USE OF PHANTOMS AND IMAGE DATASETS FOR REGULATORY DECISION MAKING

Nicholas Petrick. Ph.D.

Division of Imaging, Diagnostics and Software Reliability (DIDSR)
Office of Science and Engineering Labs
Center for Devices and Radiological Health (CDRH)
U.S. Food and Drug Administration (FDA)
nicholas.petrick@fda.hhs.gov

DISCLOSURES

- No conflicts to disclose

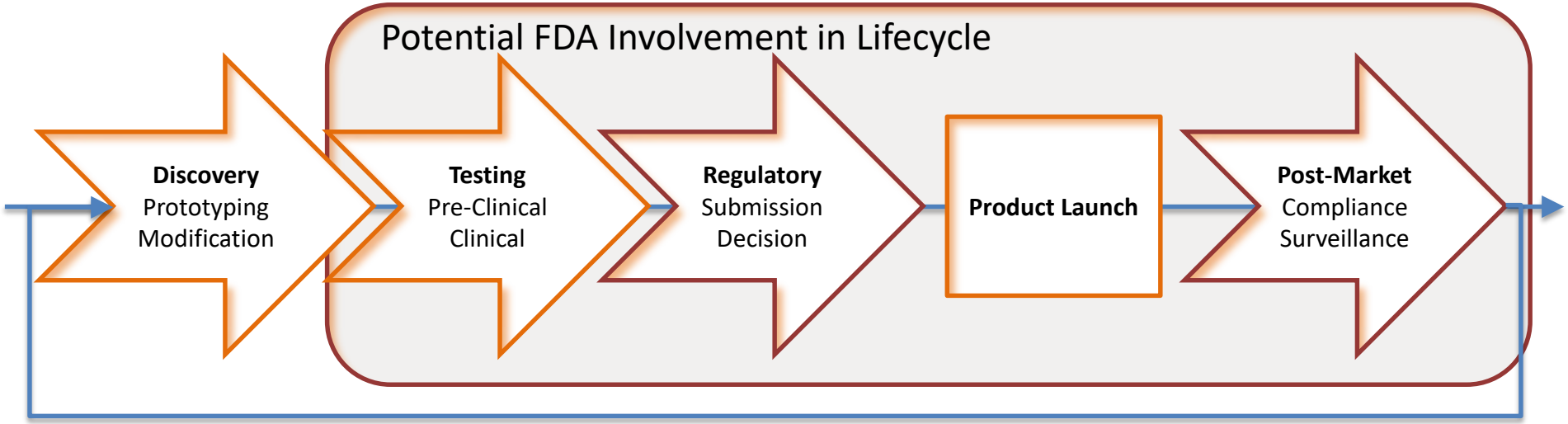
OUTLINE

- Overview of medical device regulatory framework
- Software as a medical device (SaMD)
- Medical device development tools (MDDTs)
  - Phantoms and datasets as potential MDDT candidates

Center for Devices and Radiological Health

- Protect and promote the health of the public by ensuring the **safety** and **effectiveness** of medical devices and the safety of radiation-emitting electronic products

Development Pathway



- FDA strives to speed translation of innovative, safe, and effective products to market throughout product lifecycle

Device Class & Pre-Market Requirements

Device Class	Controls	Premarket Review Process
Class I (lowest risk)	General Controls	Most are exempt
Class II	General Controls Special Controls	Premarket Notification [510(k)] or De Novo
Class III (highest risk)	General Controls Premarket Approval	Premarket Approval [PMA]

Medical Devices By Class










Class I
Lower risk

Class II
CT, MR, US imaging systems
Most imaging CADe/CADx
Some IVD tests

Class III
Higher risk
Novel Imaging systems (DBT)
Leadless Pacemakers
Bronchial Thermoplasty Systems
Some IVD Tests

General/Special Controls

- General Controls
  - General controls apply to all medical devices, unless exempted by regulations
    - Registration and device listing
    - Good manufacturing practice requirements
    - Adverse event reporting
    - …
- Special Controls
  - Controls beyond general controls necessary to establish a reasonable assurance of the safety & effectiveness. Special controls are usually device-specific
    - Special labeling requirements
    - Premarket data requirements
    - Postmarket surveillance
    - …

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ucm055910.htm

How devices come to market in U.S.

- 510(k)
  - Demonstrate substantial equivalence to predicate device
- De Novo
  - Risk-based classification for novel medical devices for which general controls, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate. Devices granted through De Novo may be marketed/used as predicates for future 510(k) submissions
- PMA
  - Demonstrate reasonable assurance of safety and effectiveness
  - Most Class III devices
- Pre-submissions (Qsubs)
  - Informal interaction with FDA (usually non-binding) prior to device submission
    - Answer questions about a specific device under development

Software as a Medical Device (SaMD)

