Essential Standards for Imaging Acquisition in Clinical Trials

April 13-14, 2010
Bethesda, Maryland

Orhan H Suleiman
Alex Gorovets
Office of Drug Evaluation IV
Office of New Drugs
Center for Drug Evaluation and Research

Imaging as a Research Tool

- FDA's Critical Path initiative identifies imaging as a critical tool in drug development
- Although imaging has revolutionized how medicine is practiced, imaging's potential has yet to be realized in research.

Why is imaging so important?

- Monitoring an imaging metric such as tumor size or metabolic activity may provide meaningful information sooner in a trial. They may be accurate predictors of a clinical endpoint.

- Clinical endpoints such as overall survival take longer to determine.

Cancer Clinical endpoint*

Overall survival,

Symptom endpoints (patient defined),

Disease-Free Survival,

Objective Response Rate,

Complete response,

Progression-Free Survival,

Time to Progression

*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007)

Search on this title at http://www.fda.gov

Clinical endpoints and evidence based medicine are of tremendous value, but….

some fundamental scientific concepts have been overlooked in some of these trials.

What does FDA want?

Good Science!

Many of the imaging based trials I have seen simply lack some fundamental scientific information, such as standardization, calibration, and reproducibility.

Many of us here today believe that if these trials were conducted properly, they can be:

- Smaller
- Better
- Less expensive
- Conclusive

Why do I suspect these trials are not optimal?

When I asked a representative of an Imaging Contract Research Organization (CRO) at the annual meeting of the Drug information Agency (Atlanta, 2007)

- "what kind of phantoms do you use at your sites?"

"We don't use phantoms, we use patients!"

It is obvious that historically well established imaging quality control testing methods and the use of phantoms have not been adopted in some imaging based trials. Lack of such testing will introduce unnecessary variability into how images are acquired and analyzed. This translates into statistical uncertainty, which affects the outcome of the trial.

Do trials fail because of lack of quality control testing (QC) and failure to use phantoms?

Possibly- a recent ultrasound trial failed to demonstrate an imaging change (IMT*)- no where in the publicly published protocol did I find mention of phantoms or QC testing for the equipment! They did, however, state that they used the same sonographer and software!

*Intima medial thickness

After consulting with ultrasound colleagues about this trial…I was told…

- "….this is done all the time, they do not consult with the engineers or physicists when designing these trials!"
- "Transducers are the most sensitive piece of equipment, if dropped, performance can change dramatically."
- "What they tried to measure was theoretically beyond the limiting resolution of ultrasound!"

Fundamental Concepts

- Equipment quality control (QC) and quality assurance (QA) are essential - analogous to assurance of drug quality and purity, Chemistry-Manufacturing-Control (CMC).

- Phantoms – standard test objects which are periodically imaged to assure consistency in imaging performance, modality and task specific.

- Today's sophisticated imaging requires software standardization.

Fundamental Concepts

- Quantitative analysis also requires:
  - Standardization of the amount of drug.
  - Standardization of patient metrics, such as size, and geometric positioning.
  - Standard analysis.
  - Data transmission, storage, archival and retrieval.

