Measurement of Yttrium-90 at NIST

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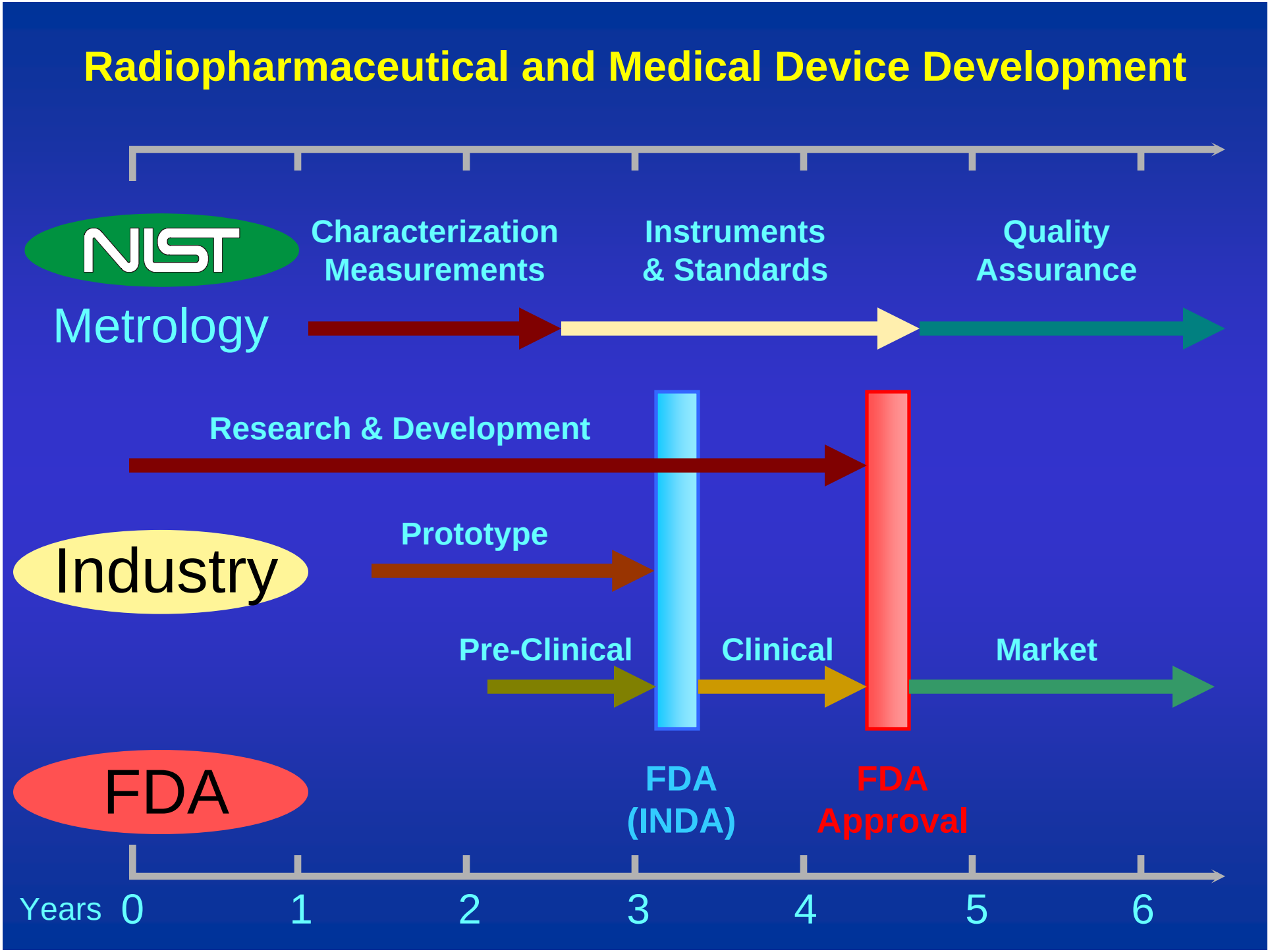
Topics

- 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
NIST
Metrology
Characterization Measurements
Instruments & Standards
Quality Assurance
Research & Development
Industry
Prototype
Pre-Clinical
Clinical
Market
FDA
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

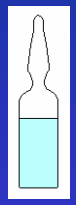
- Requires an *unbroken chain* of comparisons (with stated uncertainties) to stated reference
- Only *measurement results* are traceable – not procedures, instruments, etc.
- *Provider* of result is responsible for claims of traceability
- Assessing validity of claim of traceability is responsibility of *user* of reported value
- Traceability can be certified through approved NIST program (such as NIST/NEI MAP)
- http://www.nist.gov/traceability

Chain of Measurements

Uncertainty

Sources

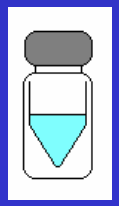
1 %

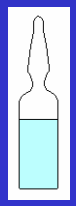


NIST

(Primary standard)

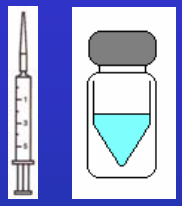
3 %





Source Supplier

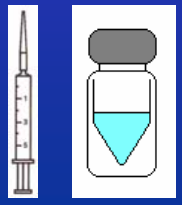
(Secondary lab; Direct traceability)



