International Standards
IAEA- US – Canada

August 4, 2011
American Association of Physicists in Medicine
Vancouver, British Columbia, Canada

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Disclaimer statement

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.

How standards evolve.

- Education - professional forums, publications…..
- Consensus for Good Practice
- Voluntary Standards
- Mandatory Standards (Regulations)
- Enforcement.
- Litigation (regulator of last resort).

How do regulatory standards work internationally?

- No different than they work within the United States!
- A patchwork of voluntary and mandatory standards among different jurisdictions.

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Science and public health is often the foundation upon which such regulatory policy is based.

- International Organizations (IAEA, ICRP, ICRU, IEC, ISO, UNSCEAR)
- National Organizations (non- US)
- NCRP, NRC, CRCPD, FDA (Health Canada, GSF, NRPB, etc.)

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States and Other Agencies

- Conference of Radiation Control Program Directors
- Organization of Agreement States
- State and local municipalities
- Counties
- Territories

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Each agency has it's own rules.

- Voluntary standards (guidance, "should", lack enforcement)
- Mandatory regulations
  - Often promulgated based on legal requirements
  - Most government agencies have an open process of rulemaking. Federal rulemaking:
    - Proposed notice of intent for rulemaking
    - Proposed rule with public comment period
    - Final rule

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Not all processes are open!

- Many professional and industrial organizations limit discussion only to their membership or committees.
- Some even restrict access to their final reports unless purchased.
- However, there has been an effort for free access, e.g. NAS* allows free pdf internet downloads (by chapter); and in recent years the ICRP has allowed public comments on its draft documents.

*National Academy of Sciences

In the United States there are many ways to educate and regulate via standards:

- Reimbursement standards
  - Centers for Medicare and Medicaid Services (CMS)- "reasonable and customary"
  - Insurance Companies
- Product Standards
  - Food an Drug Administration (FDA)- "safety and efficacy"
  - Testing Laboratories
- Professional standards
  - Licensing/ Registration (States)
  - Certification (Professional Boards)
  - Accreditation
    - Joint Commission on the Accreditation of Healthcare Organizations (JCAHO)
    - American College of Radiology (ACR)

Effective dose, E, despite limitations, is a valuable dose standard, but has been adopted very slowly in the United States!

A more perfect metric would also adjust each organ dose for age, sex, and other dose modifying factors such as dose rate.

NASA and NCI have models that do this.

Tissue Weighting Factors (w_t)

Organ (Tissue) Reports:	26	60	DRAFT/103
Gonads	0.25	0.20	0.05/0.08
Breast	0.15	0.05	0.12
Red BM, lung	0.12	0.12	0.12
Thyroid	0.03	0.05	0.05/0.04
Bone surfaces	0.03	0.01	0.01
Colon, stomach (NC- not calculated)	NC	0.12	0.12
Bladder, liver, esophagus	NC	0.05	0.05/0.04
Skin	NC	0.01	0.01
Salivary glands, brain	NC	NC	0.01
Remainder	0.30	0.05	0.10/0.12
Total	1.00	1.00	1.00

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Patchwork process of promulgating standards in the US has been problematic!

1975	FDA's RDRC* Dose limits- rem
1977	ICRP* promulgates effective dose equivalent, H.
1980's	R to air kerma, rad to Gy; rem to Sv; mCi to MBq.
1991	NRC** adopts H for radiation dose
1991	ICRP replaces H with effective dose, E.
1993	NCRP*** adopts E.
2004	ICRP proposes new w_t's, modifying how E is calculated.
2008	ICRP adopts new w_t 's.
2009	NRC considers adopting E

*Radioactive Drug Research Committee (CFR 21 361.1)
*International Commission on Radiological Protection
**Nuclear Regulatory Commission
*** National Council on Radiation Protection and Measurements

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FDA regulates most medical products
(FDA consists of many Centers)

