FDA Regulation of Whole Slide Imaging (WSI) Devices: Current Thoughts

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Outline

- Regulation of Medical Devices
  - Safety and Effectiveness
  - Intended Use
  - Device Classification
- Digital Pathology/Whole Slide Imaging Systems
  - Define
  - History of digital imaging in vitro diagnostics (IVDs)
  - WSI risk and benefits: classification
  - Major clinical study design challenges

Center for Devices and Radiological Health (CDRH)

Responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States

What is a medical device?

- 5 MP digital camera
- Captures still images or videos
- LCD display at 320 x 240 resolution
- Three objectives with magnification from 40X-400X
- 2 built-in light sources
- 128 MB memory

A clinical intended use would make this a medical device!

In vitro diagnostics (IVDs)

Reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. **21CFR809.33**

Determination of safety and effectiveness

- 21 CFR 860.7
- Intended use population
- Conditions of use for the device
- Probable benefit to health from the use of the device weighed against any probable injury of illness
- Reliability of the device

Safety and Effectivenss

- Safety

  - There is reasonable assurance … that the probable benefits … outweigh any probable risks. [21CFR860.7(d)(1)]

- Effectiveness

  - There is reasonable assurance that … the use of the device … will provide clinically significant results. [21CFR860.7(e)(1)]

Device Classification

- Appropriate level of regulatory control that is necessary to assure safety and effectiveness.
- Classification is risk-based and determined based upon the **intended use** of the device.

Intended Use/Indications for Use

- A general description of 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.

21 CFR 814.20 (b)(3)(i)

Device classification

- Class III
  - Highest risk
  - General Controls
  - Premarket Approval (PMA)
- Class II
  - Moderate risk
  - General Controls and Special controls
  - Premarket notification (510(k))
  - Substantial equivalence to a predicate
- Class I
  - Low risk
  - General controls (GMP)
  - 510(k) exempt
  - Registration and listing

Digital Pathology

- The use of computer technology to convert analog microscopic images into digital images
- Whole slide imaging (WSI), aka digital imaging, virtual slides, virtual microscopy
- System consisting of hardware; microscope, camera, scanner, computer, and monitor, and software.
- Encompasses image acquisition, processing, archiving and retrieval

Scope of this presentation

- Use of whole slide imaging (WSI) for primary surgical pathology diagnosis in lieu of optical microscope
- Will not cover:
  - image analysis, biomarkers
  - cytopathology or hematology
  - research or educational use

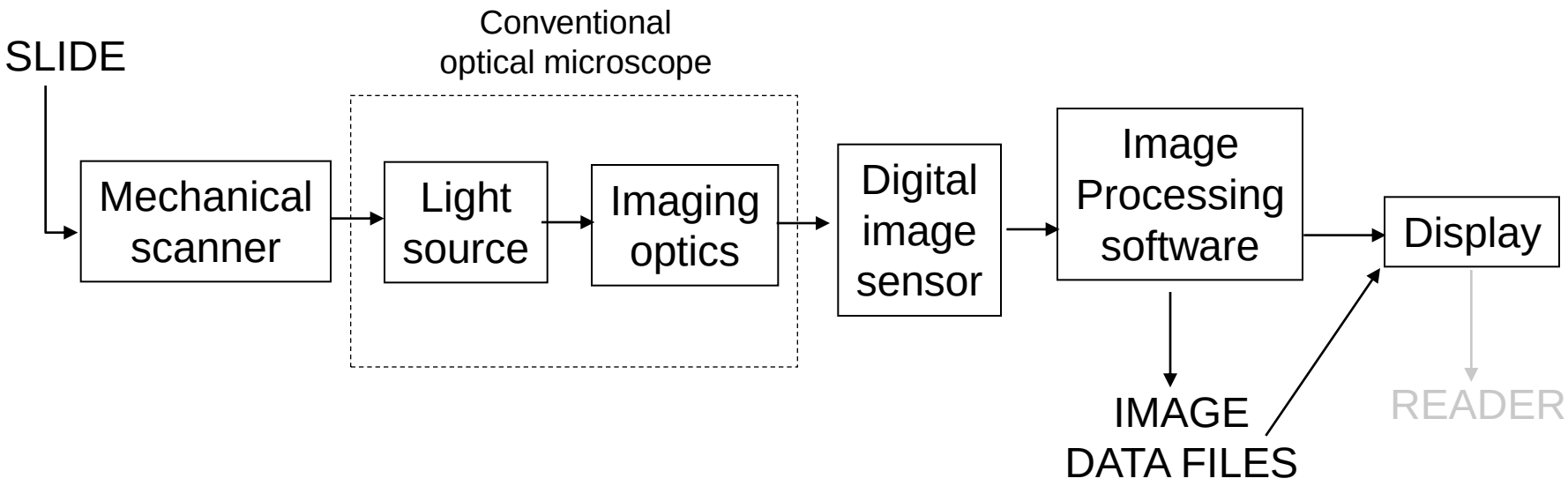
21 CFR 864.3600 Microscopes and accessories

- Optical instruments used to enlarge images of specimens, preparations, and cultures for medical purposes
- Class I (general controls) exempt from premarket notification (510k) subject to limitations in 864.9.

