

Questions for Digital Pathology Advisory Panel Meeting

DAY 1

The FDA is asking the panel for advice and recommendations for the scientific and technical characterization of the physical characteristics of images produced by the conventional light microscope and digital whole slide imaging systems (WSI) ---according to the requirements to maintain the present level of accuracy and precision expected or required for safe and effective routine surgical pathology.

Each of the questions about the optimal **bench testing methods and studies** needed for the objective analytical evaluation of the physical characteristics of OM and WSI may involve one or more of the following parts of the OM and WSI modalities:

- a. The optical physical features (magnification, numerical aperture, working distance, xyz-limiting resolution, wavelength band, field of view, depth of focus, stroke, focus resolution, ocular tilt range, optical axis offset, light source color spectrum, etc.)
 - b. The image acquisition process (the color and spatial resolution, sampling, bit-depth, and sensitivity, as well as field of view, frame rate, shutter speed, quantum efficiency, gain control, output format, etc.)
 - c. Image processing (compression, tile stitching, smoothing, sharpening, etc.)
 - d. The display system (display type, size, image resolution, dynamic range, color calibration etc.)
1. What US or global standards, guideline, industry operating practices are available to guide the characterization of OM and WSI?
 2. Are there objective methods for using physical phantoms that would be useful in the design, development and validation of WSI in comparison to the OM without the need for human reader interpretations, for example grids?
 3. Are there biological specimens (non-human or human) that could be used to objectively challenge the performance of the human observer in a more controlled way compared to a clinical study? For example, invasion of cancer through basement membrane, fine chromatin details necessary for lineage of hematopoietic cells in tumors and inflammation exudates requiring at least 40X optical objective and Z-dimension focusing, cytoplasmic fine details, etc.
 4. What features of image quality (such as resolution, contrast, compression, etc.) are critical requirements and must be achieved for safe and effective use in routine surgical pathology?
 5. Discuss the benefits and risks of one z-plane of focus for routine surgical pathology.

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DAY 2

1. FDA clearance or approval requires that digital mammography devices for screening and diagnostic intended uses must use only non-lossy compression. Many current digital WSI prototype devices employ some type of digital lossy compression. Please discuss the safety and effectiveness of lossy compression applied to diagnostic digital WSI and the trade-off between image quality and decreasing the digital file size.
2. Discuss the benefits and risks of allowing WSI for all organ systems based on the evidence from performance characteristics in a single or a limited number of organ systems?
3. Regarding clinical validation of WSI, please comment on the following components of a clinical study:
 - 3.1 Reference standard for diagnostic truth
 - Composition of panel
 - Number of panel members
 - Rules for agreement
 - 3.2 Type of clinical studies – with respect to
 - Prospective/retrospective
 - Enrichment
 - Types of specimen samples to be included
 - Total area of the whole slide or demarcated areas to be included?
 - Length of washout required
 - Selection mechanism
 - 3.3 Minimization of reader variability
 - Would the multi-reader, multi-case (MRMC) paradigm frequently used to account for reader variability in digital mammography be applicable in accounting for reader variability in the validation of diagnostic pathology?
 - 3.4 Selection of study pathologists
 - Number of study participants
 - 3.5 Performance assessment
 - Should the study pathologist be instructed to find the most clinically significant lesions or all deviations from normal?
 - On what measurements would acceptable level of performance be required (primary measurements)?
 - What additional measurements should be included in the evaluation (secondary)?
 - What hypotheses are appropriate on primary and secondary measurements?
4. Discuss factors that would be important for inclusion in precision studies.
5. Discuss what training should be required for study pathologist evaluating WSI and for pathologists in the postmarket use of WSI.
6. Are there safety and effectiveness issues in the validation of WSI that cannot be addressed by premarketing studies? Is there a need for a post-marketing study to gather additional safety and effectiveness data? If so, how should such a study be conducted?