REGULATION OF SAMD

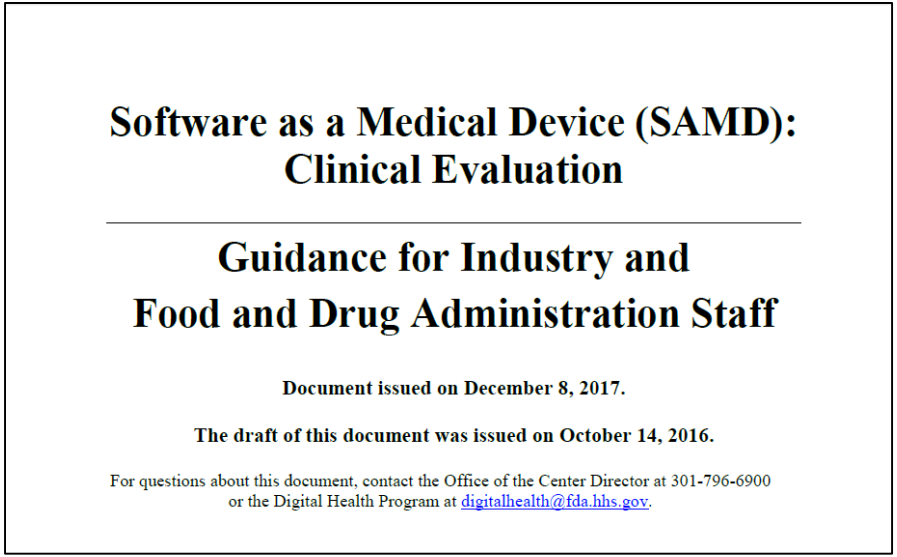
- IMDRF Working Group (WG) on Software as a Medical Device (SaMD)
  - SaMD: Software intended to be used for medical purposes without being part of a hardware medical device
    - Include machine learning (ML) algorithms for disease diagnosis & monitoring
      - Including lung cancer quantitative imaging (QI) and computer-aided diagnosis (CAD) tools
  - Outputs:
    - SaMD: Key Definitions
    - SaMD: Possible Framework for Risk Categorization and Corresponding Considerations
    - SaMD: Application of Quality Management System
    - SaMD: Clinical Evaluation

http://www.imdrf.org/workitems/wi-samd.asp

IMDRF International Medical Device Regulators Forum

IMDRF AND FDA GUIDANCE

- SAMD: Clinical Evaluation
  - Adopted as FDA guidance in 2017
  - FDA intends to consider principles of the IMDRF report in evolving approach to AI/ML and SaMD review



Software as a Medical Device (SAMD): Clinical Evaluation

Guidance for Industry and Food and Drug Administration Staff

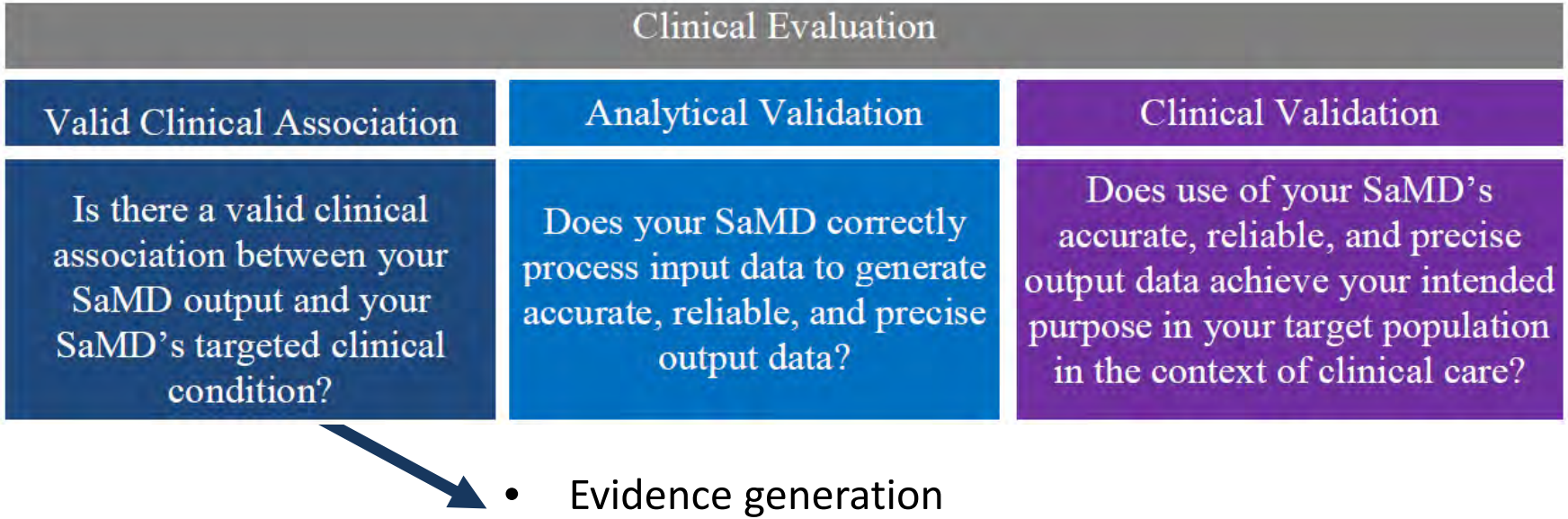
Document issued on December 8, 2017.

