Dissemination of standards – needs from a clinical perspective; possible routes to secondary standards

Stephen A. Graves, PhD
Department of Radiology
Department of Radiation Oncology
Department of Biomedical Engineering
University of Iowa

Brian E. Zimmerman, PhD
Chair, CCRI RTQI WG
Radioactivity Group, National Institute of Standards and Technology

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Disclaimer (NIST)

Certain commercial equipment, instruments, or materials are identified in this presentation to foster understanding.

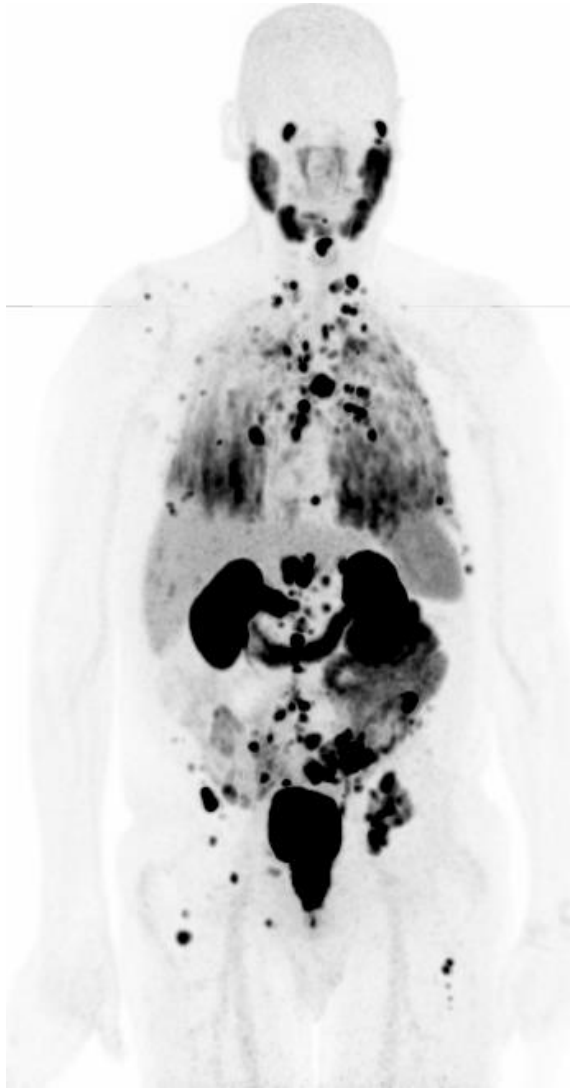
Such identification does not imply recommendation by the National Institute of Standards and Technology, nor does it imply that the materials or equipment identified are necessarily the best available for the purpose.

Background: *Activity measurements in clinical practice*

- Clinical practice of nuclear medicine is based on the assumption that we know what quantity of radioactivity is being given.

- For diagnostic nuclear medicine applications, mis-calibration of administered activity has minimal impact on the diagnostic result.
  - PET calibration is tied to the dose calibrator, so systematically miscalibrated dose calibrator readings result in accurate SUV values.
  - Single-photon imaging historically qualitative in nature

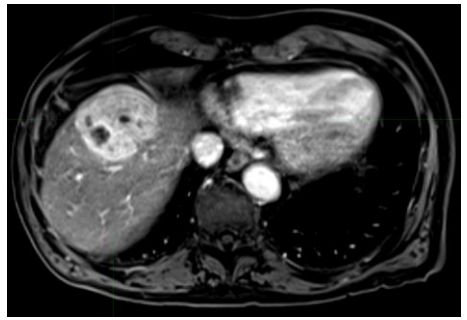
- For therapeutic applications, the medical benefit and risk is inextricably linked to the amount given.



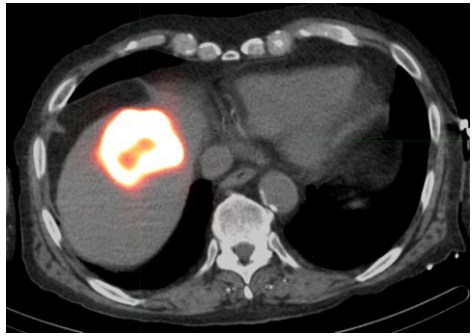
Background: *Dosimetry-guided RPT*

- Personalized dosimetry can be achieved by pre- or post-therapy imaging (PET/CT or SPECT/CT)
- Dose calculation requires accurate measurement of *in vivo* activity
- Carries a higher risk compared with fixed administration levels, which are provided directly by the manufacturer.
- Dosimetry-driven prescribing is now standard for Y-90 therapies
- **Dosimetry-driven prescribing is likely to expand to other therapeutic procedures over the next 5-10 years**
- We have a brief window of time to put in place foundational infrastructure for establishing or verifying traceable activity measurements at the clinical level.

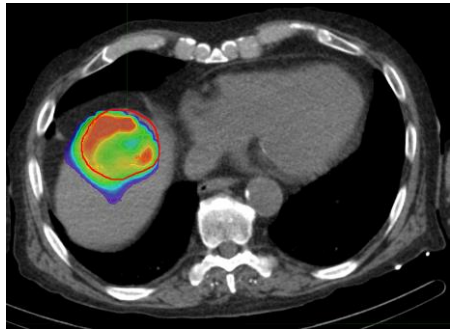
Identify target



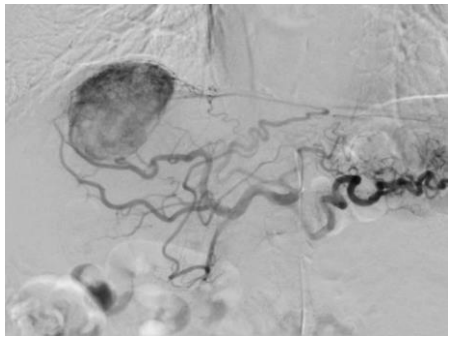
Simulate therapy



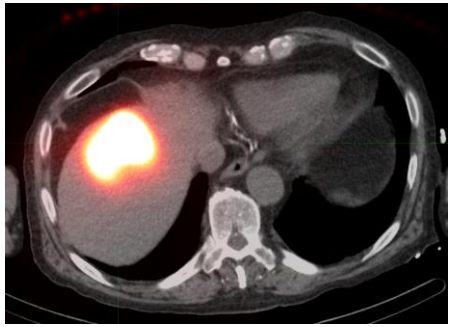
Dosimetric planning



Deliver therapy



Evaluate delivery



Need for “practical” standards

- Primary standards are developed to be chemically and physically stable over time.
- Standard reference sources need to be in a robust, reproducible geometry.
- Rarely are these sources distributed in a clinically useful geometry.
- NMIs/DIs rarely have the resources to offer direct services to end-users
- Not always an NMI’s/DI’s mission to interact directly with end users

The key may be secondary standards!

