Digital Pathology Regulatory Considerations

Pathology Informatics Summit 2019

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FDA / CDRH / OIR / DMGP

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FDA/CDRH/OIR/DMGP

I am a scientific reviewer in the Division of Molecular Genetics and Pathology

- Our group oversees the regulation of digital pathology medical devices

Disclaimer

This presentation is intended for informational purposes only and does not constitute legal or regulatory advice. Please see the Federal Food, Drug, and Cosmetic Act and 21 CFR Subchapter H for a full list of requirements by FDA.

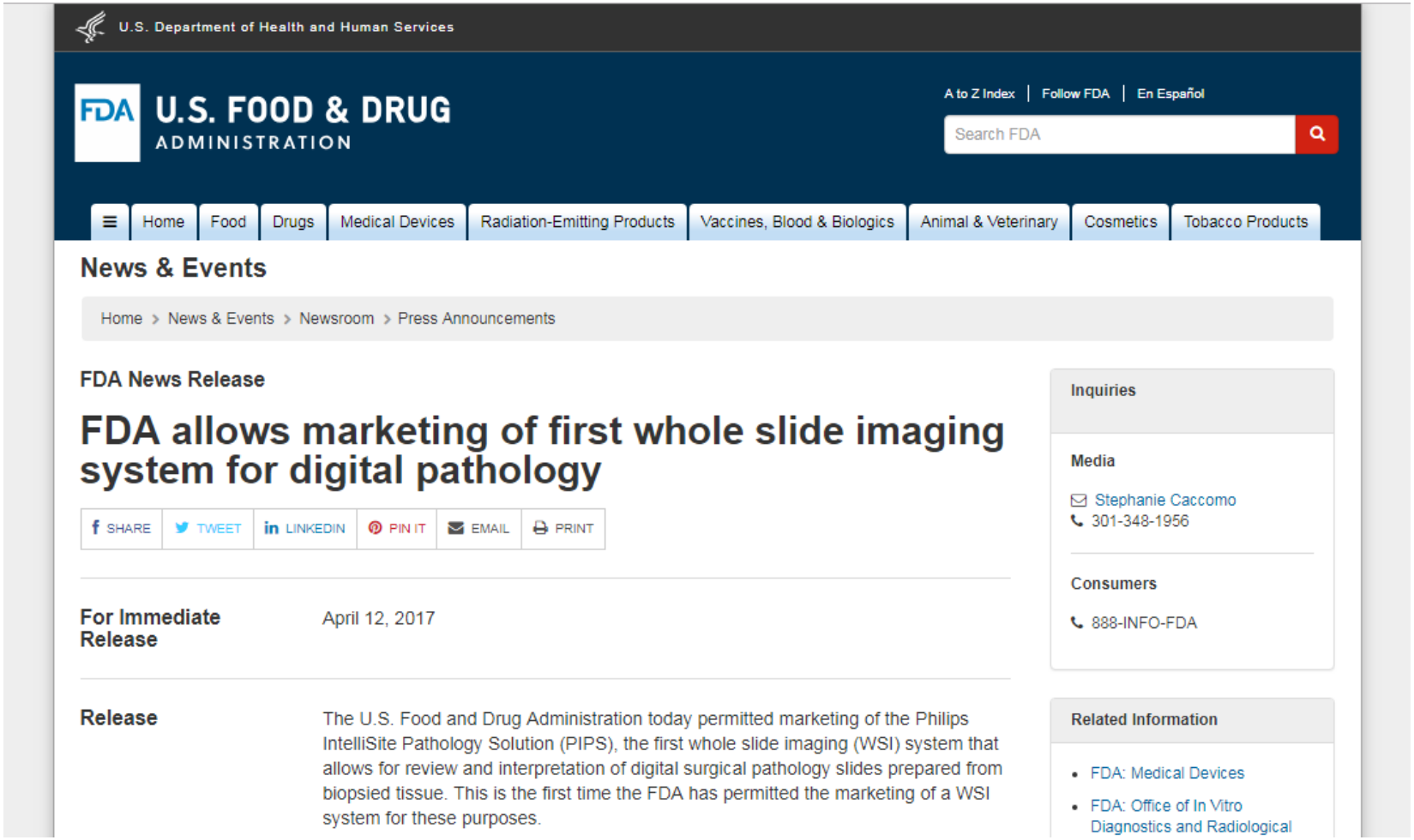
Outline

- Whole Slide Imaging System (WSI system)
  - Philips IntelliSite Pathology Solution (PIPS, DEN160056)
  - Changes to a FDA-cleared WSI system
  - A component of WSI system as a device
- Computational pathology
  - Clinical study
  - Analytical study
  - AI/ML-based algorithm

Outline

- Whole Slide Imaging System (WSI system)
  - **Philips IntelliSite Pathology Solution (PIPS, DEN160056)**
  - Changes to WSI system
  - WSI component as a device
- Computational pathology
  - Clinical study
  - Analytical study
  - AI/ML-based algorithm

Philips IntelliSite Pathology Solution (DEN160056)



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FDA News Release

FDA allows marketing of first whole slide imaging system for digital pathology

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For Immediate Release April 12, 2017

Release

The U.S. Food and Drug Administration today permitted marketing of the Philips IntelliSite Pathology Solution (PIPS), the first whole slide imaging (WSI) system that allows for review and interpretation of digital surgical pathology slides prepared from biopsied tissue. This is the first time the FDA has permitted the marketing of a WSI system for these purposes.

Inquiries

Media

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301-348-1956

Consumers

888-INFO-FDA

Related Information

- FDA: Medical Devices
- FDA: Office of In Vitro Diagnostics and Radiological

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm552742.htm

Philips IntelliSite Pathology Solution (DEN160056)

New Search | Back To Search Results

Device Classification Name	Whole Slide Imaging System
