FDA/CDRH Regulatory Perspectives on Radiomics

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CDRH Vision

Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world. The U.S. is the world's leader in regulatory science, medical device innovation and manufacturing, and radiation-emitting product safety.

OSEL Vision

OSEL's unique position in the medical device ecosystem enables the U.S. to be the world's leader in medical device regulatory science through laboratory-based research, engineering analyses, and collaborations that facilitate medical device innovation and regulatory decision-making.

Objectives

- Premarket Submissions
- Evidentiary requirements for quantitative imaging and radiogenomics (RG) applications
- Quantitative imaging and RG in the context of regulatory decisions for other medical products
- CDRH support of quantitative imaging and RG applications: research activities in addition to regulatory pathways and resources

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Premarket Submissions

- Premarket notification or 510(k)
  - Moderate risk device where special controls can mitigate the risks to health
  - Sponsor must demonstrate that the device is as safe and effective as a legally marketed device (the predicate)
- de novo
  - Establishes pathway for innovative low-to-moderate risk devices (no predicate)
- Premarket approval or PMA

Diagnostic radiological devices

- CDRH clears most diagnostic imaging devices through the 510(k) pathway, including ultrasonic pulsed doppler imaging systems, magnetic resonance diagnostic devices, computed tomography x-ray systems, full-field digital mammography, and picture archiving & communications systems

510(k) Premarket Notifications

Substantially equivalent (SE):

same intended use AND same technological characteristics OR

same intended use AND different technological characteristics (e.g., change in material, design, energy source, software) AND these differences do not raise different questions of safety and effectiveness

Intended use

- **Intended use –** purpose of the device or its function. The intended use of a device encompasses the indications for use
- **Indications for use –** The disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended

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General intended use

- Intended use of many imaging devices is very general

"..intended to produce cross-sectional images of the body by computer reconstruction of x-ray transmission data…"

"… general purposed ultrasound imaging and analysis systems providing digital acquisition, processing and display capability and clinical applications including: Abdominal, Obstetrical, …"

"…a diagnostic imaging modality that produces cross-sectional transaxial, coronal, sagittal, and oblique images that display anatomic structures of the head or body…"

"… These images and/or spectra when interpreted by a trained physician yield information that may assist in diagnosis."

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Specific intended use

"intended to measure liver iron concentration to aid in the identification and monitoring of non-transfusion-dependent thalassemia patients receiving therapy with deferasirox"

De Novo

- New, novel devices that have not previously been classified are Class III by default (and hence, PMA devices)
- *De novo* is a petition for automatic down classification (Class III to Class II or Class I)
- *De novo* petition must propose controls that would be needed to assure the safety and effectiveness of the device

Premarket Application (PMA)

- A PMA is a stand-alone premarket submission
- There is no predicate device
  - A PMA is not substantially equivalent to anything
- Application must contain sufficient scientific evidence to provide a reasonable assurance that the device is safe and effective for its intended use(s)

Examples of PMA devices

- Digital Breast Tomosynthesis (DBT) systems
- High Intensity Focused Ultrasound (HIFU)
- Mammography Computer Aided Detection Devices
- Radioactive microspheres

See Jana Delfino's AAPM 2016 Premarket presentation at https://goo.gl/eg9hRv

What is the evidence required for a radiogenomics-related or other quantitative imaging claim?

It depends on the intended use

In other words, “this device provides tools for measuring tumor volume” is not the same as “this device may be used to assess/measure changes in tumor volume greater than 5 mm^3 from CT images in patients with lung cancer”

Specific Indications for Use as well as information on device performance described in labeling or other sections of the premarket submission should be supported with appropriate performance data.

Statements of this sort:

"this device enables estimation of cancer risk"…

or

"prediction of tumor response to therapy"…

or

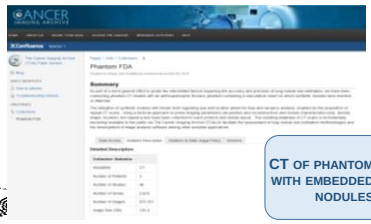
"classification/separation of patient groups"…

would need data supporting such statements

Types of evidence to support substantial equivalence

- Phantoms (including both physical and digital reference objects)
- Simulations (realistic models)
- Clinical data
  - Reader studies
  - Validation of quantitative imaging tools

PUBLIC RELEASE OF FDA PHANTOM DATA



Well-controlled phantom studies facilitate assessment of impact of image acquisition and analysis procedures on quantitative imaging performance.