Primary and Secondary Standards

Primary standard:

- A standard of the highest metrological quality that it is not calibrated by or subordinate to other standards.
- Linked to fundamental physical units (e.g., s, kg).

Secondary standard:

- A standard linked to a primary standard through an unbroken chain of comparisons or calibrations.
- By necessity have a larger uncertainty that primary standards

In both cases, a complete, documented uncertainty assessment is critical to the definition of the standard.

Reminder - Traceability

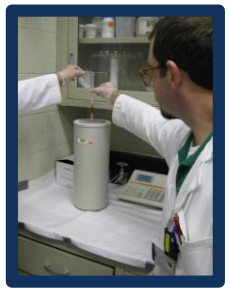
"The property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty" (*VIM*, 2021 draft)

- Unbroken chain of comparisons (or calibrations) back to a primary standard (realization of SI unit).
- Uncertainty assessment is a critical component
- Is a property of a *measurement*, not a laboratory or instrument

Definition of traceability does not prescribe how to establish and maintain it!

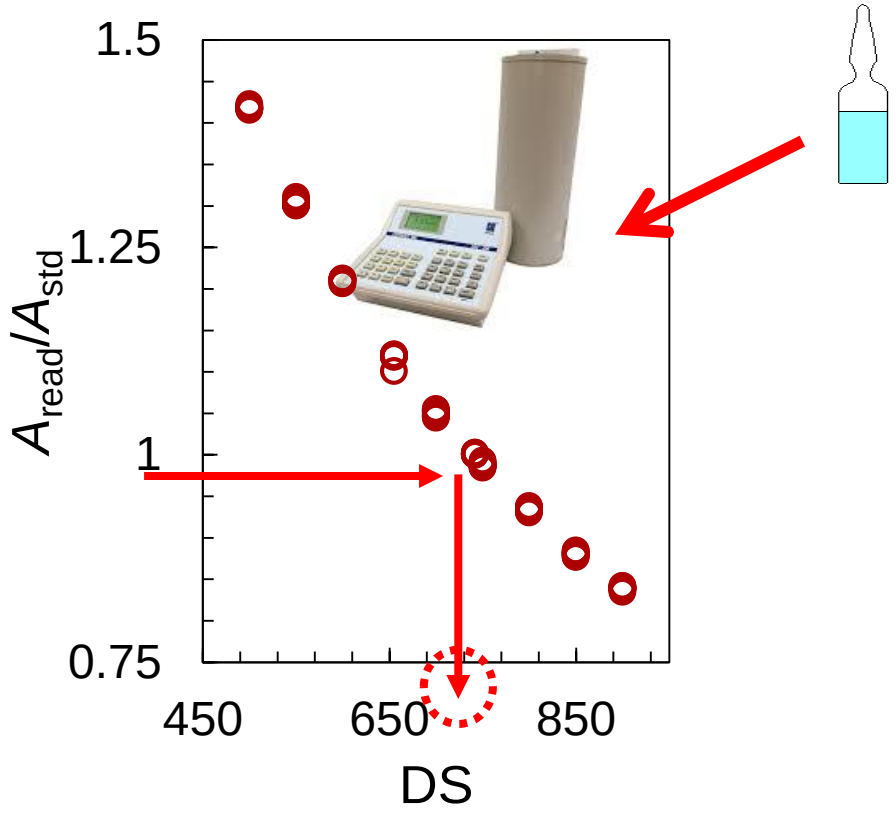
There are many paths that can be taken!

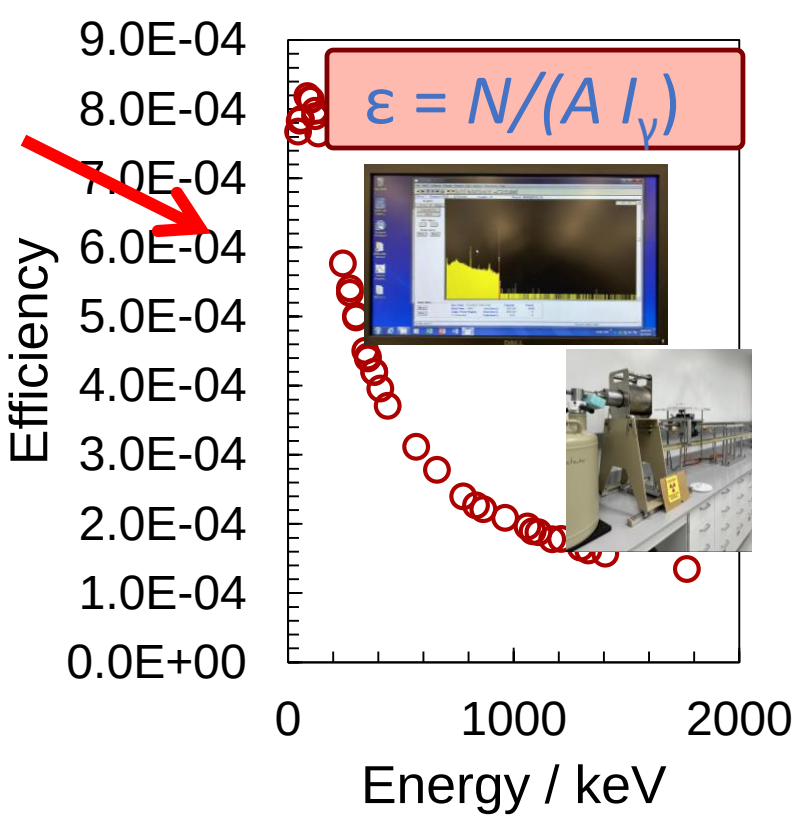
Instrumentation for Secondary Calibrations of Radioactivity

	Measurement Technique	PROS	CONS
	Air-communicating ionization chamber	• Very stable over time • Minimal time required for measurement • Excellent linearity and dynamic range	• Requires temperature/pressure correction • Not suitable for samples <10 MBq • Few commercial product offerings • Requires geometry-specific calibration • Requires isotope-specific calibration • Requires radionuclidic purity
	Re-entrant well-type pressurized ionization chamber	• Widely available • Minimal time required for measurement • Excellent linearity and dynamic range • Used by many NMIs for maintaining measurement standards	• Gas leakage can cause response drift, and thus redundant devices and stability monitoring required. • Not suitable for samples <1 MBq • Requires geometry-specific calibration • Requires isotope-specific calibration • Requires radionuclidic purity
	HPGe Gamma Spectrometry	• Very stable over time • Can measure radionuclide mixtures, or decay chains in dis-equilibrium • Does not necessarily depend on prior radionuclide-specific calibration • Very sensitive, sample activities ~0.01–100 MBq depending on counting positions utilized	• Requires efficiency vs. energy calibration (many emission energies required for this process) for each counting position • Requires dead time correction • Requires consistent peak fitting (calibration vs. samples) • Relies on accuracy and precision of nuclear data • Cannot measure pure alpha- or beta-emitters

