Measurement of Yttrium-90 at NIST

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NANP Business Meeting, 30 March 2003, New Orleans, LA
Topics

• NIST calibration efforts?

• What is NIST traceability?

• How can commercial nuclear pharmacies participate in NIST programs?

• What is known about the difficulties encountered when performing measurements in dose calibrators?

• What are the best practices for performing 90Y measurements?

• Et cetera
Radiopharmaceutical Program of the NIST Radioactivity Group

- Develop standards for new radionuclides
  - Check decay scheme data, half-life, etc.
  - Measure impurities
  - Determine measurement protocol for routine measurement
- Transfer the standards to industry through the NIST/NEI program
- Collaborate with industry to develop new measurement methodologies and instrumentation (or settings for existing instrumentation)
- Participate in international intercomparisons & BIPM
Radiopharmaceutical and Medical Device Development

- Characterization Measurements
- Instruments & Standards
- Quality Assurance

Metrology

Research & Development

Prototype

Pre-Clinical

Clinical

Market

FDA (INDA)

- FDA Approval

Years 0 1 2 3 4 5 6
The NIST/NEI Measurement Assurance Program for Radiopharmaceuticals

- Ten solution standards are distributed each year as blind samples
- Participant’s results are compared to NIST results and a Certificate of Traceability issued
- Radionuclides for distribution are decided upon by participants in the program
- Two “open months” available for participants to submit samples for calibration
- Geometry - 5mL solution in flame-sealed NIST 5-mL ampoule
# Industrial Participants in the NIST/NEI Radiopharmaceutical Measurement Assurance Program

- Amersham Health  
  Arlington Heights, Illinois  
  South Plainfield, New Jersey

- Bionucleonics Pharma, Inc.  
  Miami, Florida

- Bristol-Myers Squibb Medical Imaging  
  North Billerica, Massachusetts

- Cardinal Health Nuclear Pharmacy Services  
  Albuquerque, New Mexico (formerly Syncor)

- Institute of Nuclear Energy Research  
  Lungtan, Taiwan

- International Isotopes Idaho, Inc.  
  Idaho Falls, Idaho

- Mallinckrodt  
  Maryland Heights, Missouri

- McMaster University Nuclear Reactor  
  Hamilton, Ontario, Canada

- McClellan Nuclear Radiation Center  
  Davis, California

- Missouri University Research Reactor  
  Columbia, Missouri

- MDS Nordion International, Inc  
  Kanata, ON, Canada  
  Vancouver, BC, Canada

- Proxima Therapeutics  
  Alpharetta, Georgia

- Theragenics, Inc.  
  Buford, Georgia

- (Food and Drug Administration)  
  Winchester, Massachusetts
Importance of Radioactivity Measurements in the Clinic

- Accurate activity measurements during trials needed to link dosimetry and radioactivity (assuming uptake model)
- Consistency of activity measurements among multiple trial sites
- Administered dosage specified in terms of an activity unit
  - Safety
  - Efficacy
Traceability to NIST: Official Policy

• Requires an *unbroken chain* of comparisons (with stated uncertainties) to stated reference

• Only *measurement results* are traceable – not procedures, instruments, etc.

• *Provider* of result is responsible for claims of traceability

• Assessing validity of claim of traceability is responsibility of *user* of reported value

• Traceability can be certified through approved NIST program (such as NIST/NEI MAP)

• [http://www.nist.gov/traceability](http://www.nist.gov/traceability)
Chain of Measurements

Uncertainty

1 %  
NIST (Primary standard)

3 %  
Source Supplier (Secondary lab; Direct traceability)

10 %  
Radiopharmacy (Direct or Secondary traceability)

Clinic (Secondary or No traceability)

Sources
Clinic

NIST establishes Relationship
(calibration factor or correction factor)

Establishes link between dose calibrators

Instrument Quality Control
Issues surrounding measurements of $^{90}$Y

- Pure $\beta$-emitter
- Dose calibrators only sensitive to photons; for $\beta$-emitters, measure bremsstrahlung
- Sensitive to stopping material, density
- LS counting: chemical stability
Commercial “Dose Calibrators” at NIST

- Atomlab (Model 100)
- Capintec (CRC-12, CRC-15, CRC-35R)
- MED (Isomed 2000)
- NPL (Vinten, Keithley Electrometer)
- PTW (Curiementor 3)
- Radcal (Model 4045)
Currently testing one with longer chamber, larger FOV for higher activities, longer syringes
Factors Affecting Response in “Dose Calibrators”