- Center for Drug Evaluation and Research (CDER) – Radiopharmaceuticals
- Center for Devices and Radiological Health* (CDRH) – X-ray, medical devices, accelerators, brachytherapy sources, imaging technologies
- Center for Biologics Evaluation and Research (CBER) – Blood Irradiators
- Center for Food Safety and Nutrition* (CFSAN) – Food irradiators

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Center for Devices and Radiological Health

Authority to regulate electronic and medical radiation products under 3 separate statutes

- Radiation emitting electronic products- includes consumer, non-medical electronic products.
- Medical Devices
- Mammography

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Radiation Emitting Electronic Products (Radiation Control for Health and Safety Act of 1968)*

- Mandatory Emission Performance Standards
- Consumer and Medical Products
- Microwave ovens, lasers
- X-rays (medical and security products)

* Center for Devices and Radiological Health

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Medical Device Act of 1976*

- 510 (k) – predicate device, substantial equivalency
- Class I – Minimal controls
- Class II- Special controls
- Class III
  - High risk devices
  - May require clinical trials for premarket approval (PMA).
  - *Center for Devices and Radiological Health

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Nationwide Evaluation of X-ray Trends (NEXT)

- Collaborative federal/state program which conducts surveys of patient dose from several diagnostic x-ray imaging exams
  - Chest
  - Abdomen/Spine
  - Mammography
  - CT
  - Fluoroscopy

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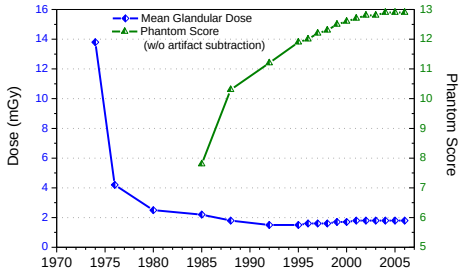
Dose and Image Quality Trends in Mammography



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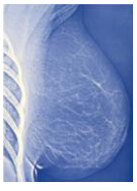
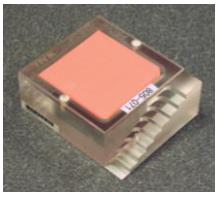
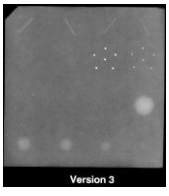
In order to detect change clinically, you need to assure the standard image remains constant.







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Mammography Quality Standards Act of 1992*

- Assures quality by establishing standards and regulating:
  - Quality control of equipment
  - Personnel
  - Image quality (Imaging and dosimetry phantom)

* Center for Devices and Radiological Health

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How are radiolabeled drugs regulated by FDA's Center for Drug Evaluation and Research?

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Basic Research: Radioactive Drug Research Committee (non-IND human research, not for diagnostic, therapeutic, safety, or efficacy)

- Formally codified in 21 CFR 361.1 (1975)
- Allows human research with radioactive drugs without an IND:
  - Research must be basic
  - RDRC must review and approve protocol
  - There is no clinically detectable pharmacologic effect from the administered drug
  - and radiation dose limits are met

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Medical Isotopes (Radiopharmaceuticals)

- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)

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What does it take to get a drug approved? Research Phase

- Clinical Research under an Investigational New Drug (IND) Application
  - Phase I- Safety "n ~ 20 – 80"
  - Phase II- Efficacy "n < several hundred"
  - Phase III- Large scale studies for benefit – risk, dosing, and physician labeling information "n ~ several hundred to several thousand"

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What does it take to get a drug approved?- Application process – New Drug Application

- NDA Process: http://www.fda.gov/cder/regulatory/applications/nda.htm#Related%20Topics:
- Application Fee for NDA ~ $1 M+

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What does it take to get a drug approved? Manufacturing Standards

- Quality and purity of product
  Good Manufacturing Practice (GMP) and Chemistry Manufacturing Control (CMC)

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Off-Label Use

- Can only be used for FDA approved, or exempt, medical products.
- Human research (with an approved or unapproved medical product) must be conducted under an:
  - IND for radiolabeled drugs, or
  - an RDRC for radiolabeled drugs;
  - or an IDE for medical devices.