Radionuclide calibrator settings and HPGe efficiencies

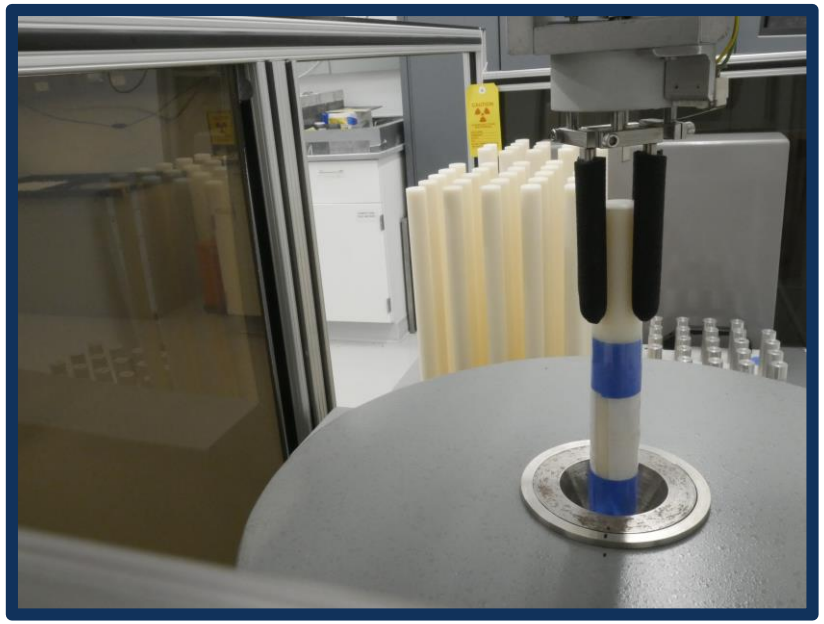
In either case, the instruments need to be calibrated against a standard in the geometry that will be used for subsequent measurements!





➢ A_{std}

Secondary standard ionization chambers



Determine calibration coefficient (pA/Bq) for specific radionuclide

- Standard geometry
- Standard composition

"Stores" primary standard for routine measurements (with slightly higher uncertainty)

Usually have better metrological control than typical clinical instruments

Background: *Reliance on Radionuclide Calibrators*

- Radionuclide calibrators are principal device for activity measurements in the clinic.

- Manufacturer-recommended dial settings are often inaccurate.
  - Generated using a MC model of the dose calibrator
  - Same model dose calibrator can have 5-10% reading differences on the same setting between units
  - Shielding can impact reading.
  - Must account for source geometry!

- Reliance on manufacturer-recommended dial settings or “supplier equivalence” can lead to significant errors.

Accurate measurements in Theranostics: An outstanding issue

Calibration setting numbers on Capintec CRC-15R and CRC-25R dose calibrators.

Isotope	Gamma factor†	From manual‡	New calibration setting		Percent difference in activity readout
	Γ (R cm^2/mCi h)		2 mL Tube	10 cc Syringe	(%)
^{52}Mn	18.4	676÷2	759±12 (÷2)	777±13 (÷2)	+10.2%
^{64}Cu	1.05	15	16±2	108±2 (x2)	−3.6%*
^{76}Br	14	495÷2	604±9 (÷2)	800±9 (÷2)	+52.6%
^{86}Y	18.9	711÷2	762±12 (÷2)	815±9 (÷2)	−44.1%
^{89}Zr	6.59	465	514±6	527±6	+11.2%
^{124}I	6.59	570	29±1	733±7	+24.6%

Wooten AL, Lewis BC, Szatkowski DJ, Sultan DH, Abdin KI, Voller TF, Liu Y, Lapi SE. Calibration setting numbers for dose calibrators for the PET isotopes ^{52}Mn, ^{64}Cu, ^{76}Br, ^{86}Y, ^{89}Zr, ^{124}I. Appl Radiat Isot. 2016 Jul;113:89-95.

Accurate measurements in Theranostics: An outstanding issue

Isotope	Reference	Method	Capintec Model[1]	Source			Result	
				Vessel Geometry	Vessel Volume V_{vessel} (mL)	Liquid Volume V_{source} (mL)	Setting Number[2] N_A (-)	Readout Difference[3] (%)
^{18}F	(Cessna, et al., 2008)	4πβ-LS	CRC-15R	NIST ampoule	5	5	472	+6.4
		"	CRC-15R	Syringe	3	1	484	+8.9
		"	CRC-15PET	"	"	"	501	+12.7
		"	CRC-12	"	"	"	500	+13.3
	(Mo, et al., 2006)	4πβ-LS	CRC-712M	Wheaton vial	-	-	459	-
	(Zimmerman, et al., 2001)	HPGe	CRC-12	Monojet syringe	12	9	482	+8.3
		"	CRC-35R	NIST ampoule	-	-	477	+6.2
	(Zimmerman and Cessna, 2000)	4πβ-LS	CRC-12	Mallinckrodt dose vial	10	5	463	+4.5
		"	CRC-12	plastic syringe	12	9	482	+7.3
^{89}Zr	(Beattie, et al., 2014)	HPGe	CRC-15R	borosilicate glass vial	20	10	517	+8.00-12.0
^{90}Y	(Coursey, et al., 1993)	HPGe	CRC-12	NIST ampoule	-	-	48 (×10)	+50
^{124}I	(Beattie, et al., 2014)	HPGe	CRC-15R	borosilicate glass vial	20	10	494 (with Cu filter)	+14.9-28.0
^{125}I	(Zimmerman, et al., 2002)	NaI(Tl)	CRC-12	plastic syringe	5	-	497	+45
		"	CRC-12	conical glass dose vial	2	-	143	-42
^{133}Xe	(Zimmerman and Cessna, 2000)	4πβ-LS	CRC-12	Dupont dose vial	3	-	181	-2.7
		"	CRC-12	NIST ampoule	-	-	184	-1.7
^{188}Re	(Zimmerman and Cessna, 2000)	4πβ-LS	CRC-12	SoloPak dose vial	5	-	620 (×10)	+22.2
	(Zimmerman, et al., 1999)	4πβ-LS	CRC-12	NIST ampoule	-	-	630 (×10)	+30