Radiopharmacy

(Direct or Secondary traceability)

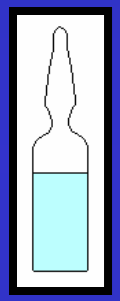
10 %



Clinic

(Secondary or No traceability)

NIST



NIST establishes Relationship

(calibration factor
or correction factor)

Establishes link between dose calibrators

Clinic

Instrument Quality Control

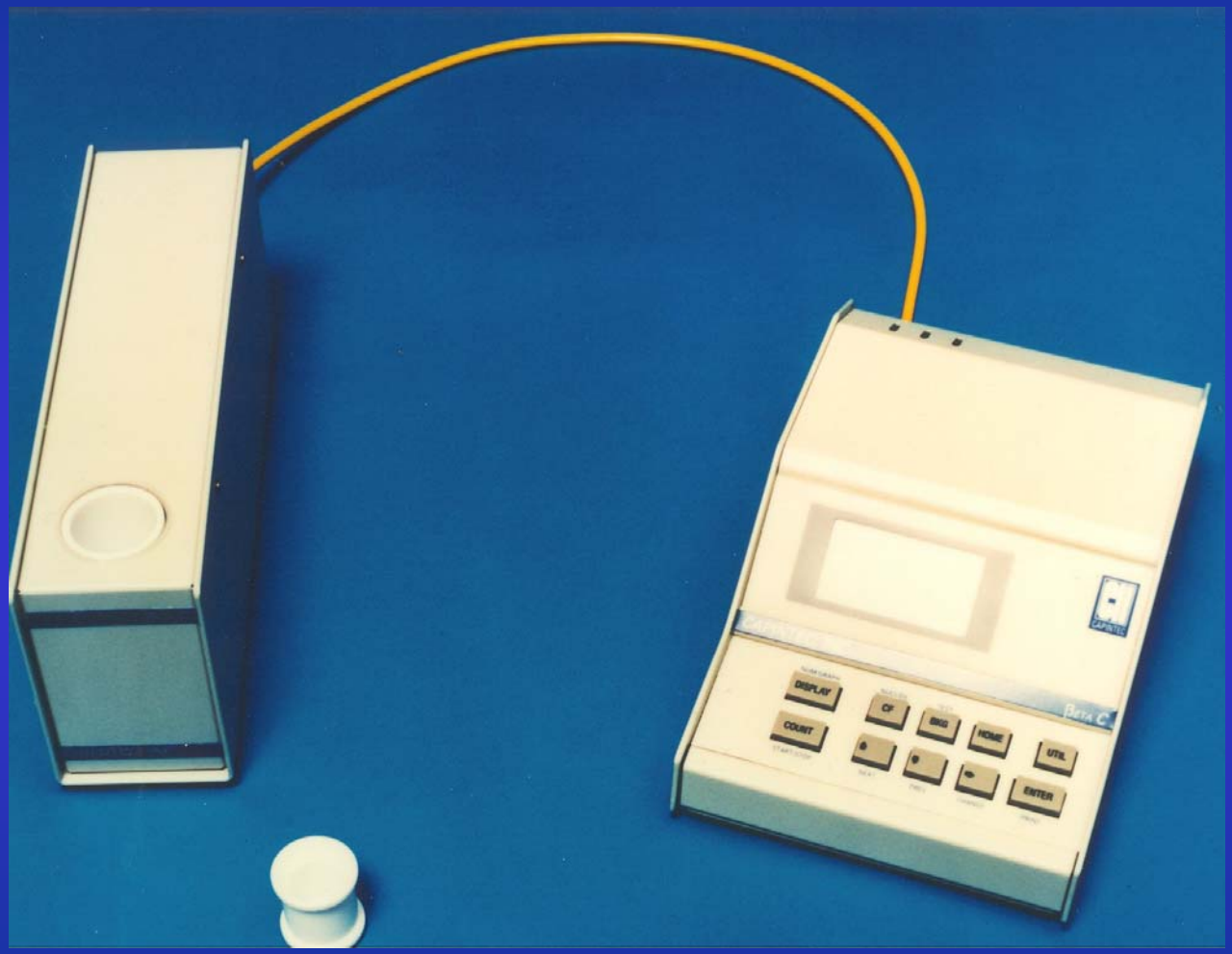
Issues surrounding measurements of ^{90}Y

- Pure β-emitter
- Dose calibrators only sensitive to photons; for β-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)

