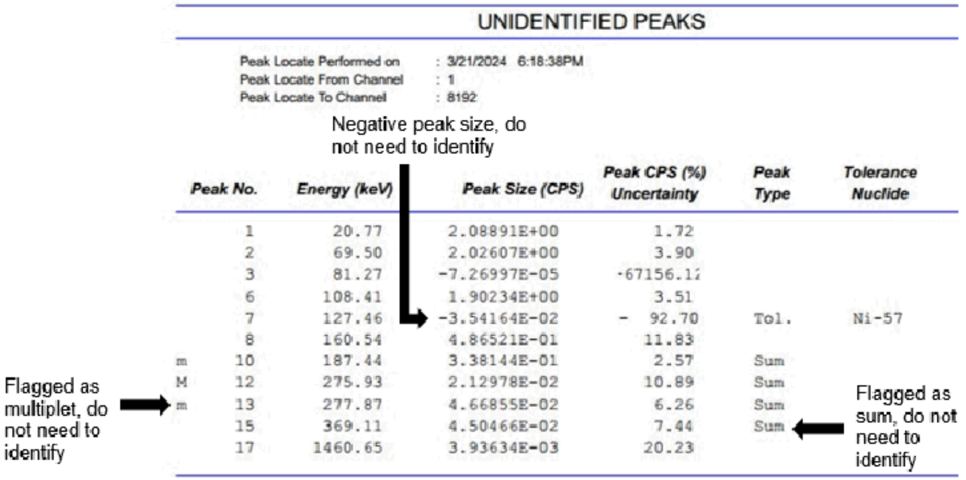
$$MDA = \frac{LOD}{\varepsilon \times F}$$

B: background count rate
t: count time
ε: counting efficiency
F: conversion factor

Specificity

Ability to unequivocally measure the radionuclide of interest (i.e., photopeak energy within ±3 keV)

Energy and efficiency calibration using NIST traceable mixed gamma standard


UNIDENTIFIED PEAKS

Peak Locate Performed on : 3/21/2024 6:18:38PM
Peak Locate From Channel : 1
Peak Locate To Channel : 8192

	Peak No.	Energy (keV)	Peak Size (CPS)	Peak CPS (%) Uncertainty	Peak Type	Tolerance Nuclide
	1	20.77	2.08891E+00	1.72		
	2	69.50	2.02607E+00	3.90		
	3	81.27	-7.26997E-05	-67156.1[illegible]		
	6	108.41	1.90234E+00	3.51		
	7	127.46	-3.54164E-02	- 92.70	Tol.	Ni-57
	8	160.54	4.86521E-01	11.83		
m	10	187.44	3.38144E-01	2.57	Sum	
M	12	275.93	2.12978E-02	10.89	Sum	
m	13	277.87	4.66855E-02	6.26	Sum	
	15	369.11	4.50466E-02	7.44	Sum	
	17	1460.65	3.93634E-03	20.23		

Representative Apex Gamma report highlighting unidentified peaks

Summary

- Radionuclidic identification and purity methods are important from the perspective of patient/operator safety and regulatory compliance.
- Guidelines for radionuclidic purity are radioisotope dependent, only established radioisotopes have well-defined purity requirements.
- Radionuclidic purity methods need to be adjusted to each radioisotope and production route. No one size fits all, however, purity requirements should be the same.
- Continuous development and improvement of radionuclidic purity methods can benefit all.

Acknowledgements

- NorthStar Medical Radioisotopes

  Radiochemistry and Analytical Laboratories Team

- Mirion Technologies
- Some of the ^{225}Ac used in this research was supplied by the U.S. Department of Energy Isotope Program managed by the Office of Isotope R&D and Production.

References

- USP Monographs
  - Sodium Pertechnetate Tc 99m injection
  - ⟨821⟩ — Radioactivity
  - ⟨1821⟩ — Radioactivity-Theory and Practice
- IAEA-TECDOC-1856 *Quality control in the production of radiopharmaceuticals*
- IAEA — Technical Reports Series No. 470
- The International Pharmacopoeia, Twelfth Edition
- M. Tosato, et al., *Alpha Atlas: Mapping global production of α-emitting radionuclides for targeted alpha therapy,* Nuclear Medicine and Biology (2024), DOI
- Gillings et al., *EANM guideline on the validation of analytical methods for radiopharmaceuticals*, EJNMMI Radiopharmacy and Chemistry (2020) DOI

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What questions do you have?

IBA Rhodotron® TT300-HE

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