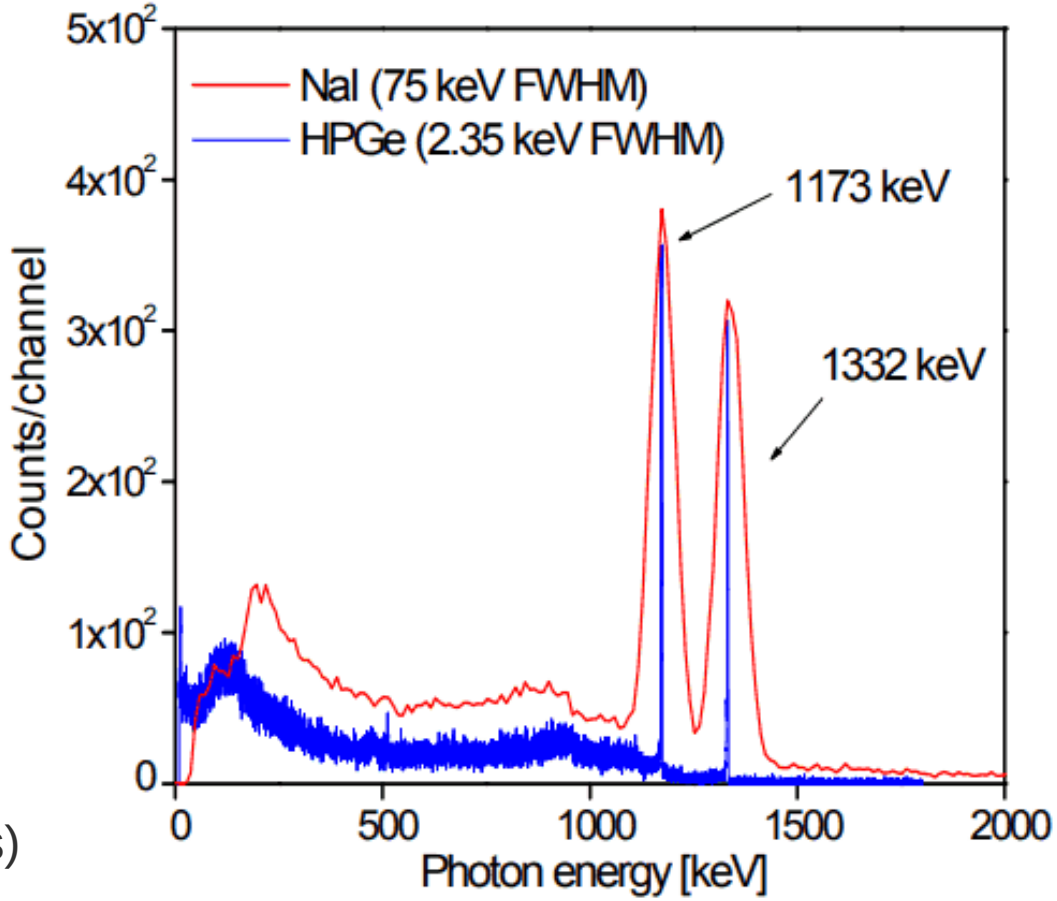
Literature provides clear evidence that empirical calibration settings should be determined or checked against a standard whenever a change in geometry is encountered.

Several new guidance documents being developed by IEC/ISO, AAPM, CCRI are becoming consistent in that recommendation.

Rationale for HPGe detectors

- Wide dynamic range
- High sensitivity and SNR
- Can measure mixed samples, or samples in dis-equilibrium
- Does not require isotope-specific calibration
  - (allowing for measurement of nuclides for which a primary measurement standard dose not yet exist)
- Requires geometry-specific calibration to maintain traceability
- MC-based geometry corrections are *possible*, but model must be validated using appropriate standards

High-Purity Germanium (HPGe) Gamma Spectrometry



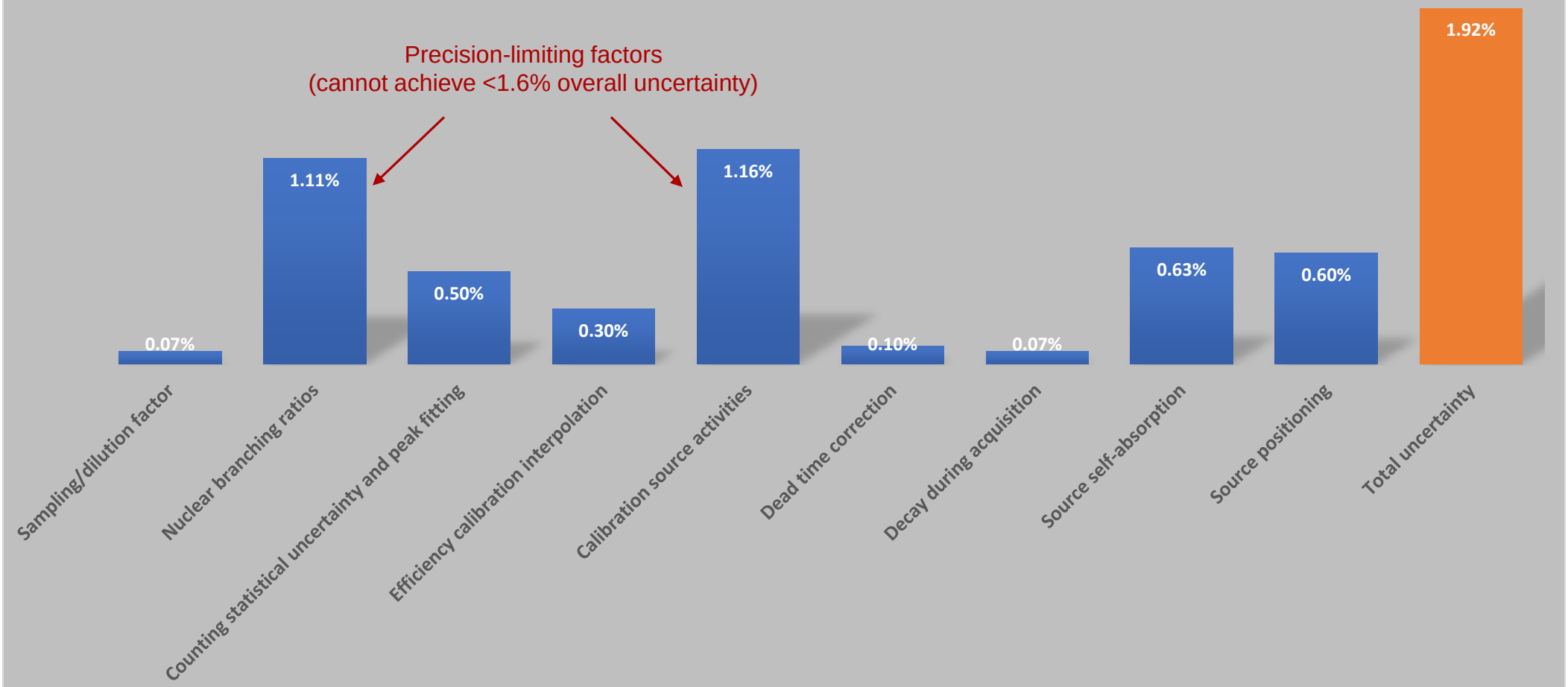
Quantitation requires:

- Reproducible peak-fitting
- Absolute detection efficiency vs. energy
- Source self-attenuation (if cal. geometry differs)
- Dead time correction

Measurement sample preparation – “massic activity”

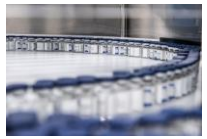
- Clinically-relevant quantities of activity are too ‘high’ to measure directly.
- Allowing for sufficient decay is an option, but uncertainty on half-life may lead to increased measurement uncertainty, as well as significant measurement delay
- Best approach is to prepare a known “mass fraction” of the primary sample.
  - If primary sample mass is known, this is simple – transfer a small amount of mass to a counting vial.
  - If primary sample mass is not known…
    - Transfer a significant fraction of the primary sample into a secondary container to obtain a known secondary mass.
    - Replace the “missing mass” of the primary sample with non-radioactive liquid.
    - Measure the change in ionization current (dose calibrator reading) of the primary sample to determine the fraction of initial mass removed.
    - Dilute the secondary sample to prepare an appropriate counting sample (known mass fraction of initial primary sample).

Sources of measurement uncertainty (*k*=1)



Other ways to disseminate the Bq

Proficiency testing/measurement assurance programs (Example)



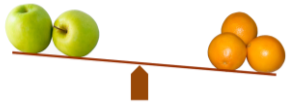
Lab selects source(s) from stock material

Lab measures sources for total activity or massic activity

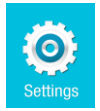
Source is sent to NIST; activity value is transmitted to NIST

NIST gravimetrically transfers solution into standard geometry

NIST calibrates activity/massic activity value

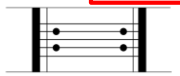


NIST, lab's values compared and information transmitted back to lab



Lab makes adjustments to calibrations as needed

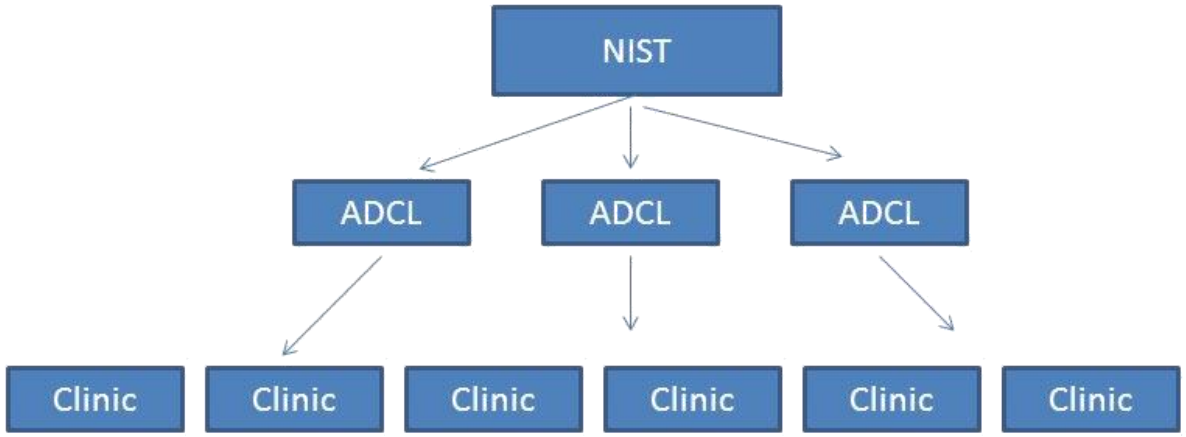
Lab performs QA/QC measurements per QMS



Repeat as often as needed per QMS or regulations

How is this handled with in other radiation modalities?

- Accredited Dosimetry Calibration Laboratories (ADCLs) for calibration of ionization detectors and sealed radioactive sources
- Initiated in 1971, institutions accredited by AAPM
- NIST Traceability maintained



Currently there are no un-sealed source calibration services offered by existing ADCLs in the US; very few, if any, world-wide

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Moving toward a secondary standards laboratory service

- Initial funding from SNMMI being used for feasibility testing and initial comparisons.
- Iowa/UAB activity ratio
  - Cu-64 = 1.009
  - Zr-89 = 0.985
  - Lu-177 = 0.980
  - Pb-203 = 0.990
- Iowa/NIST activity ratio for Lu-177 = 0.9982; UAB/NIST = 1.019

NIST

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

THE UNIVERSITY OF IOWA

Pb-203 measurement example

- ^{203}Pb received from industry partner
- At 9:20 CST on 11/16/22
  - *Industry RPT partner* **= 6.12 mCi**
    (default dial setting)
  - *Commercial radiopharmacy* **= 5.22 mCi**
    (mixed gamma source, HPGe)
  - *Iowa State Hygienic Lab* **= 5.70 mCi**
    (NIST-traceable U-233 source, HPGe)
- U-Iowa / S. Graves = **6.49 mCi (± 3.8%; 2σ)**
  - Correct dose calibrator dial setting inferred from this measurement: #319
  - Dial setting determined from NIST "Round Robin" experiment in 2019: #322

    (Previous study indicated bias of -7.5 % when using default calibrator setting)

Uncertainty Source	Type A	Type B
Sampling/dilution factor	0.07%	
Nuclear data branching ratios		1.11%
Counting statistical uncertainty and peak fitting	0.50%	
Efficiency calibration (energy interpolation)		0.30%
Efficiency calibration (traceable source activities)		1.16%
Dead time correction		0.10%
Decay correction		0.07%
Source self-absorption		0.63%
Source positioning	0.60%	
TOTAL	0.78%	1.76%
Combined (A and B)	1.92%	

Entity	Implied error relative to NIST
Industry RPT Partner	6%
Commercial radiopharm.	20%
ISHL	12%
U-Iowa	**0.9%**

HPGe Feasibility Evaluation (cont.)