Capintec βeta-C



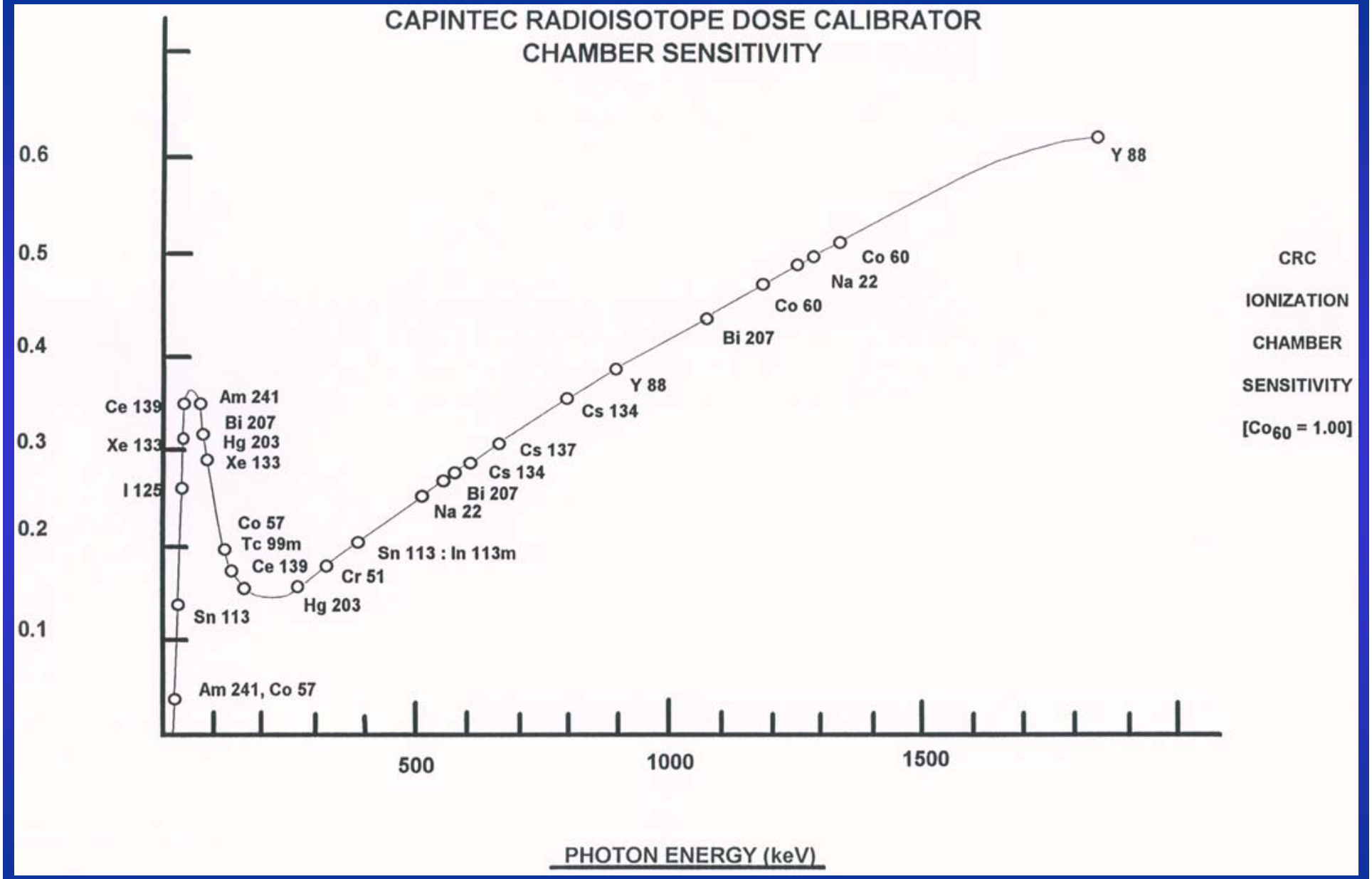
Currently testing one with longer chamber, larger FOV for higher activities, longer syringes

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 γ-rays, incorrect P_{γ}, P_{β}



Radioisotope Calibrators Owner's Manual, Rev E., Capintec, Inc. (1986)

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

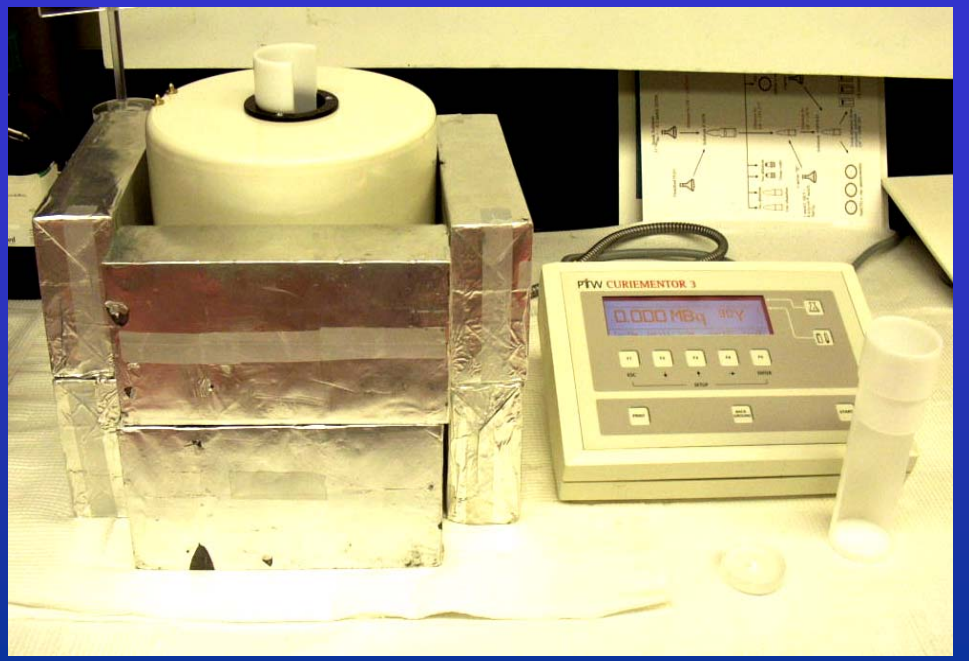
- Wider availability of NIST-traceable standards
- NIST-traceable standards in different geometries that can be used at clinical level
- Methods for establishing traceability to radiopharmacies/clinics

