FDA: Statutes, Regulations, Guidance, and Inspections
“We are all Educators and Regulators”)

Presented at New England AAPM Meeting
June 3, 2016

Orhan H. Suleiman MS, PhD, FAAPM, FHPS
Former Senior Science Policy Advisor
Food and Drug Administration (Retired)
The opinions I express today are my own. Any information I mention or cite in this presentation was obtained from publicly available sources. Similarly, the mention of any commercial products or services are neither an endorsement or criticism of the product.
The critical path towards mandatory standards (regulation)

- Education - professional forums, publications.....
- Consensus for Good Practice
- Voluntary Standards
- Mandatory Standards (Regulations)
- Enforcement.
- Litigation (regulator of last resort).
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 and 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)
Standards and Regulations on Medical radiation dose

Historically, controlling or limiting patient radiation dose was interpreted as interfering with the practice of medicine, but that has changed.

But what is a high dose? With due respect to Supreme Court Justice Potter Stewart, we “...know it when we see it”....
Mammography Dose Metrics

• 47 Roentgen- entrance skin exposure
• 14 mGray mean glandular dose
• 3 mGray dose limit for “standard” phantom
• 1.8 mGray today
• The mean glandular dose is the standard for measuring dose in mammography.
Dose and Image Quality Trends in Mammography
The “Standard” FDA, ACR commercial Mammography Phantom
Nationwide Evaluation of X-ray Trends (NEXT)

1985 mammography survey conducted as a Nationwide Evaluation of X-ray Trends (NEXT) survey.

Program uses standard, patient equivalent phantoms.

Collaborative program where an exam specific annual survey is conducted to determine radiation associated for a set of standard diagnostic exams (mammography, chest, abdomen, fluoroscopy, CT, pediatric).
Phantoms used in the Nationwide Evaluation of X-ray Trends (NEXT) survey program

Fluoroscopy

CT Head phantom
Nuclear Medicine
Early, pioneering, standard reference mathematical models-

• 1969- Medical Internal Radiation Dosimetry (MIRD) Committee- nuclear medicine organ doses using standard reference organs (Snyder et al) with Monte Carlo @ ORNL
• 1975- This model modified for external x-ray beam sources (FDA- Rosenstein)
• German Gesellschaft fur Strahlen-und-Umweltforschung (GSF)- 1982 (Kramer et al) Concept of voxel phantoms
• British National Radiological Protection Board (NRPB)- 1985 (Jones et al)
• .....mathematical, realistic, stylistic, dynamic, computational models....ICRP Pub 110 (Apr 2009).
Many “standard” reference models. Consortium of Computational Human Phantoms website:
http://www.virtualphantoms.org/
Science caused changes in regulatory concepts ...

In the 70’s....as we developed the ability to calculate organ specific radiation absorbed dose,

regulatory concepts shifted away from the whole body dose to organ/tissue doses.

One legacy example which still exists today, promulgated in 1975, ....is FDA’s radioactive drug research committee (RDRC) program.....
Radioactive Drug Research Committee
Radiation Dose Limits*

<table>
<thead>
<tr>
<th>Organ or System</th>
<th>Single Dose</th>
<th>Annual and Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole body</td>
<td>0.03 Sv (3 Rem)</td>
<td>0.05 Sv (5 Rem)</td>
</tr>
<tr>
<td>Active blood-forming organs</td>
<td>0.03 Sv (3 Rem)</td>
<td>0.05 Sv (5 Rem)</td>
</tr>
<tr>
<td>Lens of the eye</td>
<td>0.03 Sv (3 Rem)</td>
<td>0.05 Sv (5 Rem)</td>
</tr>
<tr>
<td>Gonads</td>
<td>0.03 Sv (3 Rem)</td>
<td>0.05 Sv (5 Rem)</td>
</tr>
<tr>
<td>Other organs</td>
<td>0.05 Sv (5 Rem)</td>
<td>0.15 Sv (15 Rem)</td>
</tr>
</tbody>
</table>

Based on 1975 Nuclear Regulatory Commission’s occupational dose limits

*21 CFR 361.1 (b) (3)

Radiation doses from x-ray procedures that are part of the research study shall also be included.

For research subjects under 18 years of age at his last birthday, the radiation dose does not exceed 10 percent of adult dose.
This disparity between whole body and organ dose limits was finally addressed by the International Commission on Radiological Protection (ICRP) in 1977.
The ICRP has refined the definition of dose over time.

• In 1977 the ICRP (Report 26) introduced effective dose equivalent, H.
• This was modified in 1990 (Report 60) to effective dose, E.
• In 2008 E was updated in Report 103.
• Publication 110 (2009) – Adult Reference Computational Phantoms
Effective Dose* $E$

“Risk based metric, relating partial body irradiations (individual organ or tissue, limited x-ray field) to uniform whole body irradiation.”