- Blinded samples of Lu-177 prepared, measured at Iowa and NIST.
  - Iowa result = 22.23(49) MBq/gram
  - NIST preliminary result = 22.19(20) MBq/gram

- **Difference of ~0.18% indicates agreement within uncertainty**

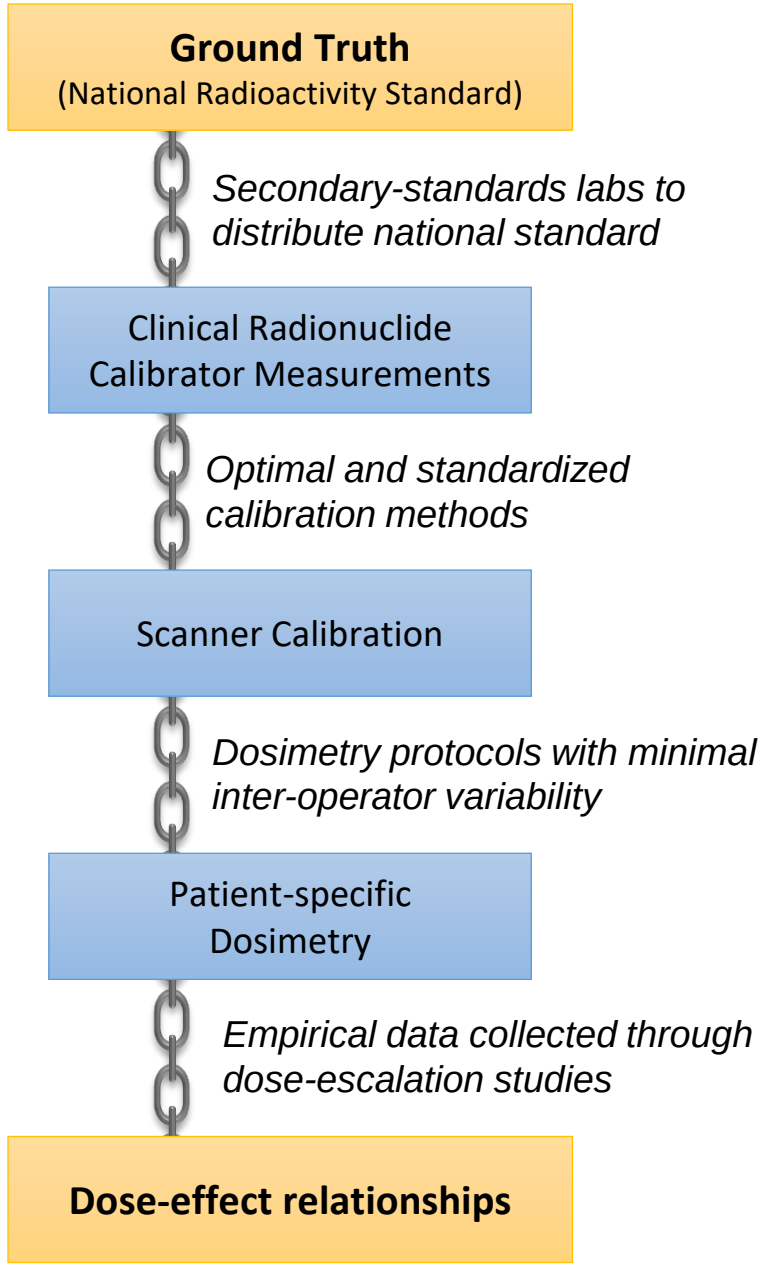
- Novartis activity specifications for ^{177}Lu-DOTATATE (Lutathera) and ^{177}Lu-PSMA-617 (Pluvicto) are approximately -3.3% and +3.2% compared to the Iowa/NIST results.

SSCLs Next steps…

- Actively fundraising to perform the necessary development work and experiments to establish NIST traceability across a wide array of radioisotopes.
- *2 – 3 year plan:*
  - Validate SOPs for absolute activity measurements
  - Evaluate measurement uncertainty sub-components
  - Establish routine NIST oversight of SSCLs
  - Propagate NIST activity standards through in collaboration with Mirion, and through direct measurement services

Conclusions

- There is an urgent need for activity measurement capabilities in our field
- HPGe-based measurement techniques appear viable for enabling secondary standards calibration laboratories
- Clinics and industry will have an inexpensive and rapid option for establishing or verifying activity calibration



Acknowledgements

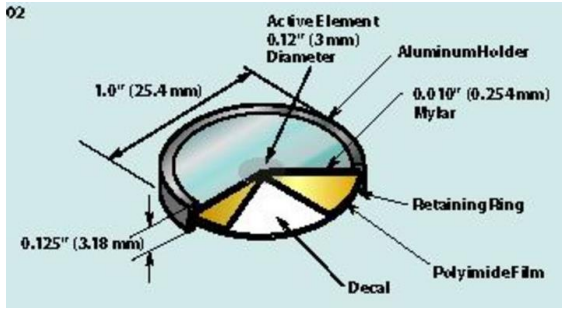
- Our team:
  - Suzanne Lapi
  - John Sunderland
  - Brian Wright

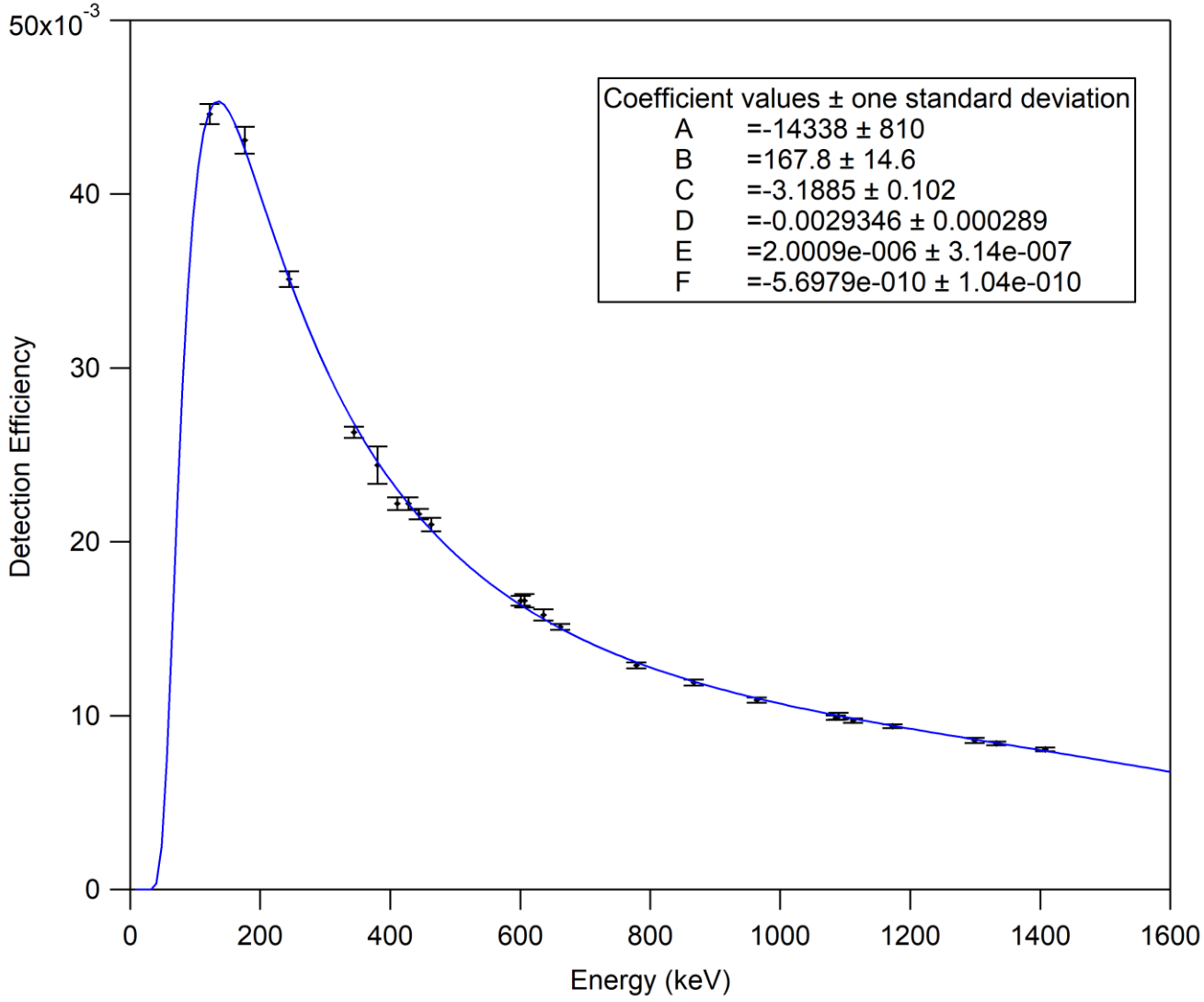
- Funding from:
  - SNMMI
  - The UAB cyclotron facility is a member of the DOE University Isotope Network and is supported through DESC0021269 (PI: Lapi)