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

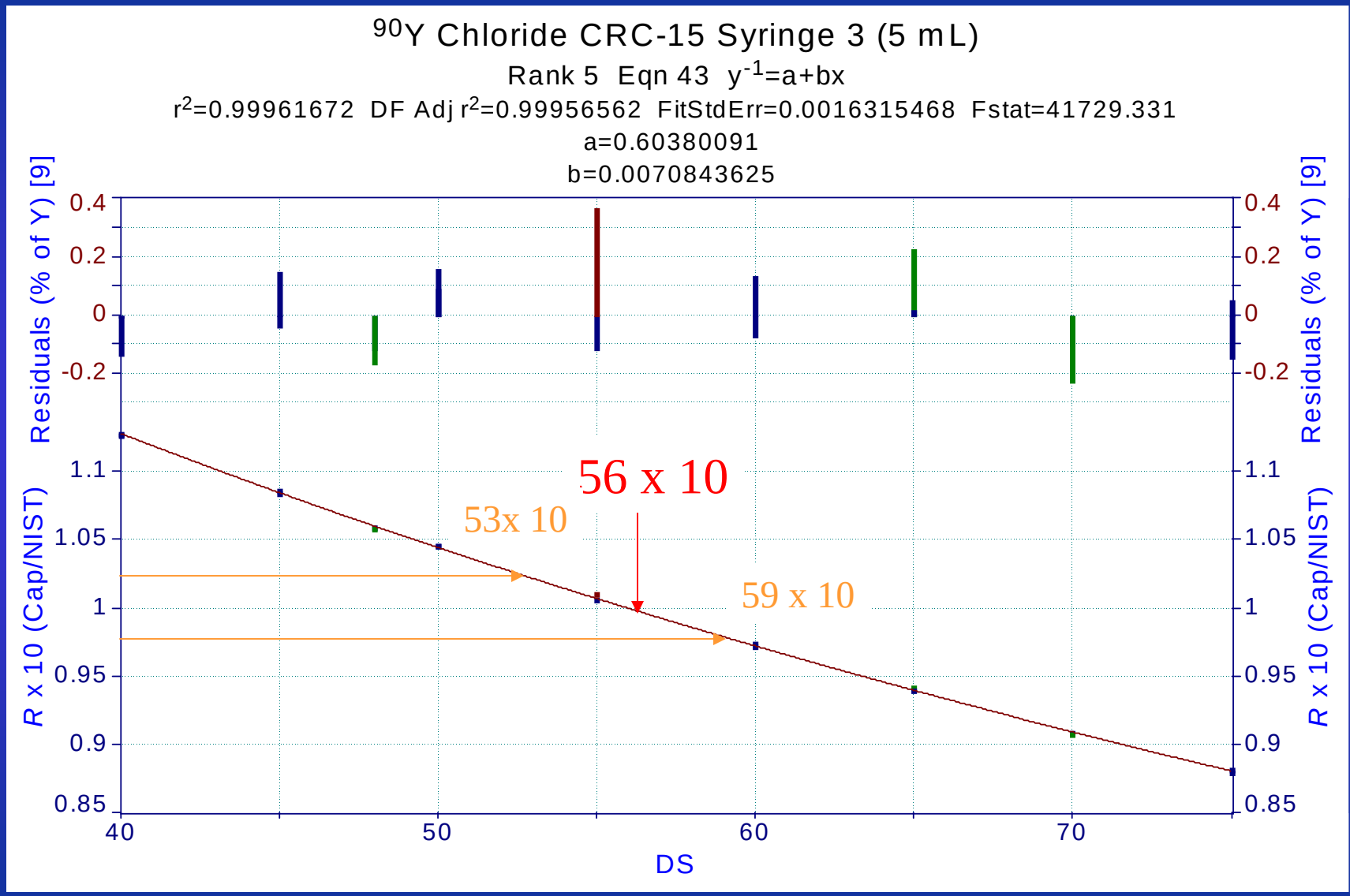
- LS Measurement of Activity
- Gravimetrically related series of sources
- Measure “Apparent Activity” at a range of dial settings
- Plot dial setting *vs.* Apparent Activity
- Solve for True Activity