The effective dose ($E$) is the sum of the weighted equivalent doses in all the tissues and organs of the body.

$$E = \Sigma_T W_T H_T$$

Where $W_T$ is the weighting factor for tissue $T$, and $H_T$ is the individual tissue or organ dose for tissue $T$.

*International Commission on Radiological Protection (ICRP Report 60, 1990)
E, a Worldwide standard

• Advantage
  – Allows comparison of radiation dose from different sources
  – Single metric

• Limitation
  – Single metric! Creates potential for people to ignore underlying organ doses, which are important for medicine and specific safety situations.
  – Ignores age and gender, so comparisons between populations of different age and gender is problematic
  – It is a radiation protection metric, not rigorously scientific, not originally designed for medicine.
## Tissue Weighting Factors ($w_t$)

<table>
<thead>
<tr>
<th>Organ (Tissue)</th>
<th>Reports:</th>
<th>26</th>
<th>60</th>
<th>103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonads</td>
<td></td>
<td>0.25</td>
<td>0.20</td>
<td>0.08</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>0.15</td>
<td>0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>Red BM, lung</td>
<td></td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
<td>0.03</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td></td>
<td>0.03</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Colon, stomach</td>
<td></td>
<td>NC</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Bladder, liver, esophagus</td>
<td></td>
<td>NC</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td>NC</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Salivary glands, brain</td>
<td></td>
<td>NC</td>
<td>NC</td>
<td>0.01</td>
</tr>
<tr>
<td>Remainder</td>
<td></td>
<td>0.30</td>
<td>0.05</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1.00</strong></td>
<td><strong>1.00</strong></td>
<td><strong>1.00</strong></td>
</tr>
</tbody>
</table>
## Typical Doses - Adults (E)

<table>
<thead>
<tr>
<th>Radiation Source</th>
<th>Effective Dose (E)</th>
<th>Equivalent to # of chest x-rays</th>
<th>Equivalent time</th>
<th>Lifetime* Cancer Mortality Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S. - 1 year</td>
<td>3 mSv</td>
<td>150</td>
<td>1 year</td>
<td>1.5 \times 10^{-4}</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>0.02 mSv</td>
<td>1</td>
<td>2.4 days</td>
<td>1.0 \times 10^{-6}</td>
</tr>
<tr>
<td>Upper GI fl</td>
<td>3 mSv</td>
<td>150</td>
<td>1 year</td>
<td>1.5 \times 10^{-4}</td>
</tr>
<tr>
<td>CT- abdomen</td>
<td>10 mSv</td>
<td>500</td>
<td>3.3 years</td>
<td>5.0 \times 10^{-4}</td>
</tr>
<tr>
<td>Tc-99m-lung perf</td>
<td>1 mSv</td>
<td>50</td>
<td>4 months</td>
<td>5.0 \times 10^{-5}</td>
</tr>
<tr>
<td>Tc-99m-bone</td>
<td>4 mSv</td>
<td>200</td>
<td>1.3 years</td>
<td>2.0 \times 10^{-4}</td>
</tr>
<tr>
<td>PET–FDG</td>
<td>10 mSv</td>
<td>500</td>
<td>3.3 years</td>
<td>5.0 \times 10^{-4}</td>
</tr>
<tr>
<td><strong>Regulatory Limits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual Gen pop</td>
<td>1 mSv</td>
<td>50</td>
<td>4 months</td>
<td>5.0 \times 10^{-5}</td>
</tr>
<tr>
<td>Worker</td>
<td>50 mSv</td>
<td>2500</td>
<td>16.7 years</td>
<td>2.5 \times 10^{-3}</td>
</tr>
<tr>
<td>Emergency Worker</td>
<td>500 mSv</td>
<td>25,000</td>
<td>167 years</td>
<td>2.5 \times 10^{-2}</td>
</tr>
<tr>
<td><strong>RDRC Limits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole body</td>
<td>50 mSv</td>
<td>2500</td>
<td>16.7 years</td>
<td>2.5 \times 10^{-3}</td>
</tr>
<tr>
<td>RBM** (50 x .12)</td>
<td>6 mSv</td>
<td>300</td>
<td>2.0 years</td>
<td>3.0 \times 10^{-4}</td>
</tr>
</tbody>
</table>

*ICRP 60 risk coefficients

**RBM = Red Bone marrow; (H_{RBM} \times w_r) = E
Effective dose, $E$, despite limitations, is a valuable dose standard.

A more perfect metric would further adjust each organ dose for age, sex, and even dose rate...at the cost of practicality. These could be addressed in the future.

Dose limits to ensure equipment safety, e.g. mammography, or chest radiography works—but what about interventional therapies?
These two examples of excessive radiation from fluoroscopy are examples of deterministic effects of radiation, where the severity is related to the dose, sometimes referred to as radiation toxicity. This differs from cancer risk, which is a stochastic risk.