Efficiency Calibration

- NIST traceable quantities of
  - ^{57}Co, ^{60}Co, ^{85}Sr, ^{88}Y, ^{109}Cd, ^{113}Sn, ^{125}Sb, ^{137}Cs, ^{139}Ce, ^{152}Eu

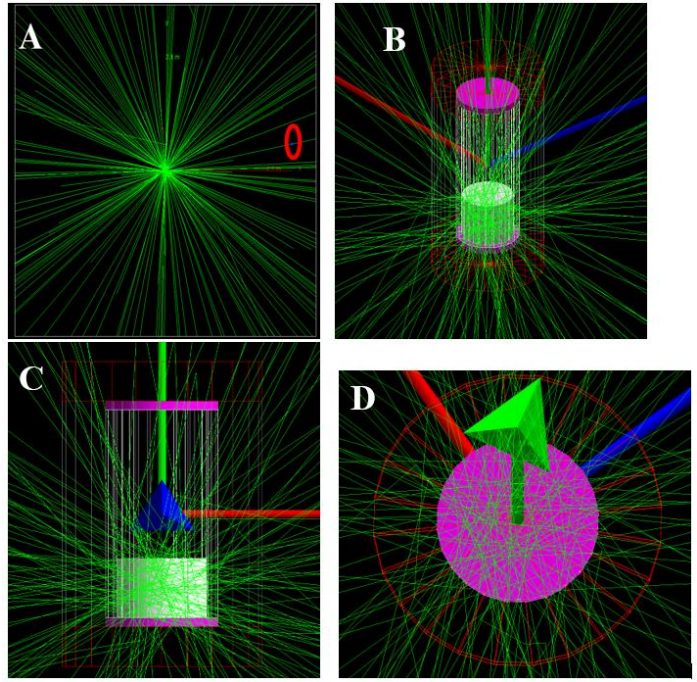
- $u_c \approx 1.16\%$ (manufacturer)

