Quantitative Imaging Biomarkers
The CDRH Perspective

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Overview

- Regulatory background
- Device evaluation process
- QIBA related activities
  - Quantitative imaging regulatory approaches
  - Quantitative imaging scientific considerations
- Perspective

Key Device Legislation

- 1938 Food, Drug, & Cosmetic Act
  - Requires devices to be safe
- 1976 Medical Device Amendments
  - Requires devices to be safe and effective
  - Pre-market notification
  - Device classification
  - Substantial equivalence
- 1990 Safe Medical Devices Act
- 1997 FDA Modernization Act (FDAMA)
- 2002 Medical Device User Fee and Modernization Act

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FDA: Center for Devices and Radiological Health

- Key Activities
  - Pre-market review
  - Post-market surveillance
  - Compliance
  - Inspections
  - Research
  - Outreach

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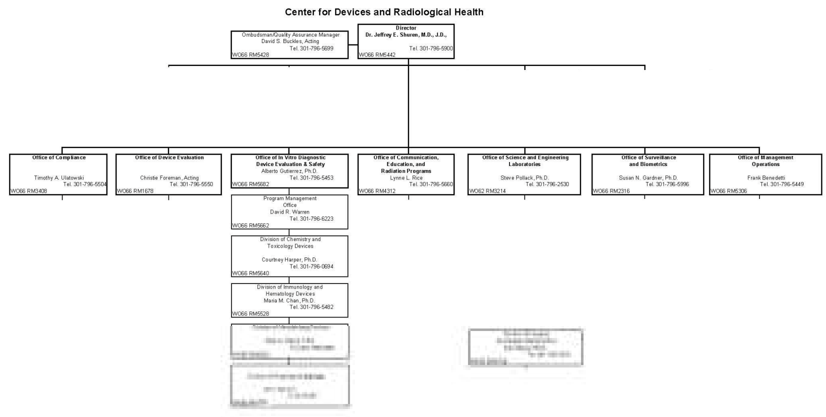

FDA: Center for Devices and Radiological Health

- For radiological devices, the pre-market device evaluation is lead by:
  - Office of In Vitro Diagnostic Device Evaluation and Safety
    - Division of Radiological Devices
- Additional scientific, statistical, and/or clinical expertise is available from:
  - Office of Science and Engineering Laboratories
  - Office of Surveillance and Biostatistics
  - Office of Communication, Education, and Radiation Programs

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Device Evaluation: 510(k) Example

- A manufacturer wants to upgrade their CT system with a new volume estimation algorithm
- Manufacturer submits a 510(k), which is a regulatory process for showing "substantial equivalence" to another device on the market
- Manufacturer can follow FDA's guidance documents for recommendations for the 510(k) format, labeling, and testing

- FDA determines
  - There is no change in the intended use
  - No new types of safety and effectiveness questions
  - Performance testing is acceptable
  - The device is substantially equivalent and can be marketed

Device Evaluation: PMA Example

- A manufacturer wants to market a first-of-a-kind computer-aided diagnostic device to establish tumor regression

- They request a pre-submission meeting to get informal feedback from an FDA review team on the preliminary data and/or pivotal study design

- They submit a Pre-Market Approval (PMA) application, which is a regulatory process for showing a reasonable assurance of the safety and effectiveness of the device

- FDA review team will include multiple experts (physicist, statistician, clinician, epidemiologist, etc…) who will evaluate all aspects of the PMA submission

- FDA may hold a Public Advisory Panel meeting to obtain recommendations from outside experts

Related Activities

- In addition to manufacturer/device specific activities, FDA is involved in a number of processes that can impact a broad category of devices
  - Guidance documents
  - Public advisory panel meetings
  - Initiatives (e.g., Image Gently)
  - International standards (e.g., software)
  - Committees
  - Research

Public Meetings

- FDA holds public meetings to obtain feedback from scientific and clinical experts, as well as members of the public

- General Meetings
  - November 2009: Full Field Digital Mammography, Computer Aided Detection
  - March 2010: Radiation exposure from medical imaging
  - June 2010: Device improvements for therapeutic radiation

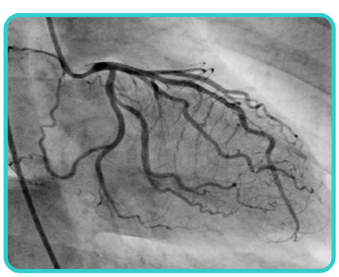
- Device Specific
  - September 2010: Hologic Selenia Dimensions 3D – Digital Breast Tomosynthesis

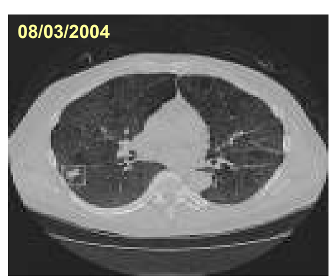
Quantitative Imaging Biomarkers: Scientific Considerations

- Imaging task selection
- Imaging modality selection
- Imaging system optimization/standardization
- Quality control
- Physician selection
- Protocol selection
- Computer assist tools
  - Computer-assisted diagnosis (CAD)
  - In-silico imaging

Task Selection

- Meaningful imaging performance assessment is task dependent





Imaging Modality Selection

- What type of imaging system will best get the job done?
- At what cost ($$)?
- At what cost (patient safety)?
- With what availability?
- Read by whom?