The draft of this document was issued on October 14, 2016.

For questions about this document, contact the Office of the Center Director at 301-796-6900 or the Digital Health Program at digitalhealth@fda.hhs.gov.

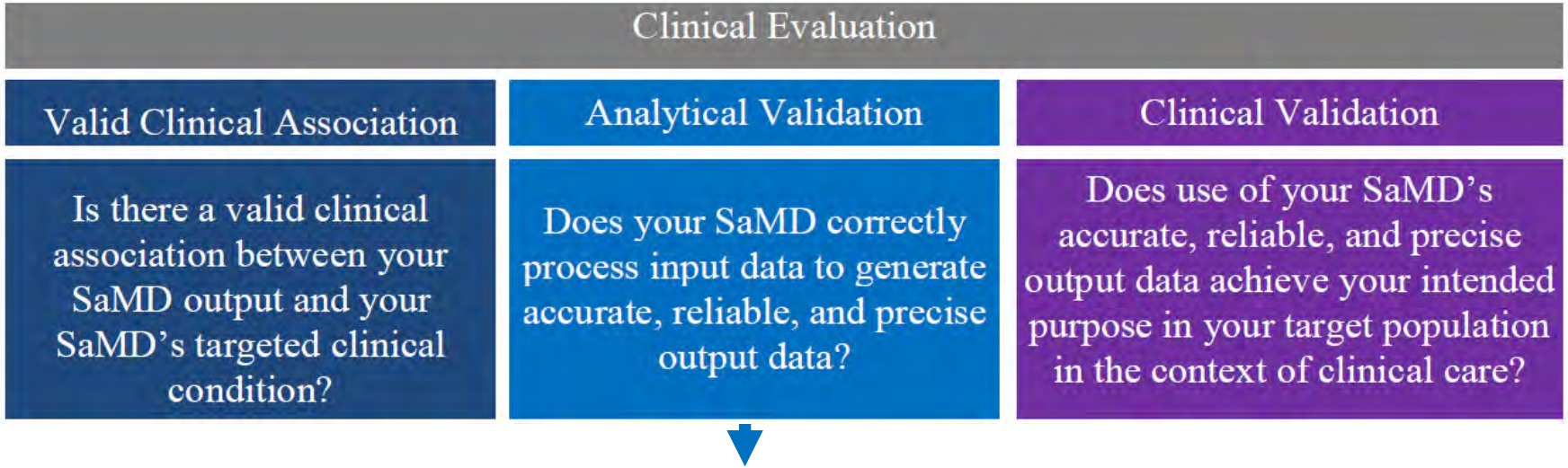
https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm524904.pdf

SaMD: Clinical Evaluation



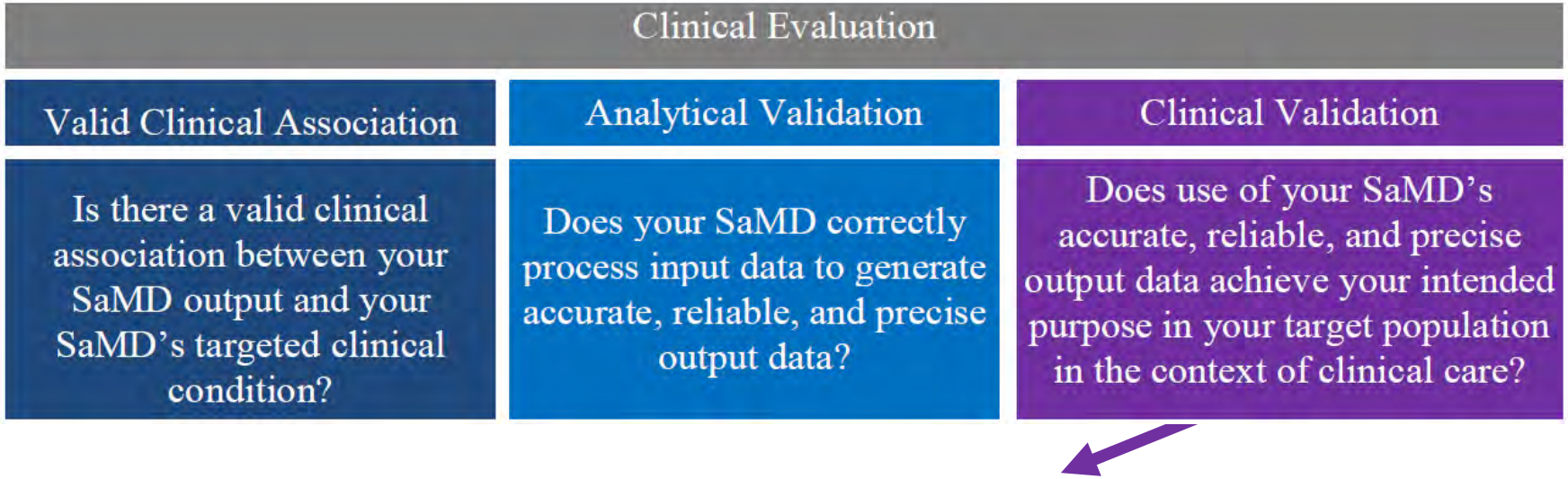
- Evidence generation
  - Literature
  - Professional guidelines
  - Secondary data analysis
  - Clinical trials/studies

