Regulatory Challenges and Opportunities for Digital Pathology

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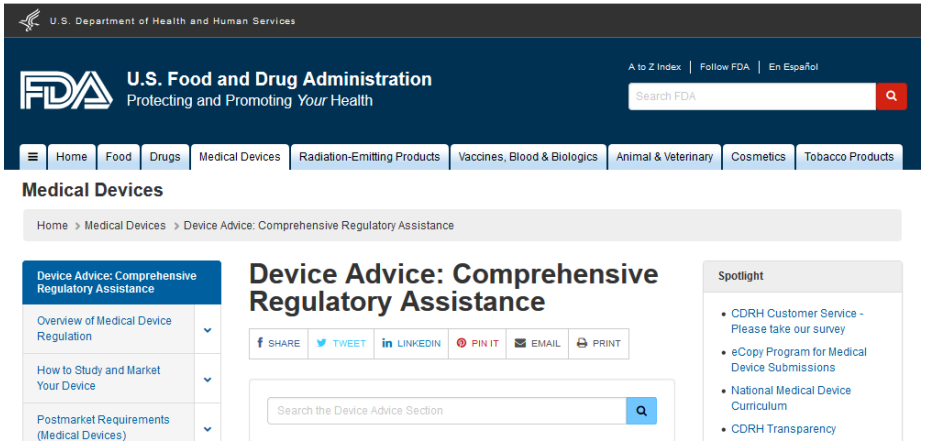
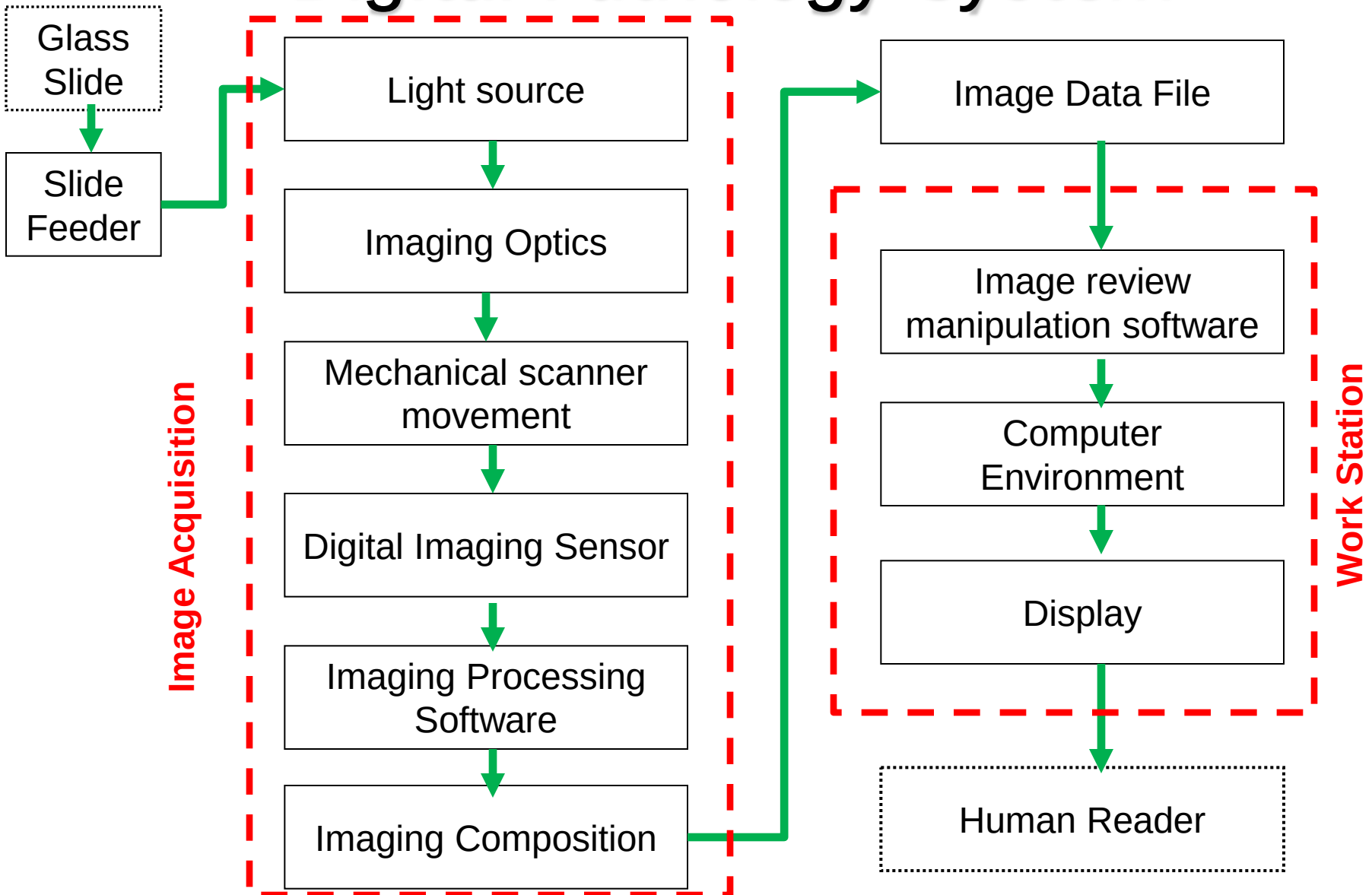