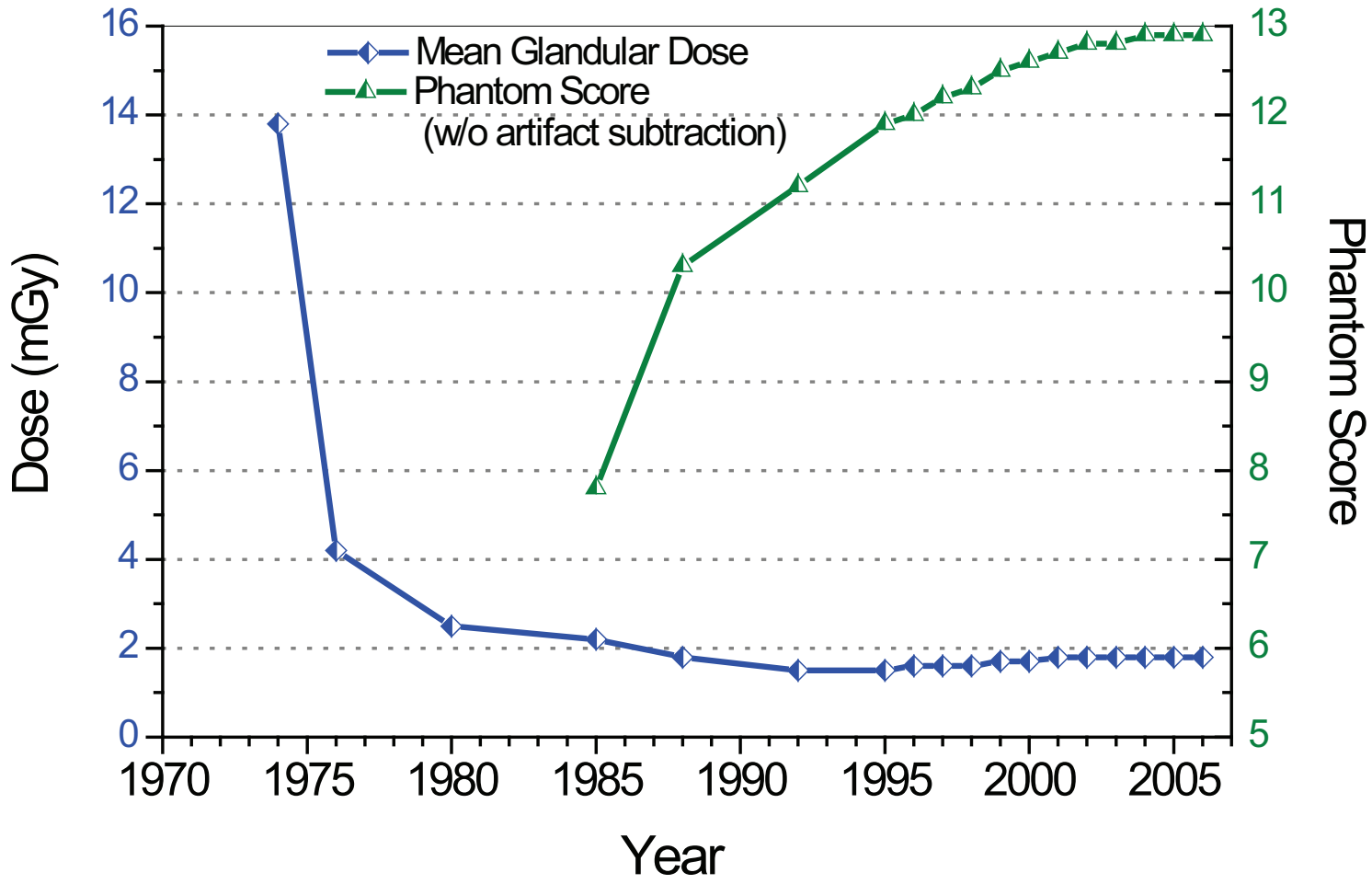
- But before we even address these, we need to address some basics…