SaMD: Clinical Evaluation



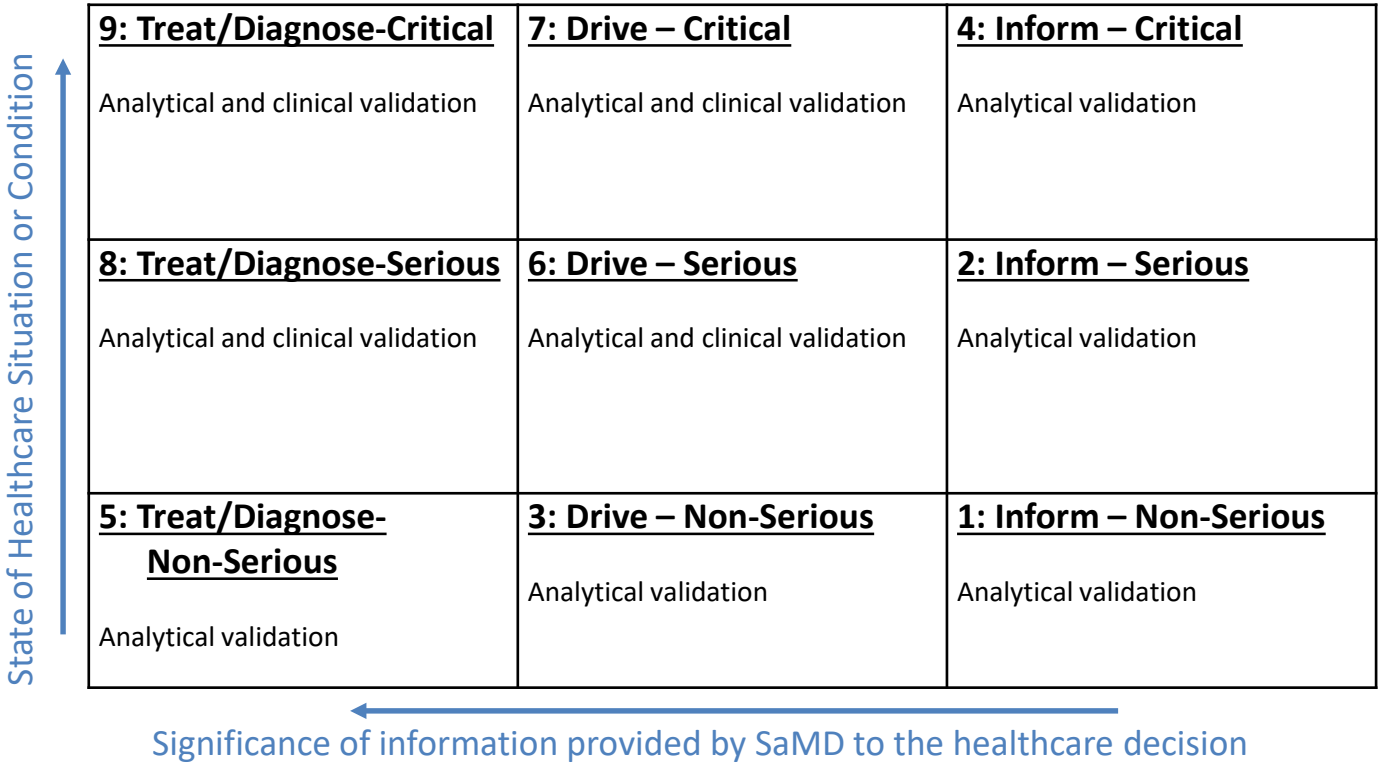
- SaMD meet technical requirements
  - Provide evidence that software correctly constructed
  - Demonstrate it meets specifications and conforms to user needs

SaMD: Clinical Evaluation



- Evidence that shows
  - SaMD has been tested in target population and for intended use
  - Users can achieve clinically meaningful outcomes

Risk-Based Regulatory Approach



Medical Device Development Tool (MDDT)

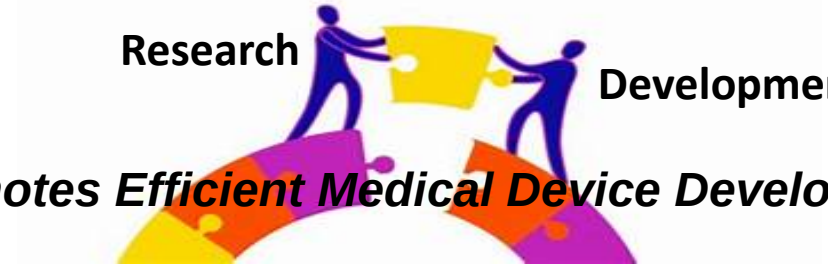
WHAT IS AN MDDT?