Skin erythema (right arm)  > 3 Sievert skin dose
Radiation burn  > 10 Sievert skin dose
“Now that there are bodies, there is no excuse!”
- 1992 Fluoro Workshop

Stochastic risks are trivial on an individual basis, and they represent an abstract and controversial level of risk, but **deterministic effects are palpable**.

Fluoroscopic skin necrosis had a dramatic effect. It was the factual “injured body”.
No formal dedicated program, Just education, and some tactical rulemaking.

- Professional articles raised concern...
- ACR/FDA 1992 Fluoroscopy Workshop
- Two FDA Advisories (1994 and 1995)
- Dose speedometer and odometer regulations (June 2006) 21 CFR 1020
- Certifications, accreditation, workshops!
- Sentinel Incident- FDA, JCAHO
- Lacked major media attention!
Effect of media can have major impact....... 

Not only did the major media impact on the eventual passage of the MQSA in 1992, it often was the critical difference, especially when the concerns of professionals and public health officials were ignored!

Although a stochastic risk, the media had impact!
Then in 2009 deterministic effects were once again visible - with large scale media attention:

“Cedars-Sinai Medical Center, the prestigious Los Angeles healthcare institution known as the hospital to the Hollywood stars, has been jolted by an FDA alert indicating that perfusion CT performed during an 18-month period exposed more than 200 stroke patients to eight times the normal dose of ionizing radiation for the procedures. “
FDA challenged industry to propose some technical solutions

• Warnings, bells and whistles, when doses are too high!

• Although FDA had the Big Stick authority to impose mandatory technical solutions, industry was able to respond much faster because of the media visibility.
So we have demonstrated an ability, with both education, and various degrees of rulemaking related to dose constraints, to make mammography, fluoroscopy, and CT safer.

• What are the challenges of the future?

• Therapeutic Dosimetry- where we shift from radiation safety and protection to efficacy. (I will discuss in more detail later.)
Statutes/Regulations/Guidance

• Congressional Statutes define federal regulatory responsibilities.
• Voluntary Standards – cannot be enforced
• Mandatory Standards are regulations!
  – Often require enabling legislation
FDA Organization
~14,000 employees

- **Office of the Commissioner**

- **OFFICE of MEDICAL PRODUCTS and TOBACCO**
  - Center for Drug Evaluation and Research
  - Center for Biologics Evaluation and Research
  - Center for Devices and Radiological Health
  - Center for Tobacco Products

- **OFFICE OF FOODS AND VETERINARY MEDICINE**
  - Center for Food Safety and Nutrition
  - Center for Veterinary Medicine

- **OFFICE OF REGULATORY AFFAIRS**
Food, Drug and Cosmetic Act (FDCA) - 1906

- Law has been amended more than 200 times.
- Laws incorporated as subchapters within Title 21.
  - Subchapter D - Drugs (Part 300 - original statute - 1906);
  - Subchapter H - Medical Devices (Part 800 - 1976)
  - Subchapter I - Mammography (Part 900 - 1992)
Radiation Emitting Electronic Products (Radiation Control for Health and Safety Act of 1968)*

- Mandatory Emission Performance Standards
- Includes consumer and medical products
- Microwave ovens, lasers, cell telephones
- X-rays (medical and security products)

* Center for Devices and Radiological Health
Medical Device Act of 1976*

- 510 (k) – predicate device, substantial equivalency to preamendment devices
- 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
Medical Products- are they a drug, biologic, or device?

Is the effect primarily physical (device), chemical (drug), and if chemical- is it naturally produced within the body (biologic)?
Radiopharmaceuticals are not all regulated by the same Center

- Drugs, whose **effect is chemical**, such as the recent cancer therapeutic Ra-223 (Xofigo), and all of the imaging drugs are approved by CDER.

- Biologics, which **occur naturally within the human body**, such as antibodies are licensed by CBER. The CD-20 monoclonal antibodies for non-Hodgkins lymphoma, Bexxar (I-131), no longer sold, and Zevalin (In-111/Y-90), were originally approved by CBER, but that authority has since moved to the Oncology office in CDER. This was an effort to consolidate all cancer drugs under one roof.

- Some radiopharmaceuticals are considered medical devices because their effect is considered physical, such as Y-90 labeled microspheres for liver cancer. The microspheres are **physically sealed sources which are physically trapped in tiny hepatic blood vessels, and are therefore considered a medical device**. These are approved by CDRH.
What does it take to get a drug approved?

Human Subject 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 “n ~ several hundred to several thousand”
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](http://www.fda.gov/cder/regulatory/applications/nda.htm#Related%20Topics):

- Application Fee for NDA ~ $1.8 M+
New Drug Application (NDA) Deadlines
(Go to: www.fda.gov and search on “NDA”)

Within 30 days of filing an application FDA either accepts the application, or returns the application with a Refuse to File (RTF) determination. An RTF may actually save the sponsor time and money over the long run, but in the short term it is often a serious wake up call which identifies serious flaws in the application.