Derivation of dose calibrator settings for ^{90}Y Zevalin®

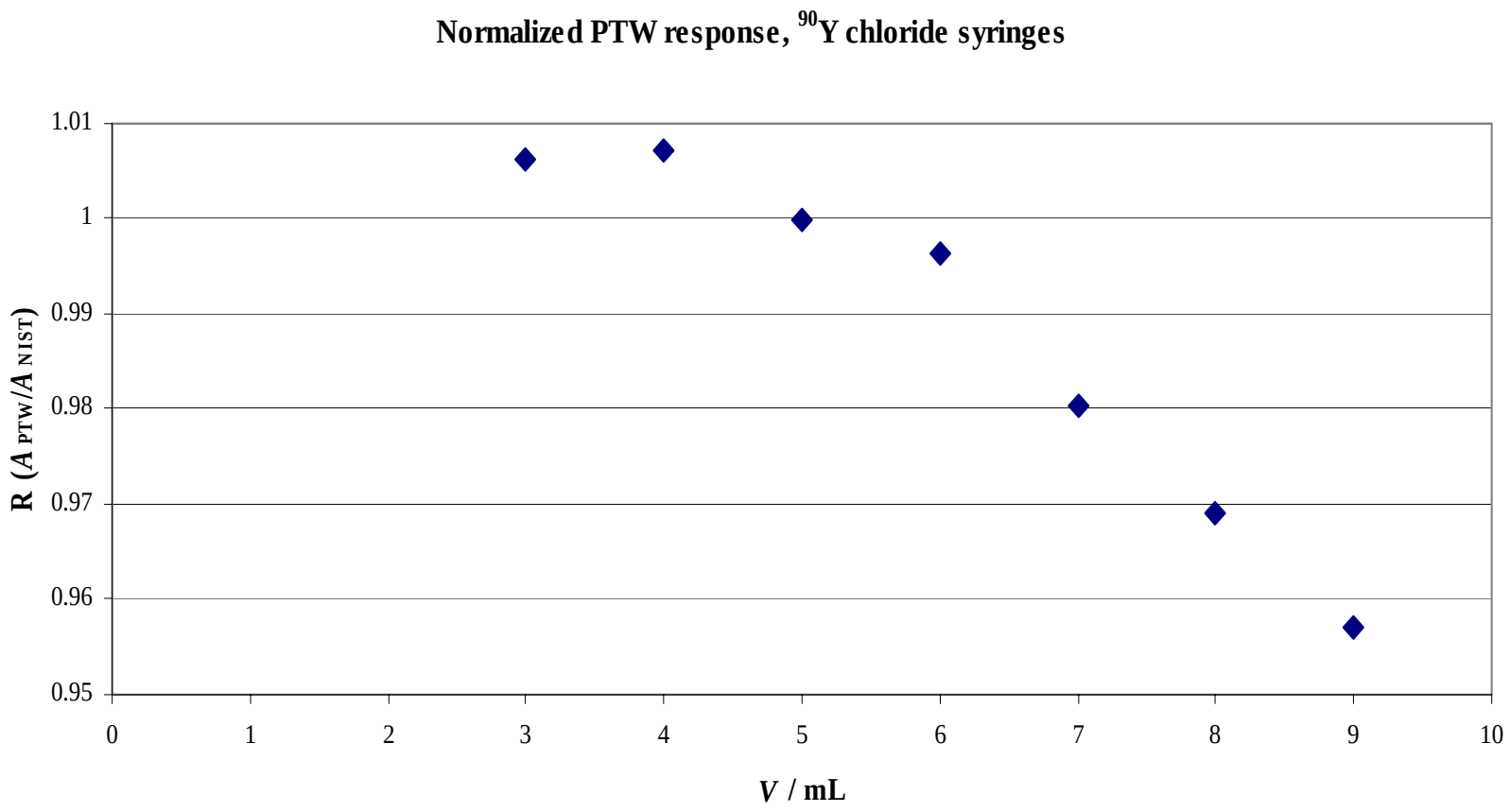
- Collaboration with IDEC Pharmaceuticals, Syncor International, Sun Nuclear, and Capintec
- Determine dial settings for 10 mL BD plastic syringes
- Investigate possible volume effects
- Check NIST standard solution vs. Zevalin® product