- **Medical Device Development Tool (MDDT)** is a method, material, or measurement used to assess effectiveness, safety, or performance of a medical device
  - MDDT Categories
    - Clinical Outcome Assessment (COA), Biomarker Test (BT), Nonclinical Assessment Model (NAM)
  - A MDDT is scientifically validated and qualified for a specific ***Context Of Use*** (COU) on the way the MDDT should be used
  - Qualification is a FDA conclusion that within the COU a MDDT has a specific interpretation and application in medical device development and regulatory review

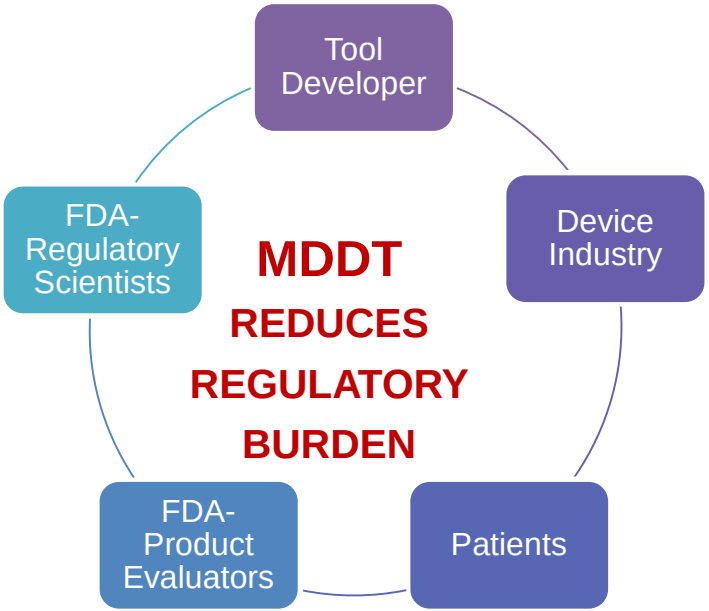
Website:
http://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/default.htm

Questions? email: MDDT@fda.hhs.gov

Medical Device Development Tool Program



Promotes Efficient Medical Device Development



Benefit of Qualifying Tools

- Fosters innovation
- Encourages collaboration by engaging broader community
  - Not necessarily just device developers
- Reduces resource expenditure
- Qualified MDDT applied in multiple device submissions
- Promotes efficiency in CDRH regulatory review resources
- Minimizes uncertainty in regulatory review process

CDER's Drug Development Tools

- **Drug Development Tool** (DDT) is a method, material, or measure that can potentially facilitate drug development
  - Mission
    - To qualify and make DDTs publicly available for a specific context of use to expedite drug development and review of regulatory applications
  - FDA established qualification programs to support DDT development
    - DDT Qualification Programs
      - Animal Model Qualification Program
      - Biomarker Qualification Program
      - Clinical Outcome Assessments (COA) Qualification Program

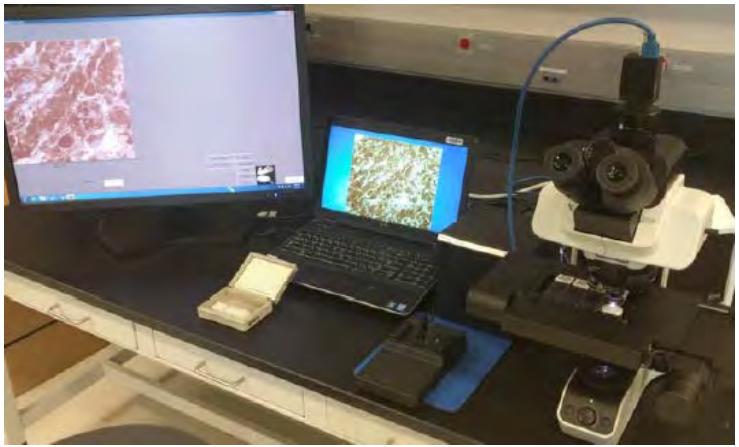
https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/

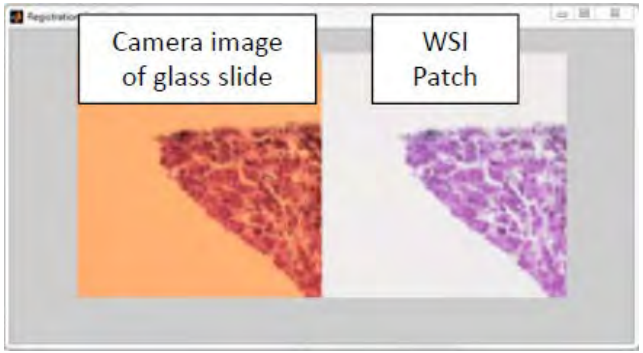
QUALIFIED MDDTS

Name of Tool	Summary of Evidence	Product Area(s)	Tool Type	Date Qualified
Minnesota Living with Heart Failure Questionnaire (MLHFQ)	MLHFQ Qualification Summary	Cardio	COA	03/19/2018
Kansas City Cardiomyopathy Questionnaire (KCCQ)	KCCQ Qualification Summary	Cardio	COA	10/19/2017