If the NDA is accepted, the application fee is cashed, and the review process begins.

A decision must be made by FDA within 6 months, although there is some flexibility in the process.

If the review proceeds satisfactorily, an inspection of the manufacturing site(s) is conducted prior to the final decision.
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

FDA does not recognize foreign approvals in lieu of FDA approval.
New drugs are not approved without an inspection, regardless of manufacturing site.
FDA not the only federal regulator of medical products: Nuclear Regulatory Commission

Authorizes via Licensing the possession of reactor produced materials

- Originally created as the Atomic Energy Commission (AEC) in 1954.

- The NRC licenses the possession and use of radioactive material, specifically source material, special nuclear material, and by-product material. Naturally occurring radionuclides such as radium were not regulated until recently, when the NRC was given authority for radium and other non-reactor produced but hazardous radionuclides.

- In 1963 the FDA began to require premarket approval of drugs following the thalidomide disaster, but FDA allowed the AEC to continue to regulate radiolabeled drugs.

- In the early 1970’s the FDA assumed the medical authority for radiolabeled drugs, as the AEC was reorganized into the NRC and the Energy Research and Development Administration (ERDA). ERDA later evolved into today’s Department of Energy.
NRC Agreement States
Radiation Dosimetry

• In my opinion, classical radiation therapy is the most science based cancer treatment—with absorbed doses as good as 5-10%!

• Radiolabeled therapies may be the wave of the future, but the dosimetry must be improved dramatically! Current absorbed doses may vary in excess of 50%, and until this is improved, the potential benefit in terms of efficacy will not be attained.
Experiences to date
(not classical dosimetry)

• Thyroid ablation with I-131.

• CD-20 labeled I-131 (Bexxar), and CD-20 labeled In-111 and Y-90 (Zevalin).

• Ra-223 (Xofigo) – improvement in OS!
As medicine evolves into a multi-disciplinary field

• Imaging will take a major role in treatment.
• Traditional lines among the disciplines will blur, and change. We observe this with nuclear medicine.
• The skill and expertise of the imaging and therapy physicists must be adopted for future radiotherapies.
Before finishing my talk......

• The last project I was involved with before retiring in 2014 dealt with the global shortage on Mo-99.

• Due to time constraints, I will be very brief, giving a short overview.

• I prefer some Q and A., and since we break into lunch, I will be available the rest of today.
Manufacturing of Tc99m

- Mo99 produced by irradiating uranium in reactor
  \[ ^{235} \text{U} + n \rightarrow \text{fission products} + ^{99}\text{Mo} \]

- Mo99 separated from fission products

- Tc99m separated from Mo99 via column
  \[ ^{99}\text{Mo} \rightarrow ^{99m}\text{Tc} \rightarrow ^{99}\text{Tc} + 140 \text{ keV } \gamma \]
Alternative Manufacturing of Tc99m

• Mo99 can also be produced by irradiating Mo98 or Mo100 using an accelerator based process:

\[ {}^{98}\text{Mo (n,\gamma)} \rightarrow {}^{99}\text{Mo} \]

\[ {}^{100}\text{Mo (\gamma,n)} \rightarrow {}^{99}\text{Mo} \]

• Mo99 then incorporated into Generator System

\(( {}^{99}\text{Mo} \rightarrow {}^{99m}\text{Tc} \rightarrow {}^{99}\text{Tc + 140 keV \gamma} )\)
Three FDA approved products in U.S.

- **Mallinckrodt Ultra TechneKow™**
- **Lantheus TechneLite®**
- **GE Healthcare Drytec™**
The Canadian Reactors
(Largest producer of Mo99)

The National Research Universal (NRU) reactor has produced as much as 67% of global Mo99. It became operational in Chalk River in 1956, and was to cease operation in 2005.

The NRU was to be replaced by the two Maple reactors, but due to design flaws these never became operational. Consequently, the NRU remained in service beyond its planned 2005 shutdown.

Shutdowns of the NRU in 2007 and 2009 precipitated several global Mo99 shortages and resulted in the establishment of the HLG-MR.
Medical Isotope Production Without Highly Enriched Uranium (HEU)

• In this 2009 report, the National Academy of Sciences (NAS) concluded that it was feasible to replace highly enriched uranium, HEU, with low enriched uranium, LEU, to produce medical isotopes and support global threat reduction.

• There was also concern that the overall process of transitioning away from HEU based production could precipitate a drug shortage. LEU, which consists of less than 20% U235, is less efficient than HEU, which consists of more than 20% U235, in producing Mo99.
ANY QUESTIONS?

Orhansuleiman@yahoo.com