Digital Pathology vs Virtual Microscopy

- Digital Pathology
  - A dynamic, image-based environment that enables the acquisition, management and interpretation of pathology information generated from a digitized glass slide

- Virtual Microscopy
  - Practice of converting glass slides into digital slides for reviewing on a computer screen, typically over a network
  - Scanning/zooming operations, optical resolution, visual magnification, and focus similar to a microscope

Digital Pathology System



Digital Pathology Systems

- Digital Read
  - Manual interpretation of pathology information generated from a digitized glass slide
  - IHC (e.g., HER2, ER, PR)
  - H&E (whole slide image or WSI)
- Image Analysis
  - Computer-aided interpretation of pathology information generated from a digitized glass slide
    - Field of Views (FOVs)
    - Manual Overrides
  - IHC/FISH (e.g., HER2, ER, PR, ALK)
  - Cytology (e.g., blood smear/WBC differential, Pap smear)

Whole Slide Image (WSI)

- Whole Slide Image (WSI)
  - A digitized histopathology glass slide created on a slide scanner
  - The digitized glass slide represents a high-resolution replica of the original glass that can then be manipulated through software to mimic microscope review and diagnosis
  - Also referred to as a virtual slide
- Whole Slide Imaging
  - The acquisition process of creating a virtual slide or whole slide image on a slide scanner

Intended Use of WSI Systems

- Intended Use – Intended for primary surgical pathology diagnosis in lieu of optical microscopy
  - Not an adjunct

- Indications for Use – Broad applications
  - Different organ systems
  - Different diseases/conditions/cases (e.g., simple vs complicated, common vs rare)
  - Different specimen types (e.g., cytology preps vs biopsies)
  - Different stains (e.g., H&E, special stains)
  - Different users (e.g., generalists vs specialists)
  - Different clinical settings (e.g., intranet vs internet access)

FDA Considerations for WSI Validations

- Components vs System
  - Technical assessment of individual components vs Characterization of integrated systems or subsystems
- Non-Clinical vs Clinical
  - Technical vs non-technical (e.g., human elements)
- Clinical Representation vs Statistical Power
  - Number of organs vs numbers of cases per organ
  - Number of readers vs number of cases
  - Consecutive/representative cases vs enrichment cases
    - Different organ systems or diseases/conditions

  →Claims vs limitations
- Premarket vs Postmarket

Technical Assessment of WSI System

- Does the system function accurately and reliably in image acquisition and processing processes?
- Levels of Testing
  - Components
  - Integrated subsystems
  - Complete system
- Methodology of Testing
  - Test materials
  - Testing methods
- Product specifications and limitations