EXAMPLE OF A POTENTIAL MDDT

- eeDAP: Evaluation environment for digital and analog pathology
  - System for registering glass slide with digital whole slide image (WSI)
  - Allow pathologist to evaluate same FOV on analog microscope and WSI
    - Eliminate location variability for faster & more precise comparisons of technologies





Gallas et al., https://githib.com/DIDSR/eeDAP

CDRH Qualification Decision Framework

- Consideration for qualifying a proposed MDDT
  - MDDT description
  - Context of use
  - Public Health Impact
  - Strength of evidence
    - Does scientific evidence demonstrate that MDDT reliably and accurately measures what is intended, is scientifically plausible, and is reasonably likely to predict the outcome of interest?
  - Assessment of advantages and disadvantages
    - Within specified context of use and given the available strength of evidence, do the advantages outweigh potential disadvantages of making decisions based on measurements obtained using the MDDT
    - Of particular importance are regulatory, public health, and/or clinical impact.

https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM374432.pdf

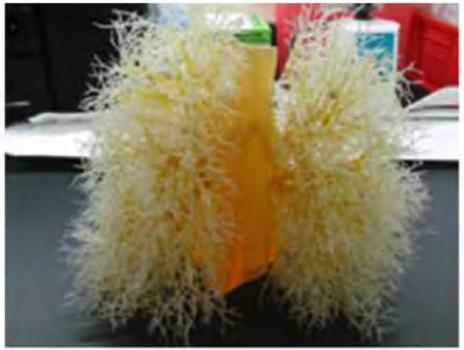
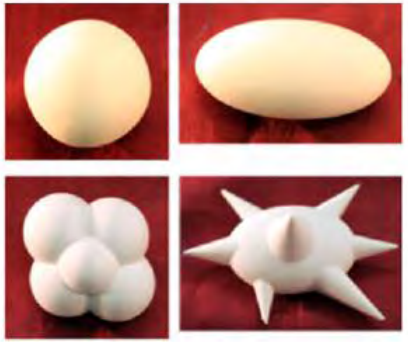
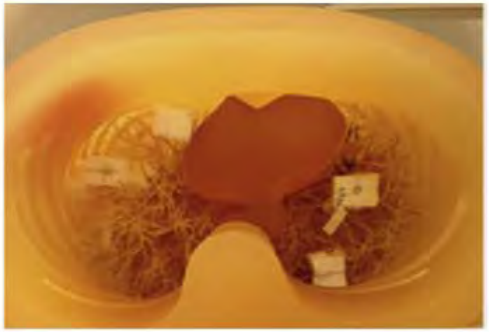
POTENTIAL MDDTS: CT PHANTOMS

Quantitative Imaging

- CT lesion volume as a quantitative measure of actual tumor size in vivo
  - Anthropomorphic lung phantom
  - Accumetra phantom

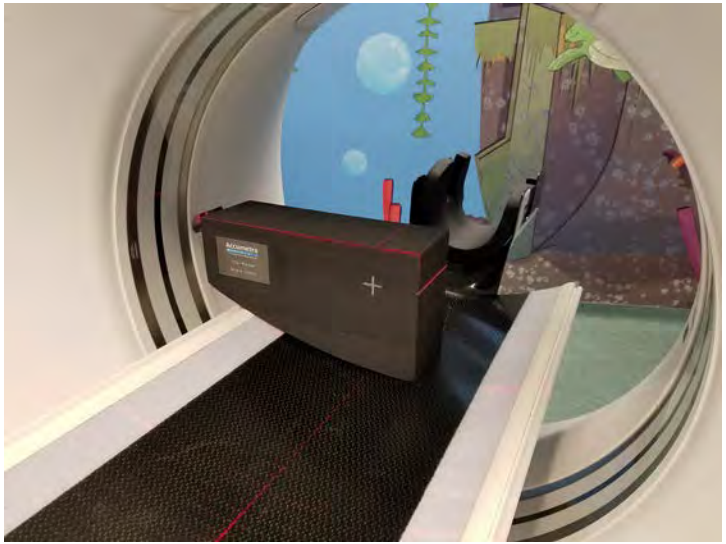
Quantitative Imaging Biomarker Alliance: https://www.rsna.org/QIBA/

KYOTOKAGAKU/FDA LUNG PHANTOM

- QI tool technical assessment to support a QI lesion volume tool claim
  - Statistical measures of tool volumetry accuracy
  - Currently used in QIBA advance disease volumetry profile conformance testing