Imaging System Optimization

- Great variety of technique factors available
- Beware of using a variety of systems set up differently
- Differences for pediatric patients, size, gender considerations
- In silico imaging—computer simulation—can help in system optimization

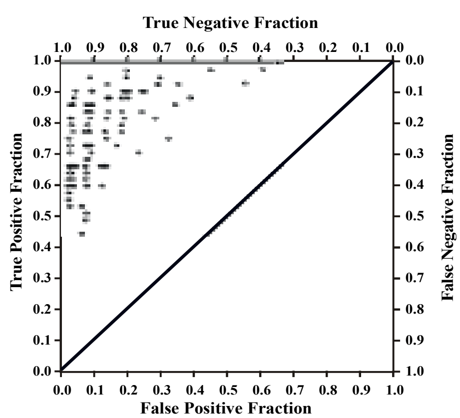
Quality Control

- Ensure system stability, systems uniformity
- Implemented by your friendly neighborhood medical physicist
- Using imaging QC phantoms (appropriate to your task)

Need a comprehensive QC program
(in action as well as on paper)

Physician Selection

- Not all Drs. were created equal

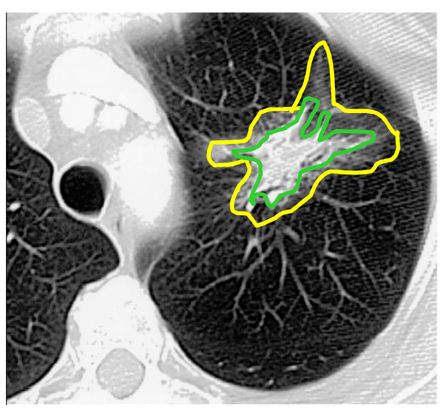


Protocol Selection

- Include all of the above
- Hire a good statistician
- Use a preliminary study to estimate study parameters
- Use in-silico imaging to ditto
- Include ample training
- Stick to your protocol

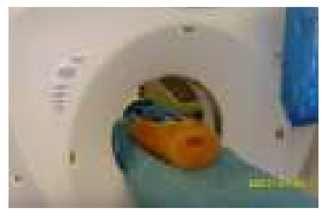
Use CAD Tools

- Reduce physician variability
- Increase accuracy



Quantitative assessment of tumor drug response with thoracic CT imaging

- Project team at Division of Imaging and Applied Mathematics, OSEL/CDRH/FDA
  - Marios A Gavrielides
  - Lisa M Kinnard
  - Rongping Zeng
  - Kyle J Myers
  - Nicholas Petrick
- Support by FDA, NIBIB, NCI



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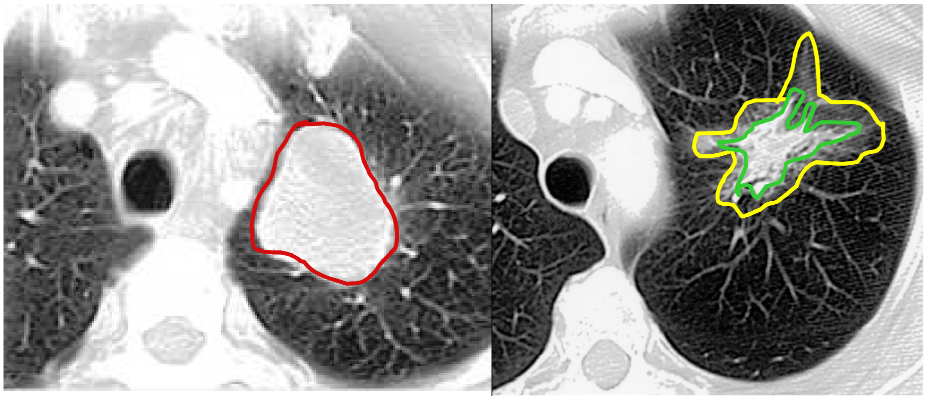
Volume measurement method



Courtesy of Larry Clarke, NCI

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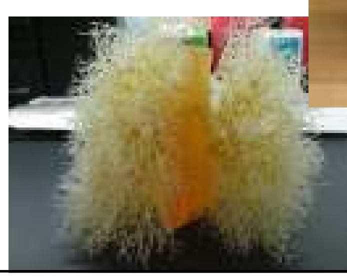
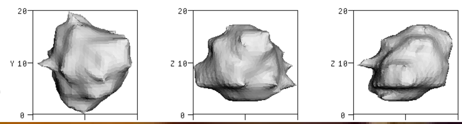
Lung CT phantom studies

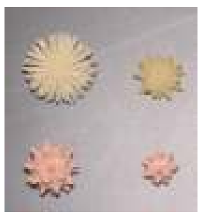
- Anthropomorphic phantom from Kyotokagaku, Japan
  - lung vasculature
  - synthetic nodules
  - allows for studies on realistic scenario of nodule attachments



Lung CT phantom studies

- Nodule sets
  - Aspheric nodules (CIRS)
    - Elliptical shapes
    - Spiculated nodules
    - Lobulated nodules





Nodule layouts

- Preliminary scans to determine materials to secure nodules
  - surgical suture prolene 5.0

Phantom Study Deliverables 1

- Public Image Database
  - Phantom thoracic scans
    - Across range of imaging protocols, nodules sizes, shapes, attachments
    - Associated truth of nodule volume
    - Available to software developers and researchers
      - Allow for determination of bias and variance
- Understanding/quantifying sources of error
  - Related to size measures (volume, RECIST, WHO)
  - Relative contribution to the error of different sources (imaging parameters, nodule characteristics, software tools)