Analytical Validation of WSI System

- Does the system output digital images accurately and reliably for interpretation in the hands of the intended users with various sources of variability?
  - Precision
  - Instrument-to-Instrument Reproducibility
  - Reader-to-Reader Reproducibility
  - Feature Studies
    - Accuracy and reproducibility in identification of histological features critical to diagnosis or differential diagnosis of diseases

Feature Study for WSI Validation

- Objective
  - Accuracy and precision of pathologist identification of a set of challenging histological features of interest using WSI
- Experiment Design
  - 20 histopathological features “in their natural environment” (e.g., psammoma bodies, tumor margins, micrometastases)
  - Each feature selected from ≥3 different organ systems
  - WSI scanning at a magnification consistent with the power at which the feature is typically identified by pathologists (40x or 60x).
  - Multiple (≥3) sites/scanners and readers

Clinical Validation of WSI System

- Does WSI system allow intended users to make diagnosis of surgical pathology specimens as accurately and reliably as optical microscopy?
  - Serious consequences to public health if misdiagnosis caused by suboptimal images

Clinical Study Design

- Overview
  - 4 Clinical study sites
  - 1 Scanner at each site → 4 scanners in total
  - 4 Readers (pathologists) at each site → 16 readers in total
    - Generalists vs specialists representative of intended use population
  - ~2,000 cases representing multiple organ systems
    - Single-slide cases (~1,500) vs multi-slide case

Example List of Study Cases

EXAMPLE OF PROPOSED WSI STUDY BY ORGAN, DIAGNOSIS AND PROCEDURE:
(TOTAL 2000 CASES FOR THIS EXAMPLE)

We encourage the sponsor to include rare and unusual diagnoses (as many as 5%) in the larger (>100) groups

#oS ≡ Number of Slides per Case; CNB ≡ Core Needle Biopsy; TUR ≡ Transurethral Resection; LEEP ≡ Loop Electrosurgical Excision Procedure

ORGAN	# OF CASES		SUBTYPES (procedures)		#oS	Notes
BREAST	300		50	Benign/Atypical CNB	1	1 slide for CNB; 1-5 slides for Lumpectomy
			50	Benign/Atypical Lumpectomy	Multiple	
			50	In-Situ Carcinoma CNB	1	
			50	In-Situ Carcinoma Lumpectomy	Multiple	
			50	Invasive Carcinoma CNB	1	
			50	Invasive Carcinoma Lumpectomy	Multiple	
PROSTATE	300		120	Benign Core Bx	1	1 slide for Core Bx; More than 1 slide for Resection
			30	Benign Resection	Multiple	
			120	Adenocarcinoma Bx	1	
			30	Adenocarcinoma Resection	Multiple	
LUNG/BRONCHUS/Larynx/oral cavity/nasopharynx	100		25	Benign/Inflammatory Bx Only	1	1 slide for Bx; At least 1 of tumor and 1 of bronchial margin for Resection
			25	Dysplasia Bx Only	1	
			30	Carcinoma Bx	1	
			20	Carcinoma Resection	Multiple	
COLORECTAL	150		50	Benign/Inflammatory Bx	1	1 slide for Bx; At least 1 of tumor and 1 of margins for Resection (Nodes - consider excluding as nodes are tested separately)
			50	Adenomas Including Severe Dysp Bx	1	
			40	Adenocarcinoma Endoscopic Bx	1	
			10	Adenocarcinoma Resection	Multiple	
GE Junction	100		50	R/O Barrett's/Dysplasia Bx	1	1 slide for Bx
			50	Non-Neoplastic/Inflammatory Bx	1	

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  - Each pathologist makes diagnosis of each case under optical microscope and WSI
    - Special stains slides, if available, may be provided upon request
  - Expert panel diagnosis or original signout as the truth
  - Primary Endpoint: Non-inferiority in diagnosis error rates