ACCUMETRA IQ PHANTOM



Children's hospital

NIH

CTLX1 phantom scan

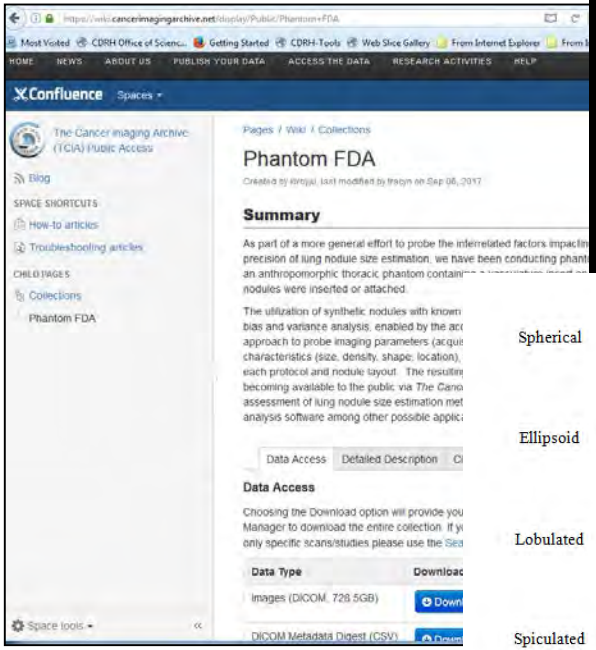
- Potential context of use
  - Image quality assessment of CT system for lung cancer screening

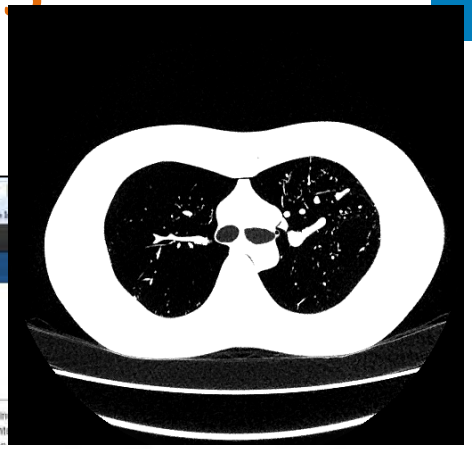
Curtesy Rick Avila, Accumetra

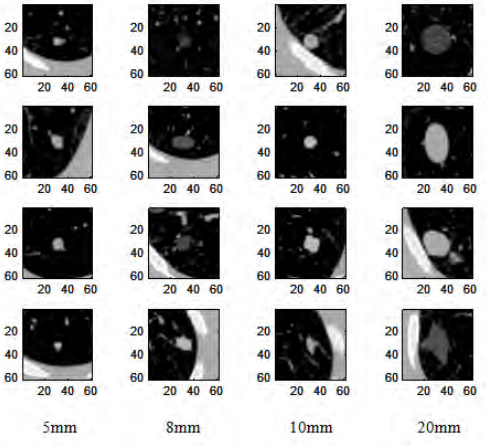
POTENTIAL MDDTS: CT DATASETS

PHANTOM CT SCANS

- Technical assessment to support QI lesion volume tool claim
  - Accuracy assessment
    - Linearity/bias
  - Currently used in QIBA advance disease conformance testing



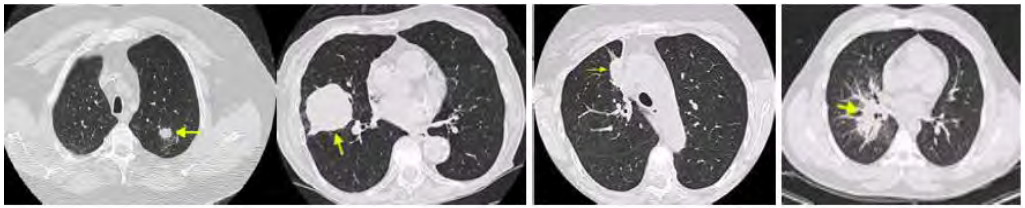


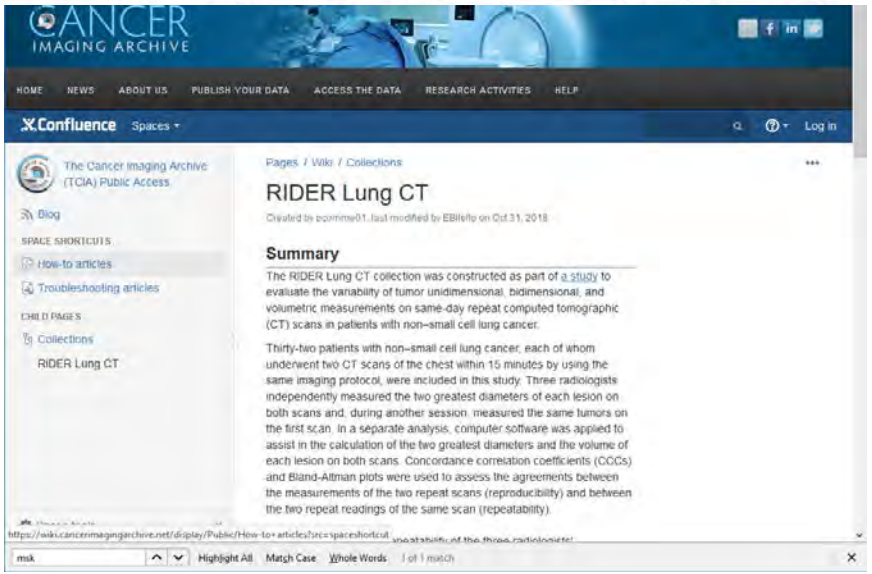


https://wiki.cancerimagingarchive.net/display/Public/Phantom+FDA

RIDER COFFEE-BREAK CT SCANS

- Technical assessment to support a QI lesion volume tool claim
  - Precision assessment
    - Repeatability
    - Reproducibility
  - Currently used in QIBA advance disease conformance testing