Quality Control and Phantoms

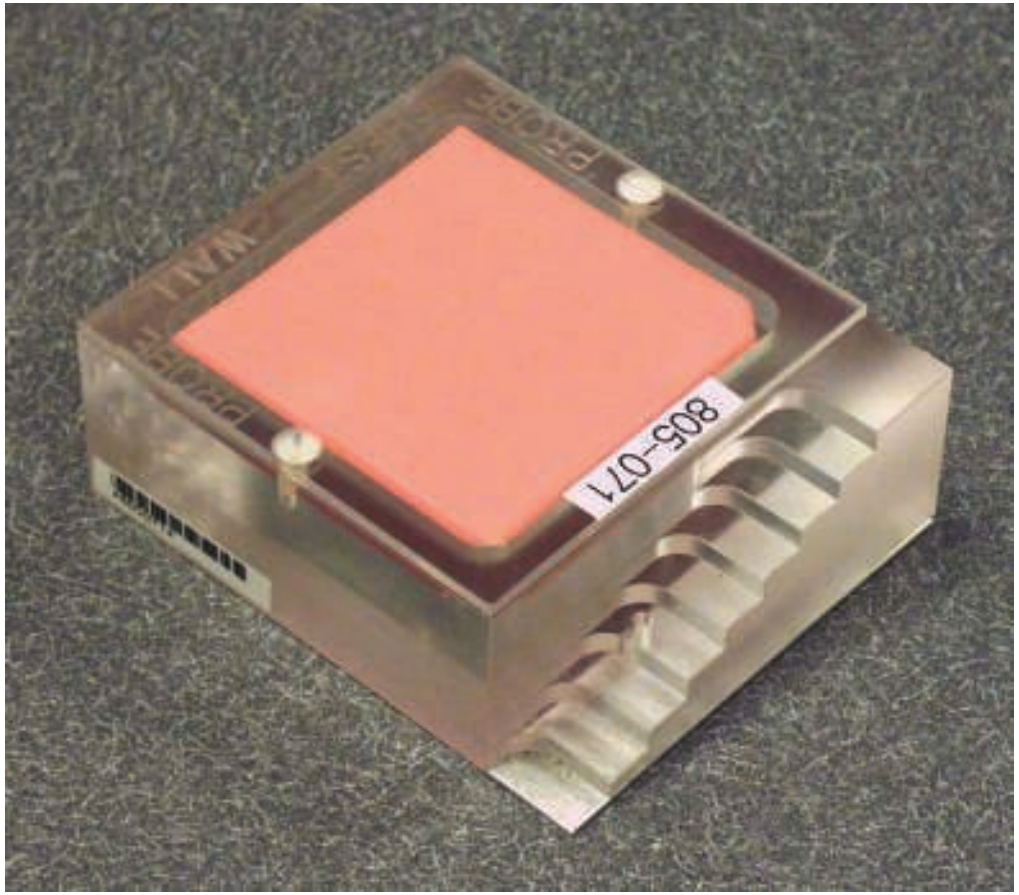
Decades old concept!

Visit any mammography site in the United States if you do not understand quality control.

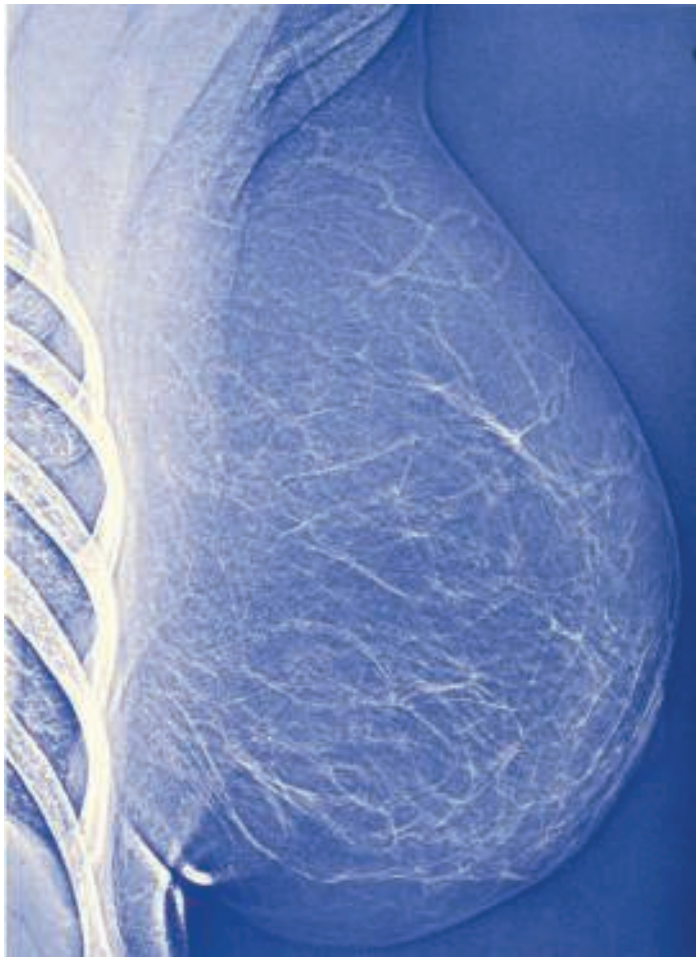
Dose and Image Quality Trends in Mammography