There is no such thing as off-label use for an unapproved, uncleared, unlicensed medical product.

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Manufacturing Responsibilities

Pharmaceuticals: Good Manufacturing Practice (GMP) – 21 CFR Parts 210, 211, 212 (proposed), 600-680

Medical Devices: Quality System (QS) regulations – 21 CFR Part 820

Guidance for Industry and FDA Current Good Manufacturing Practice for Combination Products
http://www.fda.gov/cder/guidance/OCLove1dft.htm

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Licensing

- FDA does not license radioactive materials
- Radioactive materials licensed by the Nuclear Regulatory Commission (NRC) or
- Radioactive materials licensed by Agreement States (36 states with formal "agreements" with the NRC
- FDA approves biological products by via the Biological Licensing Application (BLA)
- FDA approves radiolabeled drugs via the New Drug Application (NDA)
- www.fda.gov/cder/guidance/5645fnl.htm

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Current Global Issues

- Patient Release Criteria
- Global Molybdenum 99 shortage
- Deterministic effects from imaging exams

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Patient release criteria (1)

30 mCi rule – a simple practical rule, but ignored the fact that doses would vary based on each radiolabeled drug.

Often required overnight stay, or…

Therapeutic doses were administered in 30 mCi "fractions", but unlike external beam therapy, fractionation was not factored into the patient dose calculation!

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Patient release criteria (2)

In 1997 NRC shifted to dose limits for general public (1 mSV), caregivers (5 mSv), and certain family members for specific circumstances.

30 mCi rule still impacts on practice of medicine in some countries and states, requiring overnight hospitalization or limiting administered activity.

Practice still varies worldwide, and remains controversial even in the U.S.

Molybdenum shortage (Global interdependency)

- Canadian Maple Reactors were to replace aging Chalk River Reactor, but were never licensed due to design flaws.
- When Chalk River went offline, worldwide shortage ensued.
- Patchwork network of reactors from Europe, Australia, South Africa, maintained the supply, despite lack of what I perceived was a coordinated response.

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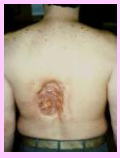
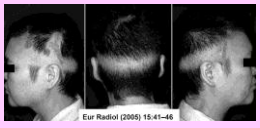
Patient radiation safety

Fluoro Skin necrosis



CT hair loss



Cardiac damage?

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Many voluntary educational initiatives

- NEMA Dose Check standard
- Image Gently and Image Wisely campaigns
- Improving patient awareness
- Encouraging appropriate use criteria (AUC)
- AAPM CT Summit
- FDA Radiation Dose Initiative
- Exam recordkeeping (IAEA smart card, historical FDA patient record card)

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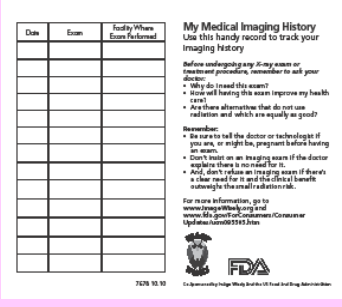

Date	Exam	Facility Where Exam Performed

7676 10.10

My Medical Imaging History
Use this handy record to track your imaging history

Before undergoing any X-ray exam or treatment procedure, remember to ask your doctor:
- Why do I need this exam?
- How will having this exam improve my health care?
- Are there alternatives that do not use radiation and which are equally as good?

Remember:
- Be sure to tell the doctor or technologist if you are, or might be, pregnant before having an exam.
- Don't insist on an imaging exam if the doctor explains there is no need for it.
- And, don't refuse an imaging exam if there's a clear need for it and the clinical benefit outweighs the small radiation risk.