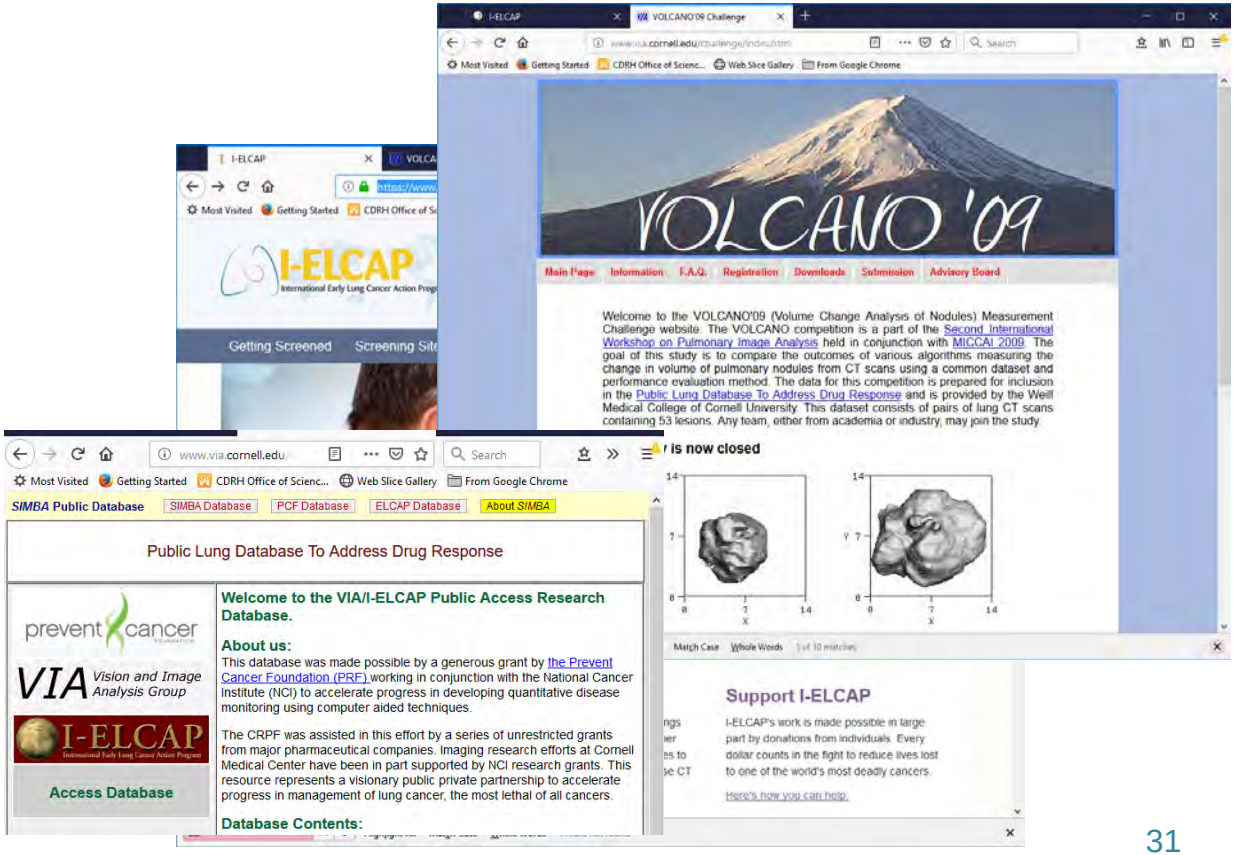




https://wiki.cancerimagingarchive.net/display/Public/RIDER+Lung+CT

I-ELCAP CT Data

- Clinical or technical assessment to support a QI, CAD or radiomic tool claim
  - Clinical CT datasets



SUMMARY

- Device Regulation
  - Devices are classified into three tiers
  - Indications for use & type of technology are equally important for deciding what validation is needed
- Software as a Medical Device
  - Software intended to be used for medical purposes without being part of a hardware medical device
  - FDA's approach to SaMD/ML is now evolving
    - Investigating risk-based framework for SaMDs
- Medical device develop tool (MDDTs)
  - Methods, materials, or measurements used to assess effectiveness, safety, or performance of a medical device
  - Potential for lung CT phantoms and datasets as MDDTs

ACKNOWLEDGMENTS

- I’ d like to acknowledge Brandon Gallas, Marios Gavrielides, Tomoe Hagio and Qin Li for providing slides on their research and regulatory work being presented in this talk


FDA
U.S. FOOD & DRUG
ADMINISTRATION