Risk Consideration for Digital Pathology

- Potential risks to patients vs mitigations
- Intended use
  - Primary diagnosis vs adjunctive
  - Screening in asymptomatic vs monitoring in diagnosed
- Representation of a glass slide
  - Area of coverage (e.g., FOVs vs complete scan)
  - Quality (e.g., color, depth, resolution)
- Degree of automation in quality controls and interpretation
- Degree of separation from glass slides

Risk-Based Device Classification

- Class I: Common, Low-Risk Devices
  - General Controls
  - Most exempt from premarket submission
- Class II: Moderate Risk Devices
  - Special controls
  - Premarket notification (510(k))
  - Substantial equivalence to a predicate
- Class III: Complex, High-Risk Devices
  - Premarket Approval (PMA)

Class III: High Risk

- Intended to support or sustain human life or prevent impairment of human health, or presents a potential unreasonable risk of illness or injury
- Serious harm to patients with an incorrect result from an IVD
  - Cancer screening tests
  - Cancer diagnosis
  - Oncology companion diagnostics
- Premarket Application [PMA]

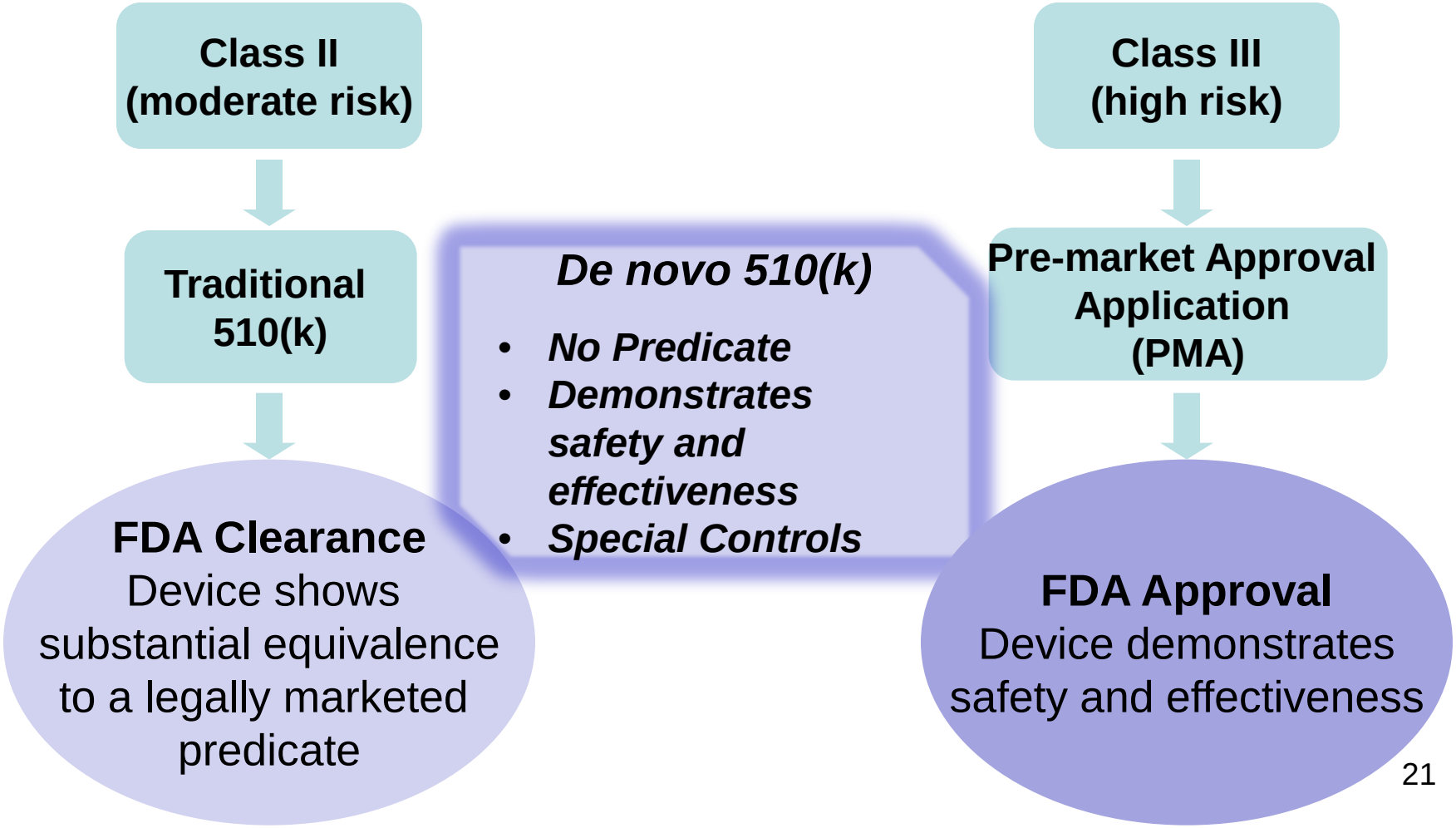
Cervical Cytology Screening Device

- Hologic ThinPrep® Imaging System (P020002): ...assist in primary cervical cancer screening of ThinPrep Pap Test slides for the presence of atypical cells, cervical neoplasia, including its precursor lesions (LSIL, HSIL), and carcinoma as well as all other cytologic criteria as defined by 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology...
- BD FocalPoint™ Slide Profiler (P950009): ...intended for use in initial screening of cervical cytology slides... identifies up to 25% of successfully processed slides as requiring no further review... also identifies at least 15% of all successfully processed slides for a second manual review...to detect slides with evidence of squamous carcinoma and adenocarcinoma and their usual precursor conditions....
