# Radionuclide metrology in support of safe and efficacious nuclear medicine

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# 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**."



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# The becquerel in nuclear medicine

#### Precision measurements of activity are the foundation for:

- BQ Decays per second (of a radionuclide)
- Reliable administration of patient dosages
- Quantitative molecular imaging
- Personalized dosimetry
- Multicenter trials



 ${}^{\bullet}$ 

Zimmerman et al., Z. Med. Phys. 27 (2017) 98.



https://www.snmmi.org/NewsPublications/NewsDetail.aspx?ItemNumber=29483





#### Radionuclide metrology for medicine

COMMISSION INTERNATIONALE DES ÉTAL ONS DE DADANA



# NIST was measuring activity before there was a Bq. And there's always been a focus on medical applications.

CERT	IFICAT.		Quantitative	
Das als Chlorid dargestellte Radiumpröparet Nr. é. entstammt St. Joachimstate/ Urangeschikned und itt demaach praktisch frei Meschor. Es enhist <i>26 50</i> Milligramm Sal. Es wurde am <i>I</i> . <i>KL</i> (492-singe- schlossen in ein Glaraborben (Thuring- ger Glas) von 027 mm Wendstrike. Enterna Durchmener 22 cm Liake	La précision de ces résultats est considérée comme assurée à une approximation de <b>0.2</b> °/ <sub>0</sub> .	These statements are considered correct to $D \cdot \mathbf{Z}^{\circ}/_{0}$ .	Biomarkers Alliance + RSNA	Hand Hand Hand Hand Hand Hand Hand Hand
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nttps://www.nist.gov/	blogs/taking-measure/saving-ma	arie-curies-last-radium-standard		

#### What is the activity of my source?



NIST



# What is the activity of my source?



In most cases, producers and end-users measure activity via

• Radionuclide calibrator (reentrant well-type ionization chamber)

Gamma-ray spectrometry







#### 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

#### NIST defines the becquerel





Absolute activity standards are the basis for radionuclide calibrator calibrations and absolute gamma-ray emission probabilities





### Recently standardized alpha-emitters

Algeta approached NIST in 2005, at the direction of FDA, to develop measurement standards for <sup>223</sup>RaCl<sub>2</sub>. With the success of this "first-in-class" alpha-therapeutic, we have seen increased demand for activity standards for other alpha-emitters with therapeutic potential.

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



#### \*NIST does not endorse commercial products.

A standard for activity of <sup>224</sup>Ra in secular equilibrium with its progeny has been developed, based on tripl

double coincidence ratio (TDCR) liquid scintillation (LS) counting. The standard was confirmed by effici

ARTI

Keywords

TDCR



Applied Radiation and Isotopes 68 (2010) 1523-1528

Contents lists available at ScienceDirect

Radionuclide calibrator responses for  $^{224}\mathrm{Ra}$  in solution and adsorbed on calcium carbonate microparticles

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iournal homepage: http://www.elsevier.com/locate/apradisc

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FI SEVIER

The new NIST primary standard for Ra-223 is transferred to secondary measurements.
Dose calibrator calibration factors first reported in 2010 are revised.
New experiments confirm the validity of the data reevaluations.

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Secondary standards for <sup>223</sup>Ra revised

ARTICLE INFO

ABSTRACT

Applied Radiation

### TDCR is well-suited for alpha-emitters





### LS counting efficiencies from decay data



#### Triple-to-double Coincidence Ratio (TDCR) counting

$$TDCR = N_{\rm T}/N_{\rm D} = \varepsilon_{\rm T}/\varepsilon_{\rm D}$$

The MICELLE2 model\* uses a Monte Carlo approach to calculate  $\varepsilon_T$  and  $\varepsilon_D$  for  $\beta^-$  decay branches

We got about 5.65 counts per <sup>224</sup>Ra decay



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

#### Measurement science $\rightarrow$ measurement $\sim$

# Achieving a primary realization of the becquerel at NIST is only the beginning

Stakeholders care about dissemination

> and traceability

#### Calibrations require precise links





### The TDCR-based <sup>224</sup>Ra activity standard



#### Radionuclide calibrator settings and $I_{v}$ s



#### From standard to measurements





- Delivery of NIST-calibrated reference sources
- Guidance on clinical calibrations
  - Benchmark calibrator settings
  - Geometry/compositiondependence
- Published results, including reviews/updates of decay data



# Nuclear medicine standards and guidances NIST

#### AAPM REPORT NO. 181



The Selection, Use, Calibration, and Quality Assurance of Radionuclide Calibrators Used in Nuclear Medicine

Report of AAPM Task Group 181

June 2012

through an unbroken chain of comparisons, all having stated uncertainties."<sup>17</sup> For radionuclide calibrators, this means that calibration settings shall be traceable to national primary standards of radioactivity.