CT OF PHANTOM WITH EMBEDDED NODULES

- CDRH makes imaging system simulation tools and statistical analysis software for reader or algorithm assessment available to the public

https://github.com/DIDSR

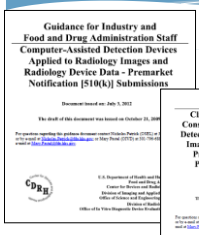
QIBA: Collaboration between government, academia, and industry

Organized by RSNA to advance methods for quantitative imaging and use of imaging biomarkers

https://www.rsna.org/QIBA.aspx

- **Profiles:**
  - One or more claims re achievable quantitative performance
  - Details re how to achieve them through best practices
- **Standardized terminology**
  - The emerging science of quantitative imaging biomarkers terminology and definitions for scientific studies and regulatory submissions, Kessler et al.
- **Standardized methods for evaluating imaging biomarkers**
  - Quantitative imaging biomarkers: A review of statistical methods for technical performance assessment, Raunig et al.
- **Standardized methods for comparing imaging biomarkers**
  - Quantitative imaging biomarkers: A review of statistical methods for computer algorithm comparisons, Obuchowski et al.
- **Examples and case studies**
  - Statistical issues in the comparison of quantitative imaging biomarker algorithms using pulmonary nodule volume as an example, Obuchowski et al.
  - Meta-analysis of the technical performance of an imaging procedure: Guidelines and statistical methodology, Huang et al.

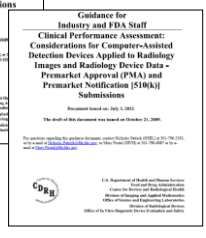
Stat Methods in Med Res, 2014


Guidance for Industry and Food and Drug Administration Staff

Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions

Document issued on: July 3, 2012

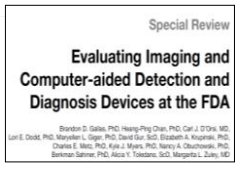
The draft of this document was issued on October 21, 2009.


Guidance for Industry and FDA Staff

Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data – Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions

Document issued on: July 3, 2012

The draft of this document was issued on October 21, 2009.


Special Review

Evaluating Imaging and Computer-aided Detection and Diagnosis Devices at the FDA

Brandon D. Gallas, PhD, Hsiang-Ping Chan, PhD, Carl J. D'Orsi, MD, Lori E. Dodd, PhD, Maryellen L. Giger, PhD, David Gur, ScD, Elizabeth A. Krupinski, PhD, Charles E. Metz, PhD, Kyle J. Myers, PhD, Nancy A. Obuchowski, PhD, Berkman Sahiner, PhD, Alicia Y. Toledano, ScD, Margarita L. Zuley, MD

Acad Radiol 2012; 19:463–477

Additional FDA Biomarker programs

- CDRH Medical Device Development Tool (MDDT)
- CDER Biomarker Qualification and Drug Development Tool (DDT)

Both rely heavily on the concept of context of use (COU) – a complete and precise statement that describes the appropriate use of the MDDT and how the qualified MDDT or biomarker is applied in device or drug development and regulatory review. The COU describes all important criteria regarding the circumstances under which the MDDT or biomarker is qualified.

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FDA Pre-submissions

- The FDA/CDRH pre-submission program allows manufacturers to request feedback from the FDA on their proposed regulatory pathway and test protocols
- Consider for quantitative imaging applications with novel or specific intended uses
- Guidance: Request for Feedback on Medical Device Submissions http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

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Take home

- CDRH is aware of radiogenomics research efforts and is ready to support these premarket submissions
- Premarket data requirements will need to support the intended use
- FDA encourages interactions with sponsors: come early!
- Several other programs applicable to supporting FDA use of quantitative imaging biomarkers and related innovations
- CDRH research and collaborations contribute to data, software, and guidance for device evaluation

Thank you

Quantitative imaging supports other medical product approval

- Quantitative imaging may also be used to help demonstrate that another medical product (device, drug, or biologic) is safe and effective
- Uses of imaging in clinical trials include: inclusion/exclusion criteria, endpoints, safety-related, dosing, and more

General to specific

Levels of Specificity for diagnostic medical devices:

1. Identification or measurement of a physical parameter (e.g., image, heart rate) or biochemical parameter (e.g., analyte)
2. Identification of a specific target population (e.g., women with dense breasts; current/former smokers with certain risk factors; children of certain age range) or anatomical location (e.g., MR of the brain)
3. Identification of the clinical use of the measurement (e.g., diagnosis, screening)
4. Identification of or implication of an effect on the clinical outcome (e.g., screening mammography reduces breast cancer mortality)