- Class III (Procode: MNM)

Unclassified Devices

- Class III by default
- Can be Class I
  - If sufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness
- Can be Class II
  - If sufficient information exists to determine that the special controls would provide reasonable assurance of its safety and effectiveness
- 513(g) or de novo

Regulatory Processes



Special Controls

- Used to mitigate the risks to patients
- Sufficient information to establish Special Controls
  - Promulgation of performance standards
  - Development and dissemination of guidelines
  - Labeling requirements or other appropriate actions
  - Postmarket surveillance / Patient registries
  - For a device intended “for a use in supporting or sustaining human life, the Secretary shall examine and identify the special controls, if any, that are necessary to provide adequate assurance of safety and effectiveness and describe how such controls provide such assurance”

- De novo or Premarket Notification [510(k)]

WSI as a Candidate for *De Novo*

- Is there sufficient information for Special Controls?
  - Performance standards
    - Technical, non-clinical, clinical studies
  - Labeling requirements
    - Training
    - Subgroup analysis: Limitations of WSI?
    - Access to glass slides?
  - Postmarket surveillance
    - Postmarket studies, Patient registries?
  - Change controls
    - Component replacement: Technical specifications?
    - When to submit a new 510(K)?

Significant Changes or Modifications

- 21 CFR 807.81(a)(3) ....The following constitute significant changes or modifications that require a premarket notification:

  (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.

  (ii) A major change or modification in the intended use of the device.