De Novo Number	DEN160056
Device Name	Philips IntelliSite Pathology Solution
Requester	Philips Medical Systems Nederland B.V. Veenpluis 4-6 Best, NL 5684 Pc
Contact	Esther Abels
Regulation Number	864.3700
Classification Product Code	PSY
Date Received	12/01/2016
Decision Date	04/12/2017
Decision	Granted (DENG)
Classification Advisory Committee	Pathology
Review Advisory Committee	Pathology
Reclassification Order	Reclassification Order
FDA Review	Decision Summary
Type	Direct

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?ID=DEN160056

Philips IntelliSite Pathology Solution (DEN160056)

EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
Philips IntelliSite Pathology Solution (PIPS)

DECISION SUMMARY
Correction Date: October 13, 2017
This Decision Summary contains corrections to the April 13, 2017 Decision Summary

A. DEN Number:

DEN160056

B. Purpose for Submission:

De Novo request for evaluation of automatic class III designation for the Philips IntelliSite Pathology Solution (PIPS)

C. Measurand:

Not applicable.

D. Type of Test:

Digital pathology whole slide imaging system

E. Applicant:

Philips Medical Systems Nederland B.V.

F. Proprietary and Established Names:

Philips IntelliSite Pathology Solution (PIPS)

https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160056.pdf

DEN160056 – Philips IntelliSite Pathology Solution

Intended Use

The Philips IntelliSite Pathology Solution (PIPS) is an automated digital slide creation, viewing, and management system. The PIPS is intended for in vitro diagnostic use as an aid to the pathologist to review and interpret digital images of surgical pathology slides prepared from formalin-fixed paraffin embedded (FFPE) tissue. The PIPS is not intended for use with frozen section, cytology, or non-FFPE hematopathology specimens.

The PIPS comprises the Image Management System (IMS), the Ultra Fast Scanner (UFS) and Display. The PIPS is for creation and viewing of digital images of scanned glass slides that would otherwise be appropriate for manual visualization by conventional light microscopy. It is the responsibility of a qualified pathologist to employ appropriate procedures and safeguards to assure the validity of the interpretation of images obtained using PIPS.