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

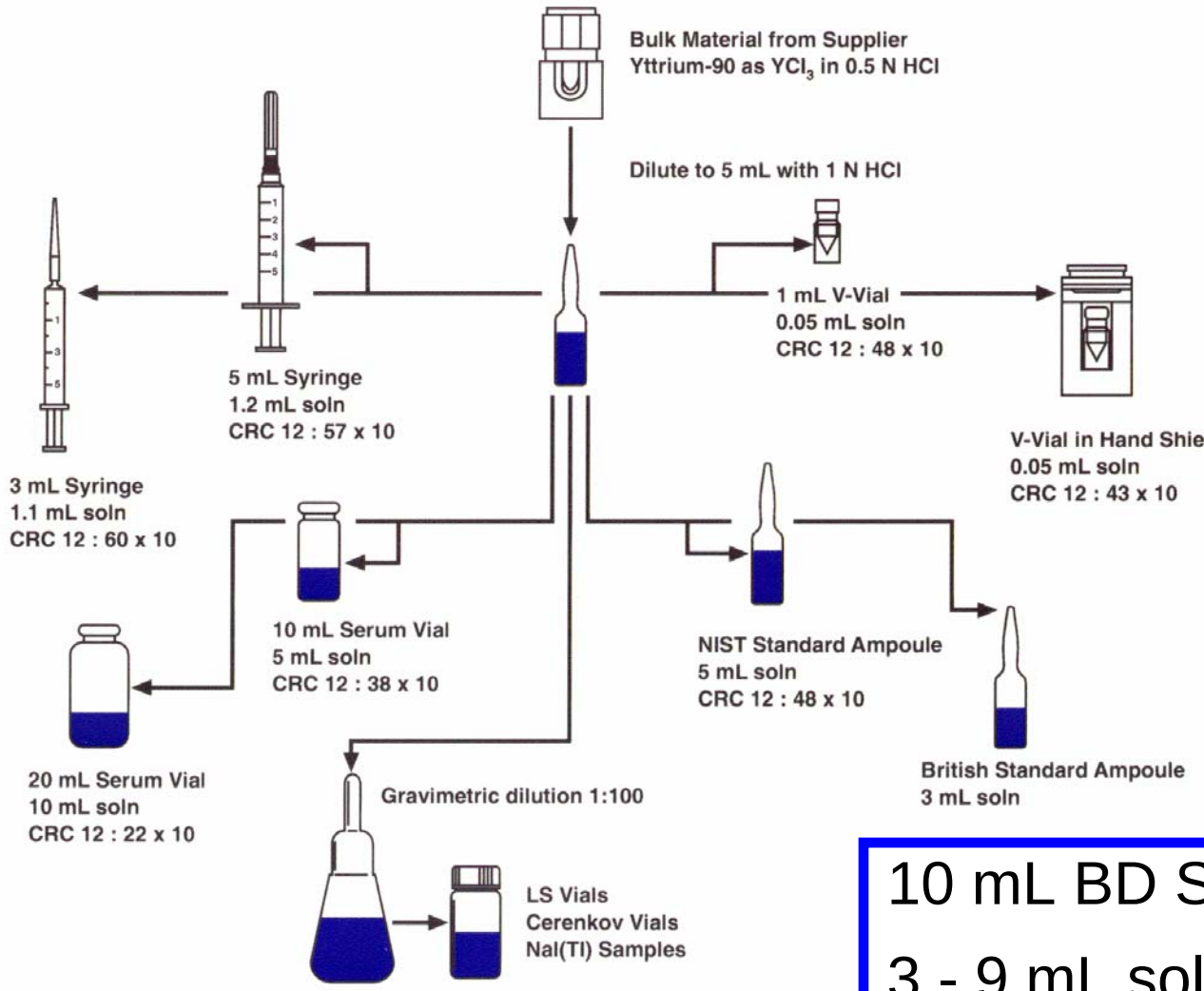

90Y Chloride CRC-15 Syringe 3 (5 mL)
Rank 5 Eqn 43 y-1=a+bx
r2=0.99961672 DF Adj r2=0.99956562 FitStdErr=0.0016315468 Fstat=41729.331
a=0.60380091
b=0.0070843625
Residuals (% of Y) [9]
R x 10 (Cap/NIST)
56 x 10
53x 10
59 x 10
DS
40
50
60
70
0.4
0.2
0
-0.2
1.1
1.05
1
0.95
0.9
0.85