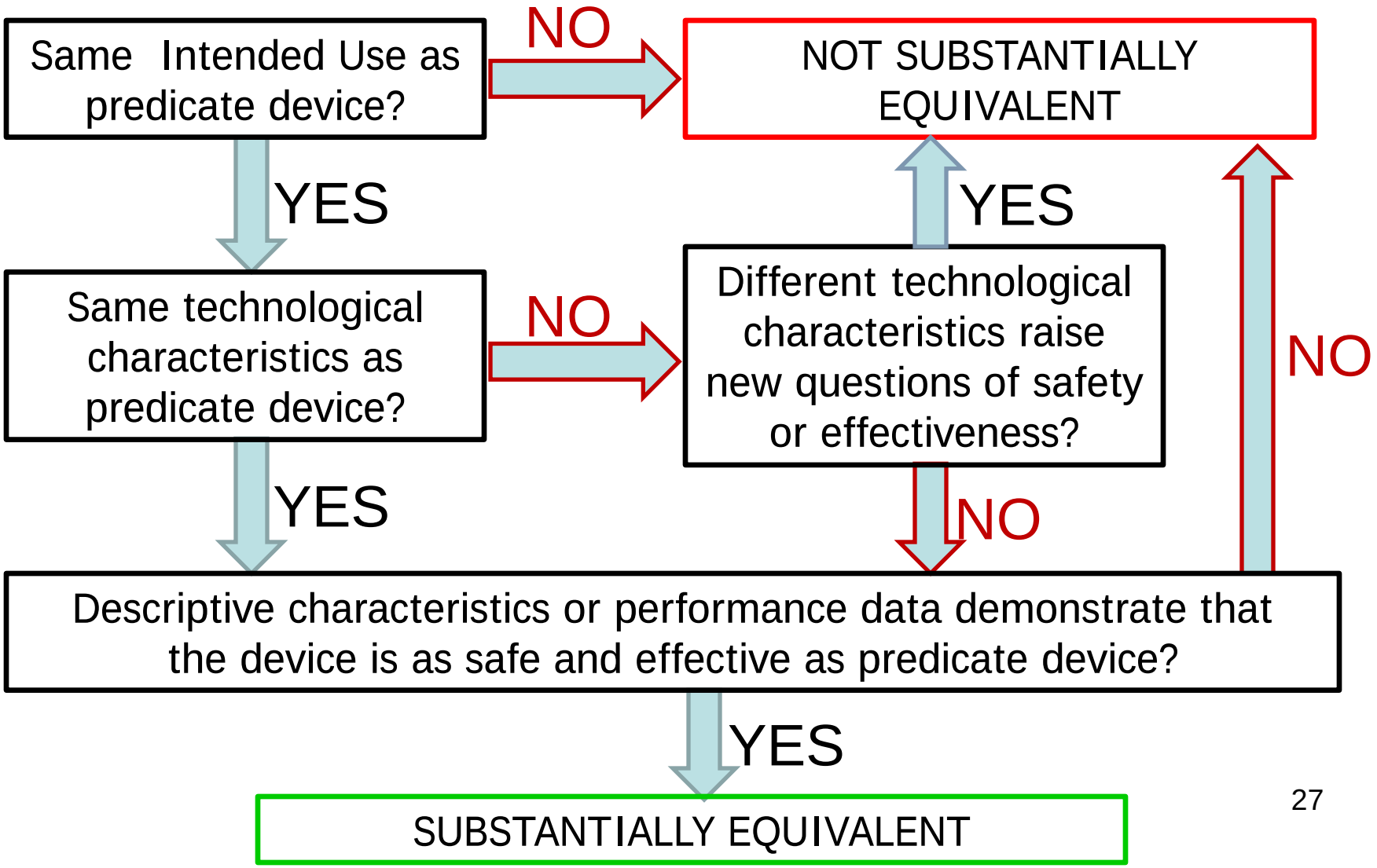
Risk Assessments

- Use an accepted method of risk assessment (e.g., ANSI/AAMI/ISO 14971) for TPLC
  - Initiating hazards, failure modes, or circumstances
  - Sequences of events leading to a hazardous situation
  - Likelihood of such situations arising
  - Likelihood of the hazardous situations leading to harm
  - Nature of the harm that could result
- Considerations for Risk Assessments
  - Risk likelihood or probability
  - Risk severity
  - Device effectiveness

When to submit a 510(k)

- Is the same method or protocol, described in the previous 510(k), used to support the change?
- Does the change affect the use of the device?
- Does a risk assessment of the changed device identify any possible new or increased risks?
- Are clinical data necessary to evaluate safety or effectiveness for purposes of determining substantial equivalence?
- Do design verification and/or validation activities produce any unexpected issues of safety or effectiveness?