For more information, go to www.ImageWisely.org and www.fda.gov/ForConsumers/ConsumerUpdates/ucm083343.htm

FDA

http://www.imagewisely.org/Patients.aspx

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Should we be concerned about multiple exams, including nuclear medicine doses?

- Cardiac risk is a known non-cancer risk associated with radiation.
- Some patients have received as many as 15 multi modality imaging exams*.
- Unlike x-ray, highest doses are not skin doses, but internal organs, and not detected.
- Mean nuclear medicine doses are twice the mean CT dose (ICRP Report 160).

» American College of Cardiology (New Orleans, April, 2011)

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How do we protect patients?

Mean Dose per Patient in the United States
(395 million total exams)

- **Nuclear Medicine*** ~ 18** million exams (4.5% of exams, 26% of collective dose) 12.8 mSv/patient (1st)
  85% of dose from cardiac procedures
- **Interventional FI*** ~ 17** million exams (4.3 % of exams, 14% of collective dose) 7.5 mSv/patient (2nd)
  53 % of dose from cardiac procedures
- **Computed Tomography (CT)*** ~ 67** million exams (17 % of exams, 49% of collective dose) 6.6 mSv/patient (3rd)
  49% of dose from abdomen/pelvis procedures
- **Conventional R/F** ~ 293** million exams (74% of exams, 11% of collective dose) 0.34 mSv/patient (4th)

– *High dose procedures performed with drug imaging agent.
– ** NCRP Report 160 Ionizing radiation Exposure of the Population of the United States (2009)

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Why aren't we seeing deterministic effects from nuclear medicine procedures?

- Highest dose to internal organs, not visible.
- Additive and delayed effects may not occur for days, weeks, or months.
- Cardiac damage from radiation difficult to differentiate from patients who may have cardiac disease and are the ones imaged.
- Dicentric analysis for radiation dose not a common test procedure (0.25 Sv threshold), but has been observed in cardiac fluoroscopy patients.

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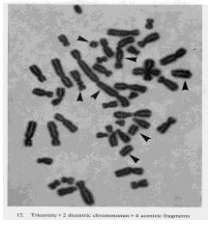
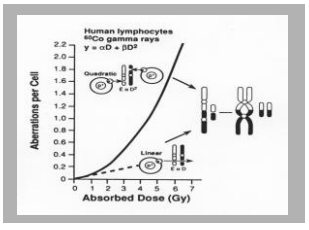
Dicentric Analysis is a potential tool to verify radiation effects from radiological procedures

TRICENTRIC / DICENTRICS / ACENTRICS





Gordon K. Livingston, Ph.D. REAC/TS, ORISE & ORAU, Oak Ridge, TN

In closing…..

- Although it is essential for qualified personnel to operate these technologies, and we need to assure such qualifications exist …
- One simple technical solution would be modality independent dose display and recordkeeping.

We have:

- IAEA Smart Card
- A movement in the U.S. for standardized medical records, including
- recording radiation dose from “high dose diagnostic procedures”

Organ dose standardization now exists for all modalities

Originally developed for the nuclear medicine community in the 1960’s by the Medical Internal Radiation Dosimetry (MIRD) committee of the Society of Nuclear Medicine and Oak Ridge National Lab. It was adapted for x-ray in the 70’s (FDA), and CT (NRPB) in the 90’s. This capability now exists in many countries and universities.

Today, many patient models exist, from infants to adults (Dose requires a patient of known size!)

This concept is the scientific basis for radiation risk assessment today and can be calculated for all modalities.

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We need to move on to the next logical step, standardized dose display and recording.

- Modality specific “dose” exists:
  - Air kerma, kerma area product for fluoroscopy
  - CTDI* for CT
  - MBq (mCi) administered activity in nuclear medicine
- Whole body dose, and dose derivatives can now be calculated, for standard patients of different sizes.
- Has this idea been discussed globally?

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