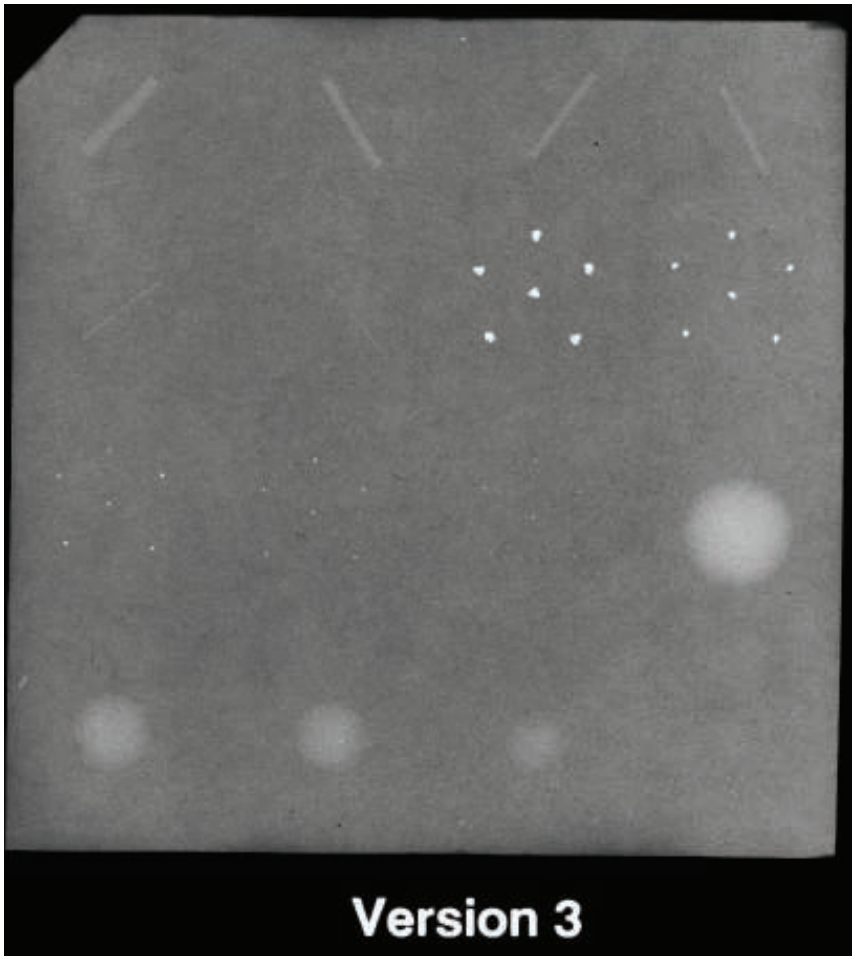


The “Standard” FDA, ACR commercial Mammography Phantom



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





In closing…
know the Science

Quality control testing with appropriate test phantoms should be used on all imaging equipment used to generate clinical images during the trial.

Ultimately successful clinical trials depend on conducting good science.

Sessions will focus on:

- Standardization of Image Acquisition
- Image Interpretation and Analysis
- Data Management

Standardization

- At site of acquisition
- Across multiple sites
- At site(s) of interpretation
- Of Data Management

Standardization

- Minimization of bias and variability
- Technical Quality
- PRE-SPECIFICATION (Charter)
- Documentation
- Verification and inspection

FDA Campus @ White Oak, Silver Spring, Maryland