Use of Dose Calibrators in Medicine

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Orhan H. Suleiman MS, PhD, FAAPM
Senior Science Policy Advisor
Office of Drug Evaluation IV (Office of New Drugs)
Center for Drug Evaluation and Research

The professional opinions I express today, and the mention or display of any commercial products, is neither an endorsement nor necessarily reflect the official position of the Food and Drug Administration or the Department of Health and Human Services.

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Why do we need dose calibrators?

Verify the amount of radioactivity patients are being administered.

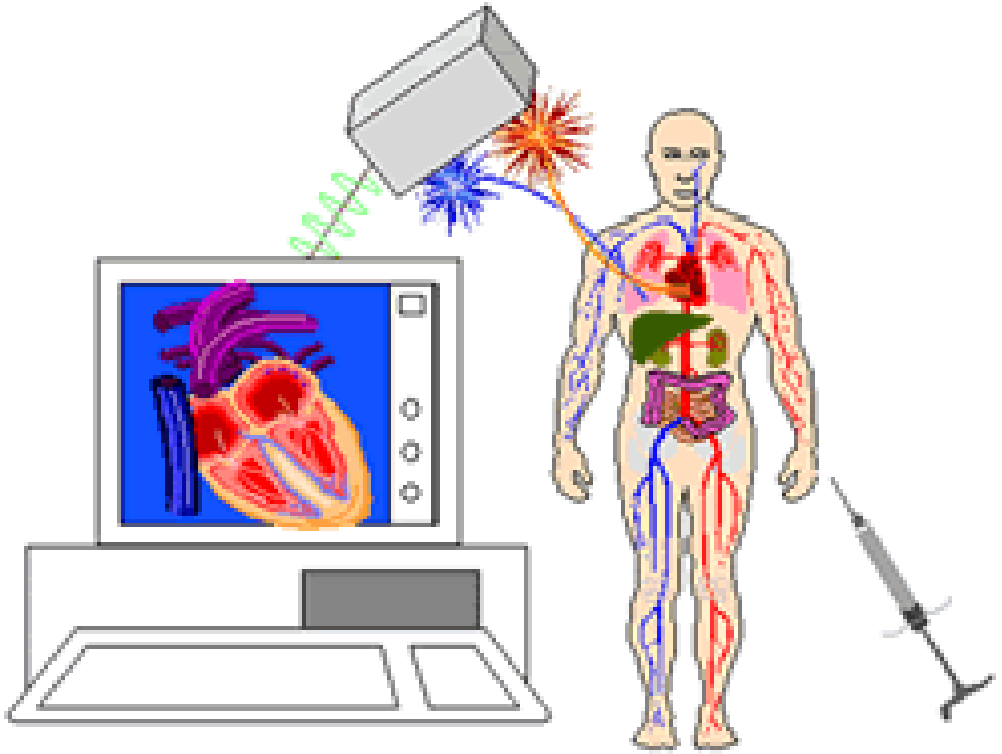
Why do we need to know the activity?

So we can estimate radiation absorbed doses to the organs and whole body.

Such doses not only depend on the (1) activity, but (2) patient size, and (3) biodistribution of the specific radiolabeled drug.

How organ dose coefficients and tables are generated is beyond the scope of this presentation.

For a specific radiolabeled drug
Activity (Bq) → Radiation dose (Gy) to organs



Accuracy of the dose is essential for therapy!

Deviations of ± 20% will impact on patient outcomes, consequently, in my opinion, external beam and brachytherapy radiation therapy are the most science based cancer treatments.

To ensure such precision and accuracy, radiation doses, equipment testing, and calibration are calculated with surprisingly consistent accuracy frequently, with qualified personnel!

Calculating radiation dose from unsealed sources is more challenging.

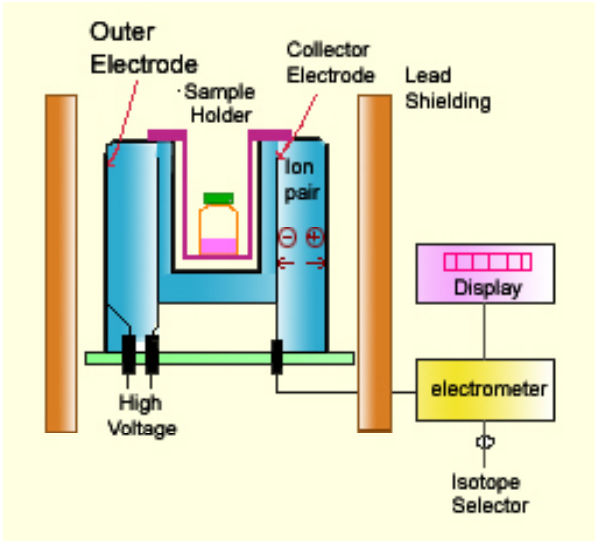
- Knowledge of administered activity
- Patient specific biodistribution
- Patient size

Precision and accuracy is becoming more important for diagnostic imaging.

- Accuracy is essential for imaging based standardized measurements, such as the calculation of standard uptake values (SUV), or monitoring cancer treatment.
- To monitor real changes in the patient, activity measurement variance must be less than the change in tumor size or metabolic activity.