Volume effect, PTW chamber



- 5 percent effect
- short chamber, response drop off near top

SOURCE PREPARATION FOR CALIBRATION OF YTTRIUM-90



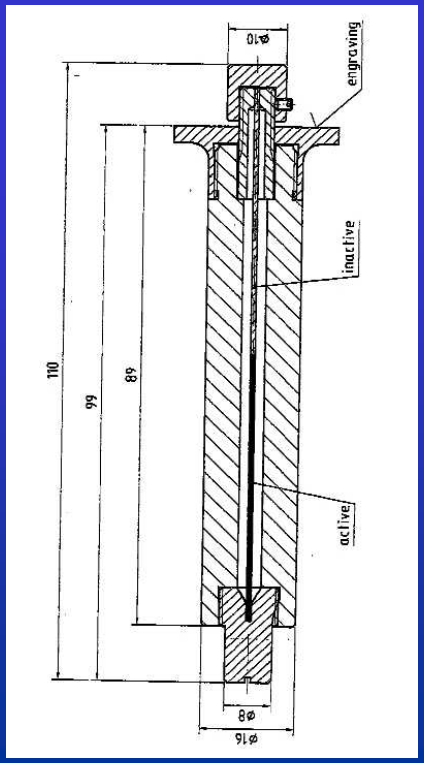
10 mL BD Syringe

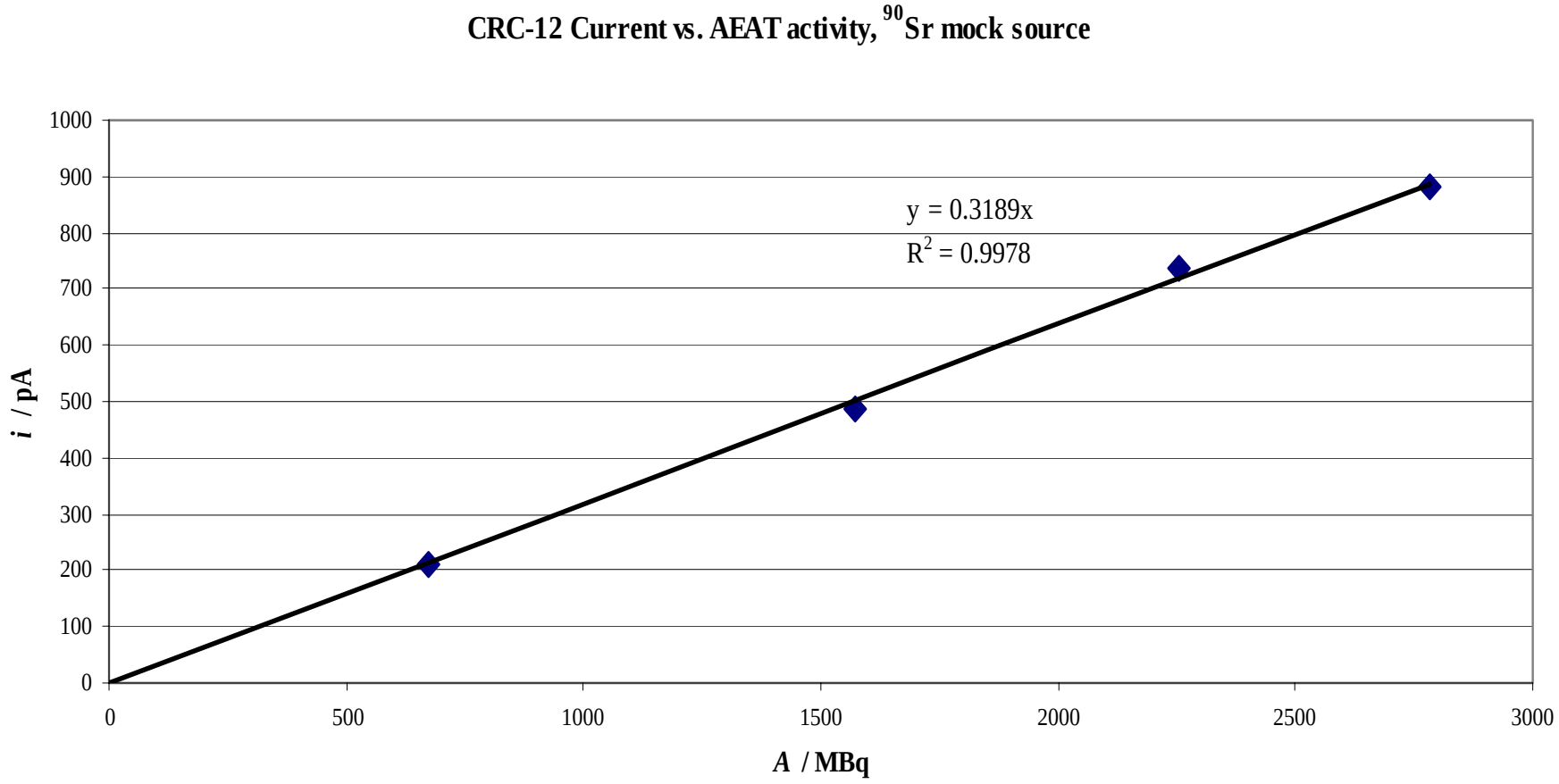
3 - 9 mL soln

CRC12: 55+/-2 x 10

AEA Technologies $^{90}Sr/^{90}Y$ "Mock" standard

- Could provide a long-lived source that will simulate ^{90}Y in a 10 mL syringe geometry
- Uses $^{90}Sr/^{90}Y$ and shielded walls to block out low energy betas (primarily ^{90}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
- ...