DEN160056 – Philips IntelliSite Pathology Solution

Study Overview

- Technical Performance Assessment
  - FDA Guidance Document: *Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices, issued April 20, 2016*
- Analytical (Feature) Study
- Clinical Study

Digital Pathology – Analytical study

To avoid and/or minimize potential bias

- Feature recognition study
  - **LIS** (Lab Information System) records are used to determine which cases/slides are used to enroll features for **natural** review magnifications (e.g. 10x, 20x, and 40x)
  - Features should be **visible under the microscope** and selected based on optical reading under the microscope
  - After WSI scan, FOV is extracted by using microscope and WSI system
  - Need to replicate the FOVs in subsequent WSI scans of the same slide without introducing reader bias
  - Need to verify the feature is within the FOV without introducing reader bias
  - FDA would ask if any features/FOVs are rejected during verification step

Digital Pathology – Analytical study

To avoid and/or minimize potential bias

- Placement and orientation of the features
  - Features should not be purposely centered
  - Orientation of the FOV should be randomized for different reads

- Primary and secondary feature analysis
  - Most FOVs contain only one feature
  - Some FOVs should contain more than one feature
  - Wildcard FOVs/features should be included

Digital Pathology – Analytical study

PIPS (DEN160056)

- 21 features with seven features per magnification level: 10x, 20x and 40x
- For each feature, three organs were selected
- For each organ, six FOVs containing one feature were selected
- Additional 21 FOVs each containing two features were selected
- 1 FOV / slide

Number of study FOVs (slides):

21 (features) x 3 (organs/feature) x 6 (FOVs/organ) + 21 = 399 FOVs

Number of study features:

399 + 21 = 420 features

Digital Pathology – Clinical study

Excerpt from the Intended Use of PIPS:

"The PIPS is for creation and viewing of digital images of scanned glass slides that would otherwise be appropriate for manual visualization by conventional light microscopy."

Review with WSI system should be evaluated by replacing optical microscopy in workflow with all other clinical settings remain unchanged

Two modalities: Manual Digital (review with WSI system) vs. Manual Optical (review with Optical Microscopy)

Two modalities should have **comparable** performance:

- Non-inferior margin based on the difference in major discrepancy rates of two modalities is less than 4%

Digital Pathology – Clinical study

Case Enrollment

- Cases should be enrolled to reflect routine clinical practice while including a sufficient number of difficult and challenging cases for larger (>100) groups
- For example, for colorectal cases, the enrollment target was 150 cases
  - 50 benign/inflammatory biopsies
  - 50 biopsies of adenomas
  - 40 endoscopic biopsies of adenocarcinoma
  - 10 adenocarcinoma resections

- Please contact our division for the Approximate Study Case Type Distribution among malignancies in different organs and their subtypes