Dose Calibrators designed to verify clinically administered radioactivity are just one type of radiation detector

Dose Calibrator



Dose calibrators primarily for gamma emitters

Primarily measure ionization

Traceability to a reference standard, preferably the same radionuclide with same energies

Alternative detection technologies and protocols exist for validating the type and amount of radiation.

Calibration of particulate radiation more challenging

Microspheres (glass or resin encased Y-90) for hepatic cancer, or

Monoclonal antibodies for the CD-20 antigen in non-Hodgkins lymphoma

- Bexxar® , I-131 labeled tositumomab
- Zevalin® ,Y-90 labeled ibritumomab tiuxetan
- (Maximum dose is limited to 32.0 mCi,1.184 GBq of Y-90)

Precision and Accuracy of Radiolabeled Drugs is not comparable to External Beam Therapy

What is the radiation absorbed dose when we don't even know the tumor mass?

And why is "Maximum dose limited to 32.0 mCi (1.184 GBq) of Y-90 for Zevalin®"

Activity is limited for Patient Safety

The inherent uncertainties in measuring activity, and estimating the radiation absorbed dose for unsealed sources is so large, that to protect against a serious overdose, administered activity is limited. This is not radiation dose in the classical sense!

Dosing for radiolabeled therapeutics is similar to chemotherapy, where systemic toxicity is limiting, not like radiation therapy where a specific target dose is calculated.

First step in improving radiolabeled therapy is to accurately assay the administered activity!

Which brings us back to the dose calibrator!

How can you calculate radiation absorbed dose, when administered activity is not known.

Regulatory requirement (1)

10 CFR Part 35.60 Possession, use, and calibration of instruments used to measure the activity of unsealed byproduct material.

(a) For direct measurements….. a licensee shall possess and use instrumentation to measure the activity of unsealed byproduct material before it is administered to each patient or human research subject.

(b) (1) A licensee shall calibrate the instrumentation ….in accordance with nationally recognized standards or the manufacturer's instructions.

Regulatory Requirement (2)

- 10 CFR Part 35.63 Determination of dosages of unsealed byproduct material for medical use.
  - (a) A licensee shall determine and record the activity of each dosage before medical use.
  - (b) (1) Direct measurement of radioactivity;
  - (c) (1) Direct measurement of radioactivity;
  - (d) "……may not use … if the dosage differs from the prescribed dosage by more than 20 percent."

Accuracy

(a) "……may not use … if the dosage differs from the prescribed dosage by more than 20 percent." –Nuclear Regulatory Commission

(b) 5% - International Atomic Energy Agency

(c) 10% American National Standards Institute

(d) USP General Chapter 821 – Use "authentic" reference sources.

(e) ~ 5% - American Association of Physicists in Medicine Report 181 (June, 2012)

One state requirement

The licensee shall follow all of the U.S. Food and Drug Administration (FDA) requirements.

This state requires the licensee to comply with the drug label requirements. Although the intent is to ensure good practice, this has the potential to cause regulatory and practice of medicine conflicts.

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

Electronics
Clock accuracy
Voltage
Zero
Background

Reference check source
Accuracy
Reproducibility
Linearity
Supplier Equivalence

*American Association of Physicists in Medicine (AAPM) Task Group Report 181, June, 2012.

United States Pharmacopeia

- Geometry
- Background
- Statistics
- Counting losses
- Carrier
- Radiochemical purity

- Radionuclidic Purity
- Labeling
- Identification and Assay of radionuclides
  - Instrumentation
  - Identification
  - Impurities
  - Comparison with calibration Standard

Reference Standards

- Radiation detection requires traceability to a national standard- often this implies the National Institute of Standards Technology (NIST)
- Primary standards- traceable directly to NIST
- Secondary Standards- traceable to primary standards

With all of this information and technology, and qualified professionals, why do we truly not know what patients are administered when using unsealed radioactive sources?

How do we ensure the patient's administered activity is correct?

Simply measuring activity in a dose calibrator does not constitute a calibrated measurement!

Some therapeutics are only calibrated by the manufacturer.

Are sites capable of accurately (1) calibrating or (2) verifying the activity of a known radionuclide?

What does calibration mean? A quality control test or measurement is not a calibration!

Should every clinical dose be verified on site?

- Is manufacturer's certification sufficient?
- Is nuclear pharmacy's certification sufficient?
- What is responsibility of site?

Future Dose Verification Challenges

- Ra-223, an alpha emitter currently undergoing clinical trials in the U.S. will present some interesting challenges to validation and therapeutic dosimetry.
- FDA approved therapeutic beta emitters such as I-131 and Y-90 continue to raise dosimetry challenges.
- Even for diagnostic radiolabeled drugs, activity calibration standards need to be readdressed to move the field forward.

In Closing: Two basic questions

- Does the definition of a dose calibrator need to be updated?
  - Traceability to a national standard.
  - Role and validity of correction factors such as energy, geometry, solution and vial attenuation.
  - Are detector make and model really sufficient?
- Should on site verification via a measurement always be performed prior to radionuclide administration?