Contacts

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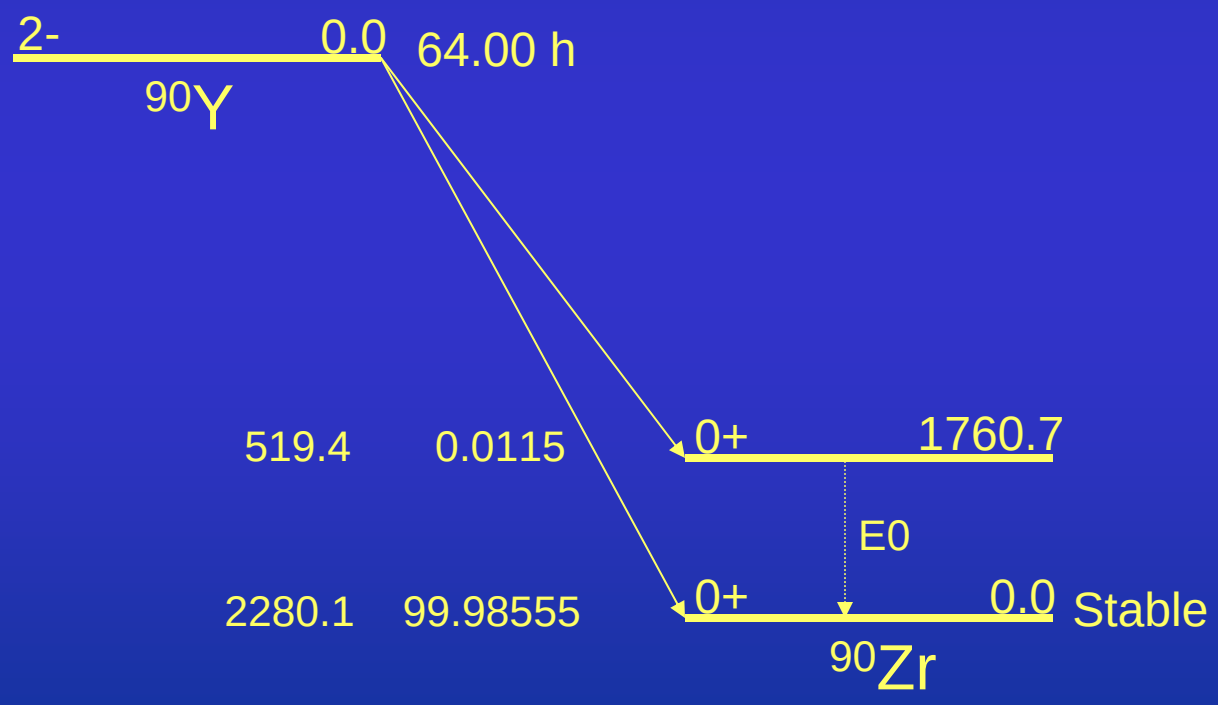
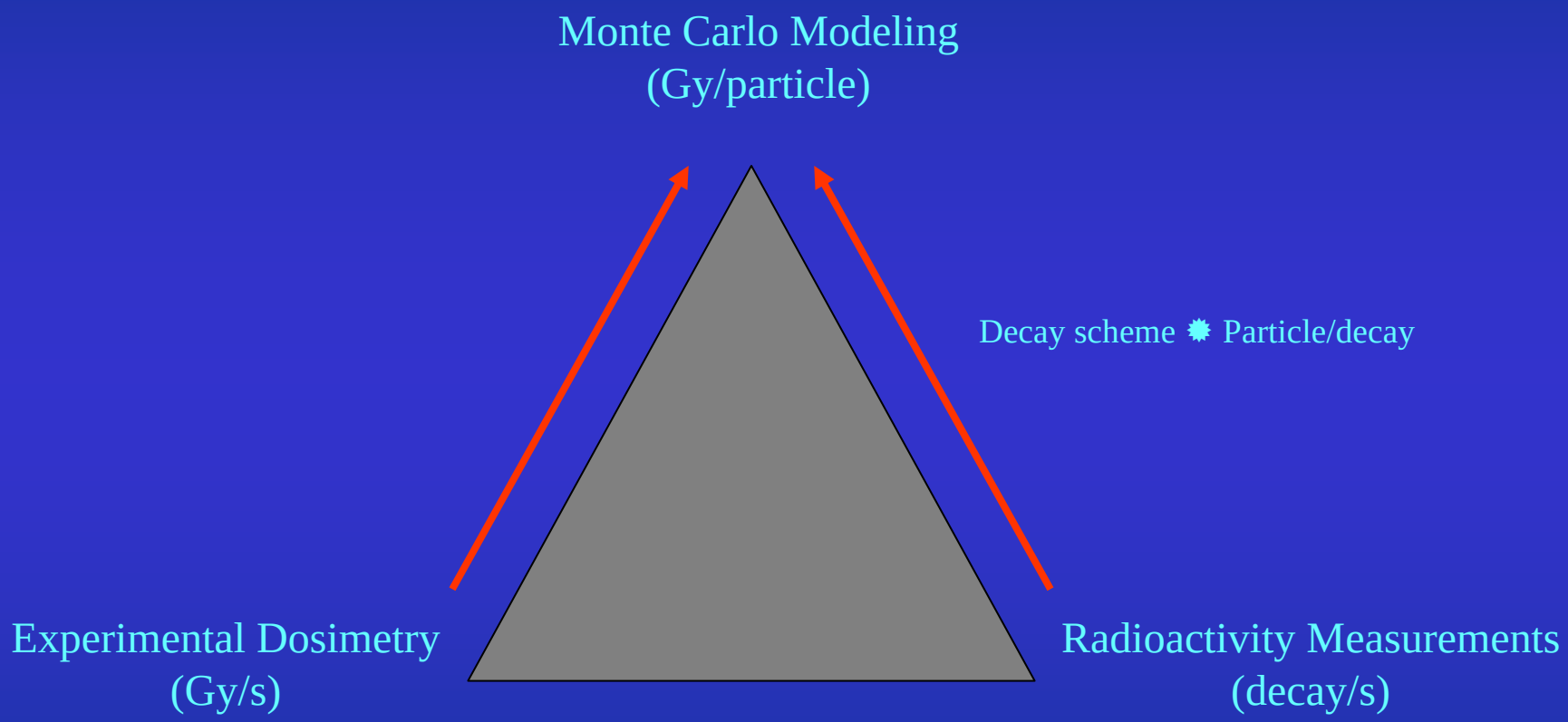
  - Mike Unterweger - (301) 975-5536, unterweg@nist.gov
- Acting Chief, Ionizing Radiation Division
  - Lisa Karam - (301) 975-5532, lisa.karam@nist.gov

^{90}Y Decay Scheme



Importance of Radioactivity Measurements in the Clinic: Clinical Trials



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