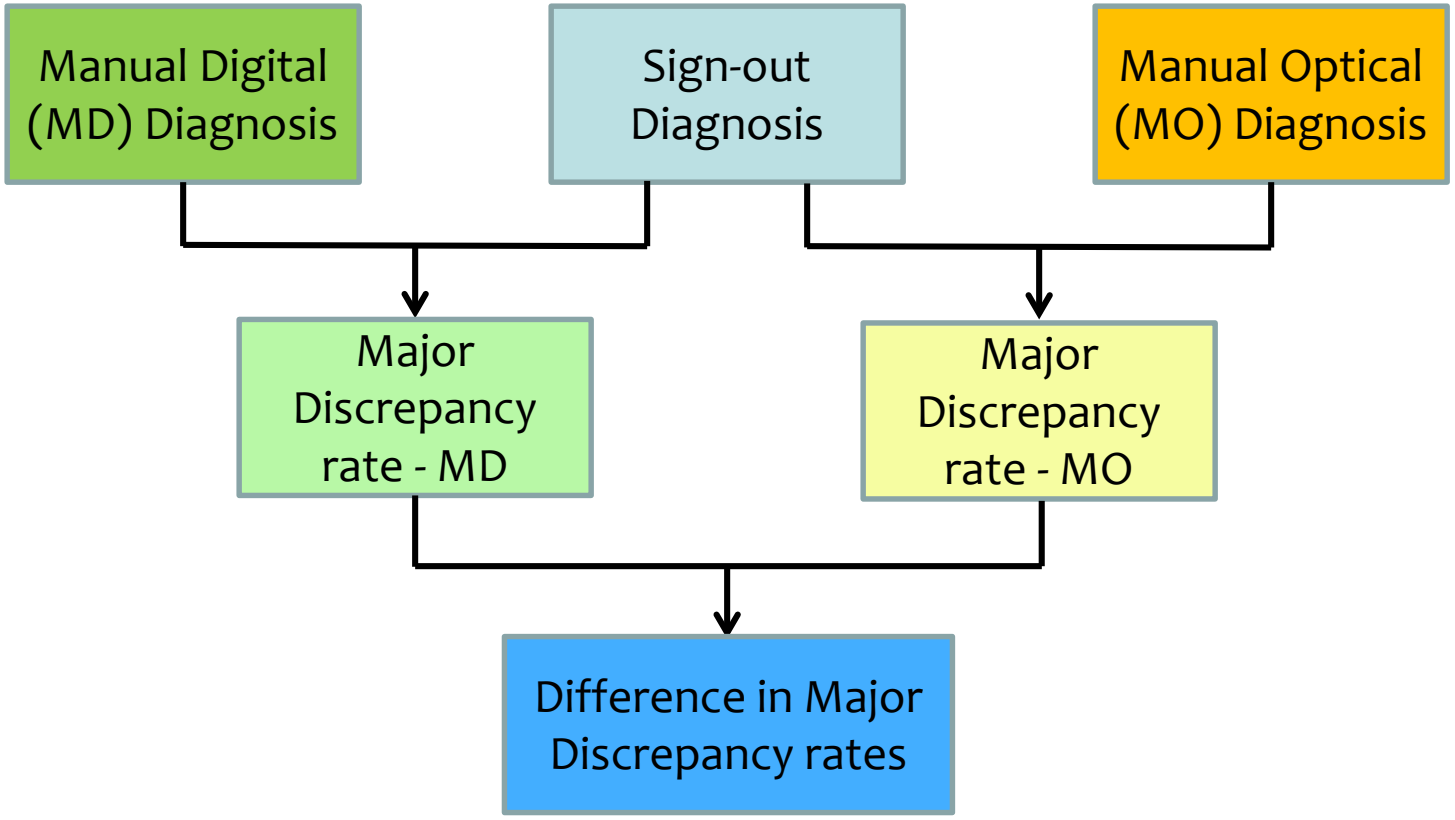
Digital Pathology – Clinical study

PIPS (DEN160056)

- Four study sites, with about 500 cases/site; 16 pathologists with 4 pathologists/site
- 1992 cases with 3390 slides were evaluated
- Slides were obtained from **consecutive** cases at least one year old with sign-out diagnosis
- Washout period between two modalities: four weeks
- Ground truth: sign-out diagnosis
- Adjudication (comparing MD and MO diagnosis to ground truth)
  - Case reports were reviewed without using the WSI system or optical microscope
  - Two adjudication pathologists conduct comparison independently
  - If two adjudicators disagree, then a third adjudicator review the case to achieve majority vote
  - In case all three disagree, consensus was arrived at in an adjudication panel meeting consisting of the same three adjudication pathologists
- 7964 MD diagnoses and 7961 MO diagnoses were established by review pathologists
- **Diagnoses were compared to ground truth for Major discrepancies that result in change of patient management**

Digital Pathology – Clinical study

PIPS (DEN160056)



Digital Pathology – Clinical study

PIPS (DEN160056)

	MD Major Discrepancy		MO Major Discrepancy		Difference in Major Discrepancy Rates (MD - MO)
	Total	Rate (%)	Total	Rate (%)	%
Observed	7964	4.9	7961	4.6	**0.4**

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Changes to WSI system

The authorization under DEN160056 (Philips, 04/12/2017) was for the **entire** WSI system that includes:

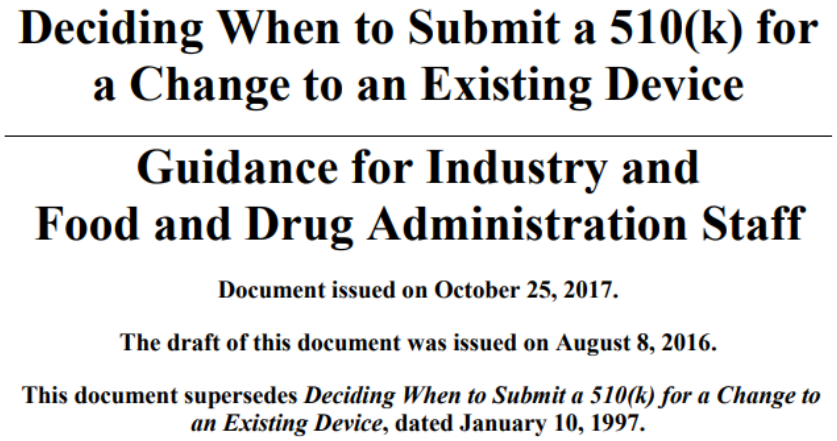
- Ultra Fast Scanner (UFS, for software UFS 1.7.1.1)
- Image Management System (IMS, for software IMS 2.5.1.1)
- Display (PS27QHDCR)

K172174 [Philips, abbreviated 510(k), cleared on 10/04/2017]

- Ultra Fast Scanner (UFS, for software UFS 1.7.1.1)
- Image Management System (IMS, for software IMS 2.6.1)
- Display (PP27QHD)

DEN160056 – Philips IntelliSite Pathology Solution

Changes to any of these three WSI components **may** require a submission of traditional 510(k).



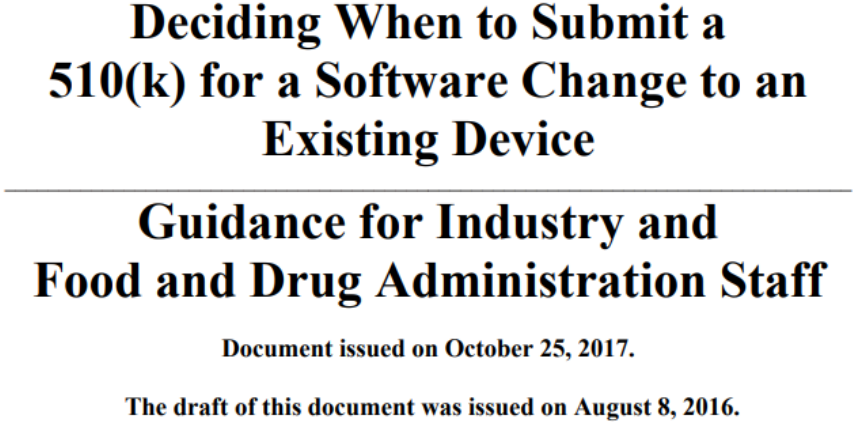
Deciding When to Submit a 510(k) for a Change to an Existing Device

Guidance for Industry and Food and Drug Administration Staff

Document issued on October 25, 2017.

The draft of this document was issued on August 8, 2016.

This document supersedes *Deciding When to Submit a 510(k) for a Change to an Existing Device*, dated January 10, 1997.



Deciding When to Submit a 510(k) for a Software Change to an Existing Device

Guidance for Industry and Food and Drug Administration Staff

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WSI component as a device – Monitor display

K172922 [Barco N.V., traditional 510(k), cleared on 12/27/2017]

- Display MMPC-4127F1 (PP27QHD)

This is the same monitor display as that in K172174. The monitor itself is now IVD-labeled.

Intended Use

The Barco MMPC-4127F1 (PP27QHD) device is intended for in vitro diagnostic use to display digital images of histopathology slides acquired from IVD-labeled whole-slide imaging scanners that have been validated for use with this device, for review and interpretation by pathologists. The display is not intended for use with digital images from frozen section, cytology, or non-formalin-fixed, paraffin embedded (non-FFPE) hematopathology specimens.