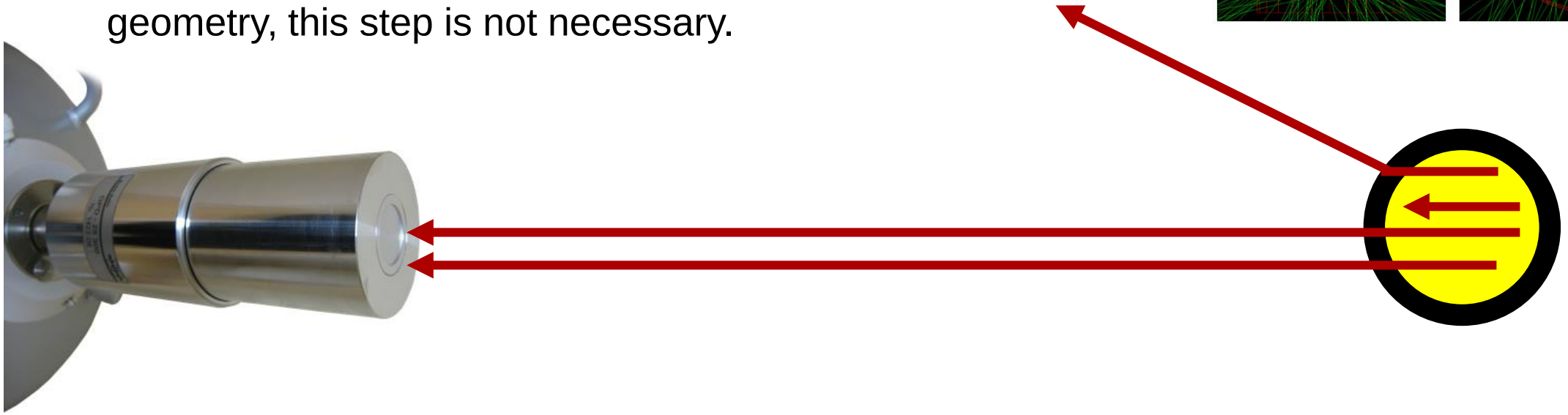




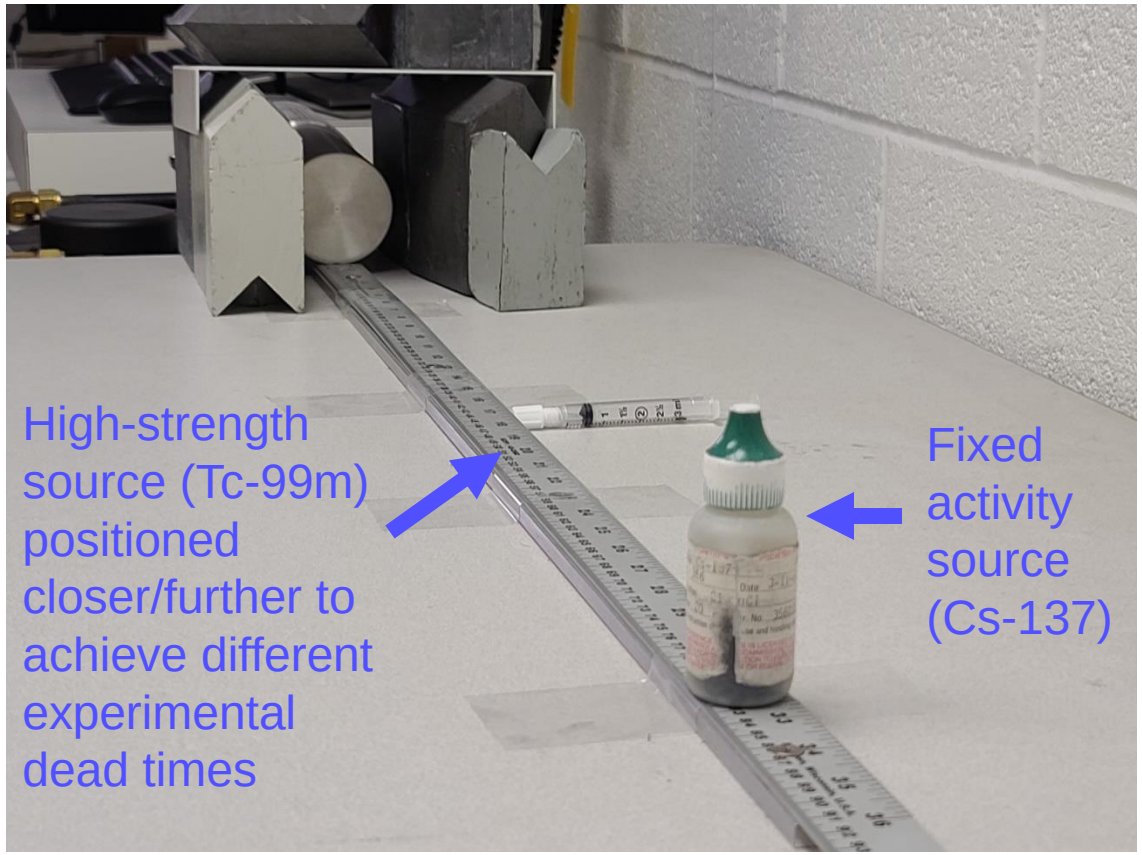
Source self-attenuation

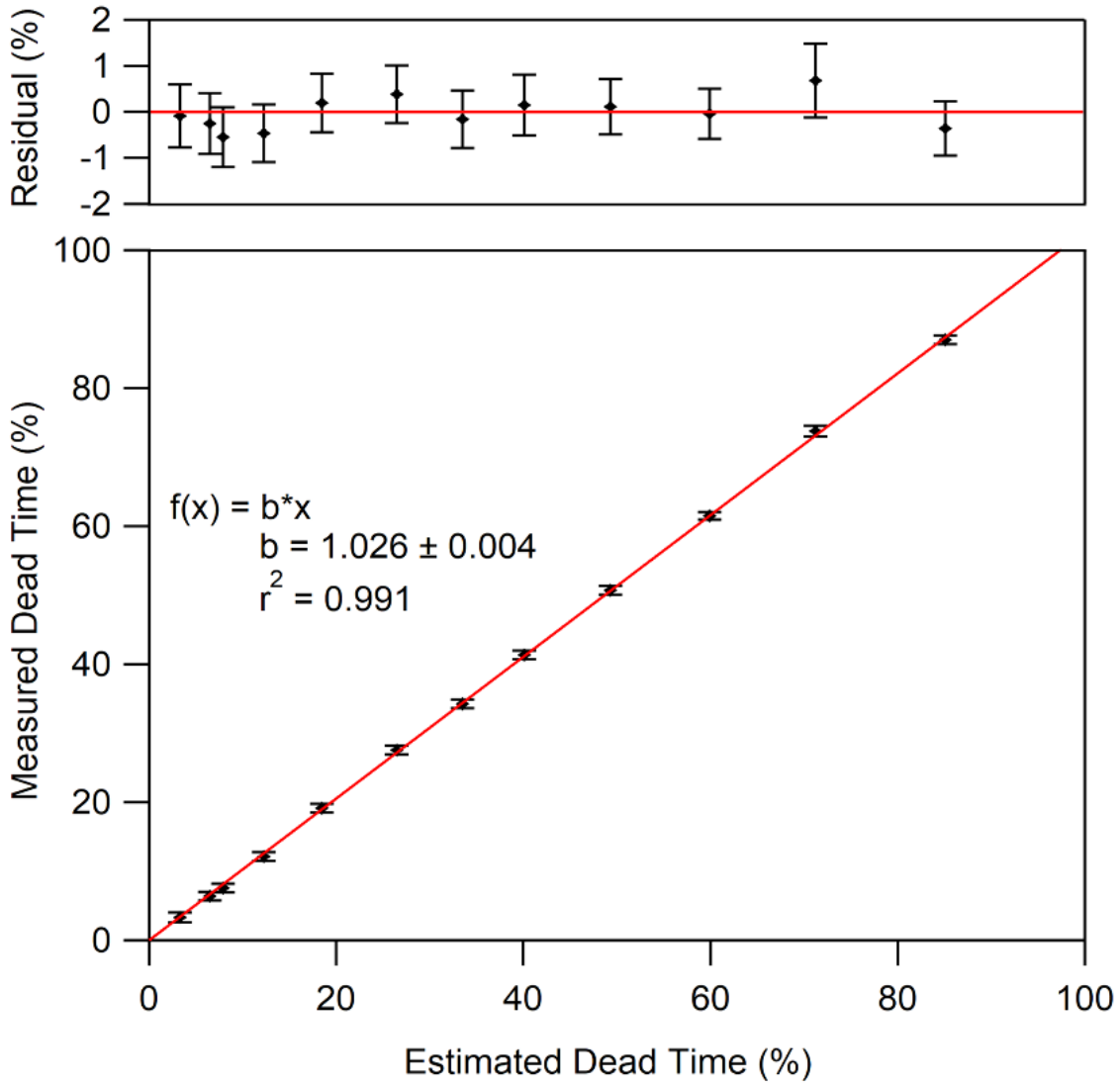
- Even small diameter syringes have significant (>1%) source self-attenuation
- Can be assessed using Monte Carlo photon transport simulations (MCNP, GATE), and verified against a standard.
- If calibration source geometry matches sample geometry, this step is not necessary.





Dead time correction calibration





Alternatively, an electronic pulsar can be introduced, however this deviates from the measurement method.

Decay during acquisition

N = measured counts in gamma peak

I_0 = initial counting rate

T_{live}/T_{real} = fractional live-time

λ = radioactive decay constant

$$N = \int_0^{T_{real}} \frac{T_{live}}{T_{real}} I_0 \, e^{-\lambda t} dt$$

$$I_0 = \left(\frac{N}{T_{live}}\right)\left(\frac{\lambda \, T_{real}}{1 - e^{-\lambda T_{real}}}\right)$$

Instantaneous count rate at start of acquisition

Measured count rate

Correction factor for decay during acquisition