21 CFR 864.9 Limitations of exemptions from 510(k) (a few)

- Exemption only to the extent that misdiagnosis as a result of using the device would not be associated with high morbidity or mortality.
- The following would not be exempt:
  - Different fundamental scientific technology
  - IVD intended for use in diagnosis, monitoring or screening of neoplastic diseases

What does this mean?



- Microscope just one component of the system
- Image acquisition, processing and display new technology for this intended use
- Diagnostic for neoplastic disease
- WSI systems can not be considered Class I exempt

IVD devices that utilize digital imaging

Class III

- Gynecologic Cytology Imaging Systems

Class II

- Automated hematology analyzers (differential cell counters)
- Chromosome analyzers
- FISH enumeration systems
- Urine sediment analyzers
- Immunohistochemistry image analysis (Her2, ER, etc)
- Manual Read of Digital Image (PR, Her2)

Regulatory Pathway for WSI

- Same intended use as microscope
- New technology trips limitations to exemption from premarket notification
- Not Class II, no predicate: currently cleared devices have **specific and limited** intended uses that are not applicable to WSI for the breadth of surgical pathology specimens
- FDA does not currently see how risk can be mitigated through special controls
- WSI are systems and are not considered, by definition, as laboratory developed tests (LDT)

WSI raises new questions of safety and effectiveness that must answered through premarket approval (PMA) (Class III)

How does FDA plan to ensure the safety and effectiveness of digital pathology devices?

- Knowledge of the risks and benefits
- Require non-clinical and clinical studies to objectively and precisely validate performance
- Clearly state limitations of WSI
- Standardization

What are the potential benefits? Will WSI improve patient care?

- Faster turnaround time?
- Increased productivity?
- Easier retrieval of images and archiving?
- Improve workflow?
- Review when pathologist not on-site (telepathology) and consultation
- Integration of image with patient's electronic medical record
- Image analysis algorithms
- Simultaneous viewing of images side by side

What are the risks?

- Is the WSI presented of such that equally good or better quality diagnoses could be made as when using the light microscope for all surgical pathology specimens?
- Differences in human interaction between the two methods, i.e. viewing and navigating on a computer screen vs. a light microscope
- Serious consequences to public health if misdiagnosis is caused by poor quality image or improper use as surgical pathology diagnosis is the “final answer” for most conditions

Major Clinical Study Design Challenges

- Clinical studies must support **intended use** in **intended use population**.
- Need adequate supporting evidence since potential change in pathological practice.
- Broad applications for WSI. How to “carve” the domain of pathological specimens to provide a realistic and manageable approach without significant concerns of off-label use?
- Potential use of information obtained from the non-clinical study to guide clinical study design.

Major Clinical Study Design Challenges, con't: Intended Use Statement

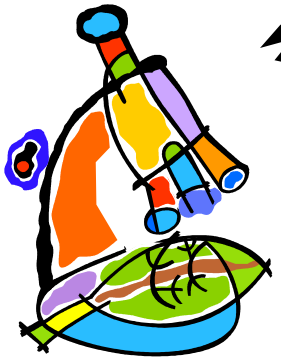
- Primary Diagnosis
- FFPE tissue, Frozen Section….
- H & E, Special Stains, IHC….
- Reasonable intended use population

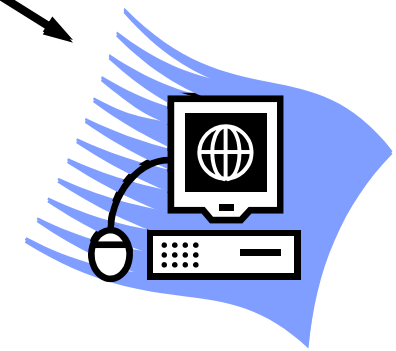
Major Clinical Study Design Challenges, con't:

- Prospectively designed study
- Case selection: Prospective and/or retrospective
- Potential case enrichment
- Evaluate accuracy, **not** agreement

Major Clinical Study Design Challenges, con't: Evaluating Diagnostic Accuracy

Clinical Reference Standard
(Expert Panel)





Participants' diagnoses by light microscopy

Participants' diagnoses by WSI

Major Clinical Study Design Challenges, con't

- Reader selection: representative of intended user
- Paired Design
- Randomized read order
- Sufficient washout period
- Blinding/Masking
- Components and level of diagnostic detail assessed

Recently Published Guidance Documents relevant to Digital Pathology

- Research Use Only (RUO) Guidance
  - Devices labeled RUO that have not been approved or cleared by the FDA as medical devices, should only be used in research and not for clinical diagnosis of patients
  - IUO is a label that should ONLY be found on an approved IDE device or one under IRB approval, so this could be used for diagnosis, but should never be sold and should not be used after the clinical study period and should never be used off-label.
- Mobile Medical Application Guidance
  - Mobile platforms such as iPads, smart phones, etc.
  - "mobile medical app" is a mobile app that meets the definition of "device" in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)4; and either:
  - is used as an accessory to a regulated medical device; or
  - transforms a mobile platform into a regulated medical device

Thank You!