WSI component as a device - IMS

Image Management System (IMS) is a medical device

- The graphical interface used by the pathologist to review and interpret WSI images of surgical pathology FFPE slides
- Is a medical device and requires Premarket Notification [510(k)]
  - Involves image processing to stitch WSI image tiles on the fly
  - Decides which tiles are needed during panning/zooming and navigation
- The IMS in PIPS does not have image analysis functionalities
- A De Novo premarket submission [but not a 510(k)] may be needed if the graphical interface software device has image analysis functionalities (e.g. scoring, classification, categorization of the malignancy) to aid pathologist review and interpretation

WSI component as a device - IMS

Image Management System (IMS) – Regulatory considerations

- Scenario 1: Replacing the IMS in an IVD-labeled WSI system (e.g. Philips PIPS)
  - An agreement with Philips is needed to account for any changes to the scanner, WSI image format, etc.
  - 510(k) premarket application
    - Use the IVD-labeled WSI system as predicate
  - Recommended studies:
    - User interface evaluation (e.g. human factors);
    - technical performance assessment (system level, including color reproducibility, zooming, spatial resolution, tissue coverage, stitching error, turnaround time, minimum system requirements, etc);
    - Analytical validation testing such as device precision may be needed
    - Clinical study may be needed

IMS + non-IVD scanner

- Scenario 2: IMS with a non-IVD labeled scanner
  - Need to bring the non-IVD labeled scanner under your Quality System
    - An agreement with scanner manufacturer is needed to account for any changes to the scanner, WSI image format, etc. IMS and scanner should be marketed together as a system
  - Alternatively, the scanner manufacturer to submit a parallel premarket application
  - TPA, analytical and applicable clinical studies are needed to demonstrate the performance of the **system** (scanner + IMS)
  - 510(k) premarket application
    - Use another IVD-labeled WSI system as predicate

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Computational pathology

De Novo regulatory pathway may be required if

- Not of high risk
- Process pathology whole slide images
- Provide surgical/pathological diagnostic information

High risk device may require premarket approval (PMA)

- The device provides automatic primary diagnosis without pathologist intervention

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Computational pathology – Clinical study

Clinical study should be designed to validate the **intended use** of the device in the **intended clinical settings**

Computational pathology – Clinical study

Ground truth may be obtained from

- Adjudication panel by reviewing individual slides/cases
- Sign-out Diagnosis (least burdensome approach)

Adjudication requirements for establishing the ground truth:

- For each case, two pathologists are randomly selected from the panel of three pathologists
- Two pathologists independently review the case
- If two pathologists do not agree, then the third pathologist should review by being blinded to the discordant result by other two pathologists
- Apply majority rule
- If all three pathologists disagree, then all three pathologists should review together and reach a consensus diagnosis

Computational pathology – Example Clinical study design

Other considerations

- Case/slide enrollment procedure should be pre-specified and unbiased
- If the User Interface is not IVD-labeled, then should conduct study in following three modalities:
  - Manual Read (using optical microscope) of glass slides
  - Digital Read (using the Graphical Interface) of WSI images
  - Image Analysis Aided Read of WSI images
- Washout period between two modalities: >= four weeks
- Sub-groups/sub-types should be adequately represented
- Overall Percentage Agreement (OPA) may not be sufficient. Agreement for each category should be assessed.
- Benefit / risk analysis: the device should bring added value

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Computational pathology – Analytical study

Repeatability / Reproducibility is needed for

- Localization
- Classification
- Quantification
- Other measurements (size, domain, etc.)

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Considerations for AI/ML-based algorithm

- Type of AI algorithm: Locked vs. Adaptive
- Intended use
  - concurrent
  - Aid after standard care review
  - replacing
- The Agency would like to know how the product/algorithm was developed and validated in the development phase and prior to analytical and clinical validation of the software device
- The validation study (clinical study) needs to be general enough with broad conditions
- How to monitor the device performance
- How to handle complaints
- A protocol to specify how the software will be updated and when a premarket application is required for the changes

Questions?

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