- Photon energy
- Vial geometry
- Volume of liquid filling
- Density of Solution
- Composition of Solution
- Position in chamber
- Proper Maintenance & Procedures
Problems with using “recommended settings”

• Results are dependent upon many physical factors
  – Different container
  – Density of solution
  – Filling volume

• Settings are determined by interpolation, dependent upon level scheme data
  – Bremsstrahlung
  – Additional $\gamma$-rays, incorrect $P_\gamma$, $P_\beta$
Possible Pitfalls Of “Dose Calibrator” Measurements

• Incorrect dial setting
  – old 775x100 setting 50% high for ampoule

• Position in chamber
  – using non-standard “replacement” source holder

• Solution Density or Composition?
  – no difference found (within unc.) between chloride solution and Zevalin® product
Current Needs

- Wider availability of NIST-traceable standards
- NIST-traceable standards in different geometries that can be used at clinical level
- Methods for establishing traceability to radiopharmacies/clinics
Solutions?

• Private distribution of NIST-traceable standards in desired geometries (as in $^{125}$I)

• Development of “mock” standards for short-lived radionuclides

• Secondary system based on ADCL model to accredit laboratories that can distribute traceable standards in several geometries to large numbers of sites
Collaborations with industry

• Development of primary standards for new radionuclides

• Determine calibration factors for instrumentation
Measurement of Dial Settings

- LS Measurement of Activity
- Gravimetrically related series of sources
- Measure “Apparent Activity” at a range of dial settings
- Plot dial setting vs. Apparent Activity
- Solve for True Activity
Derivation of dose calibrator settings for $^{90}$Y Zevalin®

• Collaboration with IDEC Pharmaceuticals, Syncor International, Sun Nuclear, and Capintec
• Determine dial settings for 10 mL BD plastic syringes
• Investigate possible volume effects
• Check NIST standard solution vs. Zevalin® product
Experimental

- Prepared 14 syringes with volume range 3-9 mL, with repetition at 3, 5, 7 mL
- Prepared dilution (DF=229) for LS sources
- LS measurements with 2 different methods (8+24 sources)
- Measurements in 6 instruments
  - 3 Capintec dose calibrators
  - PTW activimeter
  - AtomLab dose calibrator
  - Capintec βeta-C
$^{90}$Y Chloride CRC-15 Syringe 3 (5 mL)

Rank 5  Eqn 43  $y^{-1} = a + bx$

$r^2=0.99961672$  DF  Adj $r^2=0.99956562$  FitStdErr=0.0016315468  Fstat=41729.331

$a=0.60380091$

$b=0.0070843625$
Volume effect, PTW chamber

- 5 percent effect
- short chamber, response drop off near top
10 mL BD Syringe
3 - 9 mL soln
CRC12: 55+/−2 x 10
AEA Technologies $^{90}\text{Sr}/^{90}\text{Y}$ “Mock” standard

• Could provide a long-lived source that will simulate $^{90}\text{Y}$ in a 10 mL syringe geometry

• Uses $^{90}\text{Sr}/^{90}\text{Y}$ and shielded walls to block out low energy betas (primarily $^{90}\text{Sr}$)
• linearity study - results linear within measurement unc.
• volume study - results similar to solution results
• established a method to provide traceability for this geometry
Conclusions

• Syringe calibration factor established
  – Report of Test available from IDEC
  – Results to be presented at ICRM conference, Dublin, Ireland, June 2003
  – Full-text to be published in ICRM Proceedings, Applied Radiation and Isotopes

• AEA 90Sr/90Y “Mock” Standard Investigated
  – Characterization measurements done
  – Methodology for NIST traceability in place
Remaining Issues

• NIST traceable solution standards for long term Quality Control

• ...
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$^{90}\text{Y}$ Decay Scheme

- $^{90}\text{Y}$
  - $2^-$
  - $0.0$ $64.00$ h

- $^{90}\text{Zr}$
  - $0^+$ $1760.7$ E0
  - $0^+$ $2280.1$ $99.98555$
  - $0^+$ $519.4$ $0.0115$

Stable
Importance of Radioactivity Measurements in the Clinic: Clinical Trials

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