ANSI N42.13<sup>™</sup>-2004 (Reaffirmation of ANSI N42.13-1986)

#### **American National Standard**

Calibration and Usage of "Dose Calibrator" Ionization Chambers for the Assay of Radionuclides

> "The accuracy of the instruments... shall be such that the measured activity of a standard source... shall be within 10 % of the stated activity..."



NUREG-1576

EPA 402-B-04-001A NTIS PB2004-105421 U.S. NUCLEAR REGULATORY COMMISSION

July 2007 Revision 2

#### **REGULATORY GUIDE**

OFFICE OF NUCLEAR REGULATORY RESEARCH

REGULATORY GUIDE 4.15 (Draft was issued as DG-4010, dated November 2006)

QUALITY ASSURANCE FOR RADIOLOGICAL MONITORING PROGRAMS (INCEPTION THROUGH NORMAL OPERATIONS TO LICENSE TERMINATION) — EFFLUENT STREAMS AND THE ENVIRONMENT

TECHNICAL REPORTS SERIES NO.

Quality Assurance for Radioactivity Measurement in Nuclear Medicine



Multi-Agency Radiological Laboratory Analytical Protocols Manual





#### "A nuclear chocolate box"

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1 H																	2 He
3 Li	4 Be											5 B	6 C β⁺	7 Ν β⁺	8 Ο β⁺	9 F β⁺	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 Р Т	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc β⁺T	22 Ti	23 V	24 Cr	25 Μ β⁺	26 Fe β⁺	27 Co β⁺	28 Ni β⁺	29 Cu β⁺T	<sup>30</sup> Zn	31 Ga γβ⁺T	<sup>32</sup> Ge	33 As β⁺	34 Se γ	35 Br β⁺T	36 Kr γ
37 Rb β⁺	38 Sr β⁺T	39 Υ β⁺Τ	40 Zr β⁺	41 Nb β⁺	42 Mo	43 Τc γβ⁺	44 Ru γ	45 Rh т	46 Pd	47 Ag T	48 Cd	49 In γ	50 Sn T	<sup>51</sup> Sb	<sup>52</sup> Te	53 Ι γβ⁺Τ	54 Xe γ
55 Cs	<sup>56</sup> Ba	<sup>57</sup> La	72 Hf	73 Τa γ	74 W	75 Re T	76 Os	77 Ir	78 Pt γT	79 Au T	80 Hg T	81 TI γ	82 Pb T	<sup>83</sup> Ві Т	<sup>84</sup> Po	85 At T	<sup>86</sup> Rn
87 Fr	<sup>88</sup> Ra т	<sup>89</sup> Ас т														_	
lantha	anides	<sup>58</sup> Ce	<sup>59</sup> Pr	<sup>60</sup> Nd	<sup>61</sup> Pm	62 Sm T	63 Eu	64 Gd	65 Tb T	66 Dy	67 Ho T	68 Er	<sup>69</sup> Tm	70 Yb	71 Lu T		
acti	nides	90 Th T	91 Pa	92 U	93 Np	<sup>94</sup> Pu	95 Am	96 Cm	<sup>97</sup> Bk	<sup>98</sup> Cf	99 Es	100 Fm	101 Md	102 No	103 Lr		

- Projects proceed under agreements with private companies or other government agencies
- Collaborative approach invites students/post-docs to NIST
- We try to keep the queue moving
- International comparisons when possible

Blower, Dalton Trans.44 (2015) 4819.

## Aligned with US FDA mission





The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

#### **Activity standards support**

- Reliable and accurate administration of radiopharmaceuticals
- Dose-response relationships
- Quantitative medical imaging & patient-specific dosimetry
- Multicenter trials

# 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



### Backup slides



# **NIST AT A GLANCE** Industry's National Laboratory







# https://www.nist.gov/calibrations

Contact: jeffrey.cessna@nist.gov

#### **NRMAP** Program



#### The NIST Radioactivity Measurement Assurance Program (NRMAP)

https://www.us-rma.org

Month	lsotope	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	TI-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 Measurement 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.