Substantial Equivalence (510(k))



Future Considerations

- Intranet, internet, mobile apps
  - Access vs fidelity vs confidentiality (cybersecurity)
- Computer-aided interpretation
  - Primary diagnosis vs adjunctive
  - FOVs vs WSI
- Clinical truth
  - No more diagnosis under optical microscopy
  - Sub-optical features
- Workflow
  - Record retention requirement vs storage/retrieval cost
  - Multiplex functionality and customized applications

Case Study: IHC Imaging Systems

- 21 CFR §864.1860 (Class II; Procode: NQN, NOT, OEO)
  - Imaging Devices for Digital Read/Imaging Analysis
    - GenASIs HiPath IHC Family (140957...)
    - Aperio ePathology eIHC IVD System/ScanScope® XT (k141109...)
    - Ventana Virtuoso™ System (k130515, k121516, k122143...)
    - BioImagene PATHIAM System with iScan (k080910)
    - ChromaVision Automated Cellular Imaging System (k032113)
    - Applied Imaging Ariol™ (k031715)
  - Assay kits
    - anti-HER2/neu (4B5, HercepTest™), anti-ER (SP1, 1D5), anti-PR (1E2, PgR 636), anti-Ki67 (30-9, MIB1), anti-p53 (DO-7)
  - Not all imaging devices cleared for use with all assay kits

A Pathologist's Struggle

"...As the breast marker analysis workflow is currently structured, pathologists would sign into the image analysis database in either RUO or IVD mode. Switching between modes requires re-logging in...

I sign out about 10 breast analysis cases a day. That means that I will have to log in to the system up to 20 times to analyze and sign the reports.

... Double logins will force pathologists to sign out all cases under RUO mode, in my opinion...

... not only do I have to login again to sign out the same case, but after I re-login, I have to search for the case from the list waiting in the cue. This takes time and is inefficient. Breast cancer cases are difficult to sign out correctly. The H&E needs to be carefully reviewed to look for normal ducts (this information should appear on the report, indicating the presence of an internal control). Areas of tumor need to be carefully selected for analysis. Stopping and starting signouts could mean not just a delay in signing out (due to human error), but important details in the H&E could be missed when evaluating subsequent stains. Matching up areas of interest is also important. I could easily see a situation where I would have to sign into a case a third time if I discovered an area of staining in an RUO antibody scan that should have been selected for the IVD antibody..."

FDA "Open Channel" Concept

"……we will allow a device manufacturer to create a partition for an end user to customize their IHC imaging analysis algorithm based on the parameters that the device manufacturer has fully validated. For instance, if and only if a device manufacturer receives FDA clearance for an algorithm that can detect and enumerate nuclear staining of an FDA-cleared IHC assay, may an "open channel" be made available for an end user to customize the algorithm for detection and enumeration of nuclear staining of an FDA-cleared or otherwise analytically validated IHC assay. The report however should clearly state that the customized algorithm has not been cleared or reviewed by FDA and it should be apparent to the end user when they are working in the "open channel" environment (e.g., different colored background, etc.)…."

Take Home Messages

- Digital pathology devices including WSI regulated by FDA based on intended use
- FDA has published the final guidance for technical assessment of WSI system for primary diagnosis
- FDA has outline WSI validation studies for sponsors
  - Clinical study to validate WSI for a broad intended use (i.e., primary diagnosis in lieu of optical microscopy)
  - Feature study to supplement non-clinical & clinical studies
- FDA is considering WSI as candidate for *de novo*
- FDA is proposing "open channel" for imaging devices
- Please consult FDA via the pre-submission process

Resources

- Technical assessment of WSI system draft guidance
  - http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm435355.pdf
- Cybersecurity draft guidance
  - http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm356190.pdf
- CDRH device advice
  - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/
- Pre-submission guidance
  - http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf
- Division of Industry and Consumer Education (DICE)
  - 800-638-2041/301-796-7100

Thank you

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