

# Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices

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## Draft Guidance for Industry and Food and Drug Administration Staff

### *DRAFT GUIDANCE*

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Food and Drug Administration  
Center for Devices and Radiological Health**

**Office of *In Vitro* Diagnostics and Radiological Health  
Division of Molecular Genetics and Pathology  
Molecular Pathology and Cytology Branch**

## **Preface**

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42 [CDRH-Guidance@fda.hhs.gov](mailto:CDRH-Guidance@fda.hhs.gov) to receive a copy of the guidance. Please use the document  
43 number 1400053 to identify the guidance you are requesting.  
44

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108 **Technical Performance Assessment**  
109 **of Digital Pathology Whole Slide**  
110 **Imaging Devices**

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111  
112 **Draft Guidance for Industry and**  
113 **Food and Drug Administration**  
114 **Staff**  
115

116 *This draft guidance, when finalized, will represent the Food and Drug*  
117 *Administration's (FDA's) current thinking on this topic. It does not create or confer*  
118 *any rights for or on any person and does not operate to bind FDA or the public. You*  
119 *can use an alternative approach if the approach satisfies the requirements of the*  
120 *applicable statutes and regulations. If you want to discuss an alternative approach,*  
121 *contact the FDA staff responsible for implementing this guidance. If you cannot*  
122 *identify the appropriate FDA staff, call the appropriate number listed on the title page*  
123 *of this guidance.*

124  
125 **I. Introduction**  
126

127 FDA is issuing this guidance to provide industry and agency staff with recommendations  
128 regarding the technical performance assessment data that should be provided for  
129 regulatory evaluation of a digital whole slide imaging (WSI) system. This document  
130 does not cover the clinical submission data that may be necessary to support approval or  
131 clearance. This document provides our suggestions on how to best characterize the  
132 technical aspects that are relevant to WSI performance for their intended use and  
133 determine any possible limitations that might affect their safety and effectiveness.  
134

135 Recent technological advances in digital microscopy, in particular the development of  
136 whole slide scanning systems, have accelerated the adoption of digital imaging in  
137 pathology, similar to the digital transformation that radiology departments have  
138 experienced over the last decade. The FDA regulates WSI systems manufacturers to  
139 ensure that the images produced for clinical intended uses are safe and effective for such

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140 purposes. Essential to the regulation of these systems is the understanding of the  
141 technical performance of the components in the imaging chain, from image acquisition to  
142 image display and their effect on pathologist's diagnostic performance and workflow.  
143 Prior to performing non-technical analytical studies (i.e., those using clinical samples)  
144 and clinical studies to evaluate a digital imaging system's performance, the manufacturer  
145 should first determine the technical characteristics that are relevant to such performance  
146 for its intended use and determine any possible limitations that might affect its safety and  
147 effectiveness. This draft guidance, when finalized, will provide recommendations that  
148 should be included in the assessment of technical characteristics of a WSI device.

149  
150 FDA's guidance documents, including this guidance, do not establish legally enforceable  
151 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and  
152 should be viewed only as recommendations, unless specific regulatory or statutory  
153 requirements are cited. The use of the word *should* in Agency guidance means that  
154 something is suggested or recommended, but not required.

## **II. Background**

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158 For over a hundred years, the reference method for the diagnosis of cancer and many  
159 other critical clinical conditions has been histopathological examination of tissues using  
160 conventional light microscopy. This process is known as surgical pathology in the  
161 United States.

162  
163 In surgical pathology, patient tissue from surgery, biopsy or autopsy goes through a  
164 process that includes dissection, fixation, embedding, and cutting of tissue into very thin  
165 slices which are then stained, for example by the hematoxylin and eosin (H&E) protocol,  
166 and permanently mounted onto glass slides. The slides are examined by a pathologist  
167 under a light microscope by dynamically adjusting the focus and using different  
168 magnifications. By integrating their interpretations obtained by microscopic examination  
169 of the tissue from all slides pertaining to a case, pathologists arrive at a diagnosis of the  
170 case.

171  
172 WSI refers to the digitization of the stained entire tissue specimen on a glass slide. The  
173 glass slide is still prepared and stained just as for conventional light microscopy.  
174 Depending on the system used, various magnifications, scanning methodologies,  
175 hardware, and software are employed to convert the optical image of the slide into a  
176 digital whole slide image. With WSI, the pathologist views the image on a computer  
177 monitor rather than through the microscope oculars.

## **III. Scope**

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181 This document provides guidance regarding only the technical performance assessment  
182 of WSI systems for regulatory evaluation. WSI systems are defined here as those  
183 consisting of (a) an image acquisition subsystem that converts the content of a glass slide

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184 into a digital image file, and (b) a workstation environment for viewing the digital  
185 images. This guidance is applicable for surgical pathology tasks performed in the  
186 anatomic pathology laboratory. It is intended to provide recommendations to industry  
187 and FDA staff regarding only the technical performance assessment data needed for the  
188 regulatory evaluation of a WSI device. This document is not meant to provide guidance  
189 for the non-technical analytical studies (utilizing clinical samples) or pivotal clinical  
190 studies necessary to support safety and effectiveness, nor does this guidance alone suffice  
191 to demonstrate safety and effectiveness of WSI systems. Interpretation of WSI images on  
192 mobile platforms is beyond the scope of this guidance.  
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### **IV. Policy**

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196 The following subsections of this section describe the technical performance assessment  
197 data FDA believes are necessary to allow for the regulatory evaluation of a WSI device.  
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#### **IV(A). Description and Test Methods for Each Component**

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This subsection details the descriptions and the test methods at the component level that should be included in the technical performance assessment of a WSI device. For purposes of this guidance only, a component is a piece of hardware, software, or a combination of hardware and software that processes the image signals flowing through the imaging chain. The concept of a component is based on the transformation of the image signals. For example, the digital imaging sensor is a hardware device that converts optical signals into digital signals. The image composition component is a software program that stitches sub-images together to form a whole slide image. A component and a physical device need not be in close physical proximity. For example, the light source component and the image optics component are usually tightly coupled within the same device, while the display calibration data is often distributed in both the color profile in the computer environment component and the on-screen display settings in the display component.

The components in a WSI device can be grouped in two subsystems: image acquisition and image display. The image acquisition subsystem digitizes the tissue slide as a digital image file. The image display subsystem converts the digital image file into optical signals for the human reader. In the paradigm of telemedicine, the digital image file can be electronically sent to a remote site for reading, so the image acquisition subsystem and the image display subsystem do not need to be physically coupled. Methods for independently testing the image acquisition and display subsystems are described in Section IV(B).

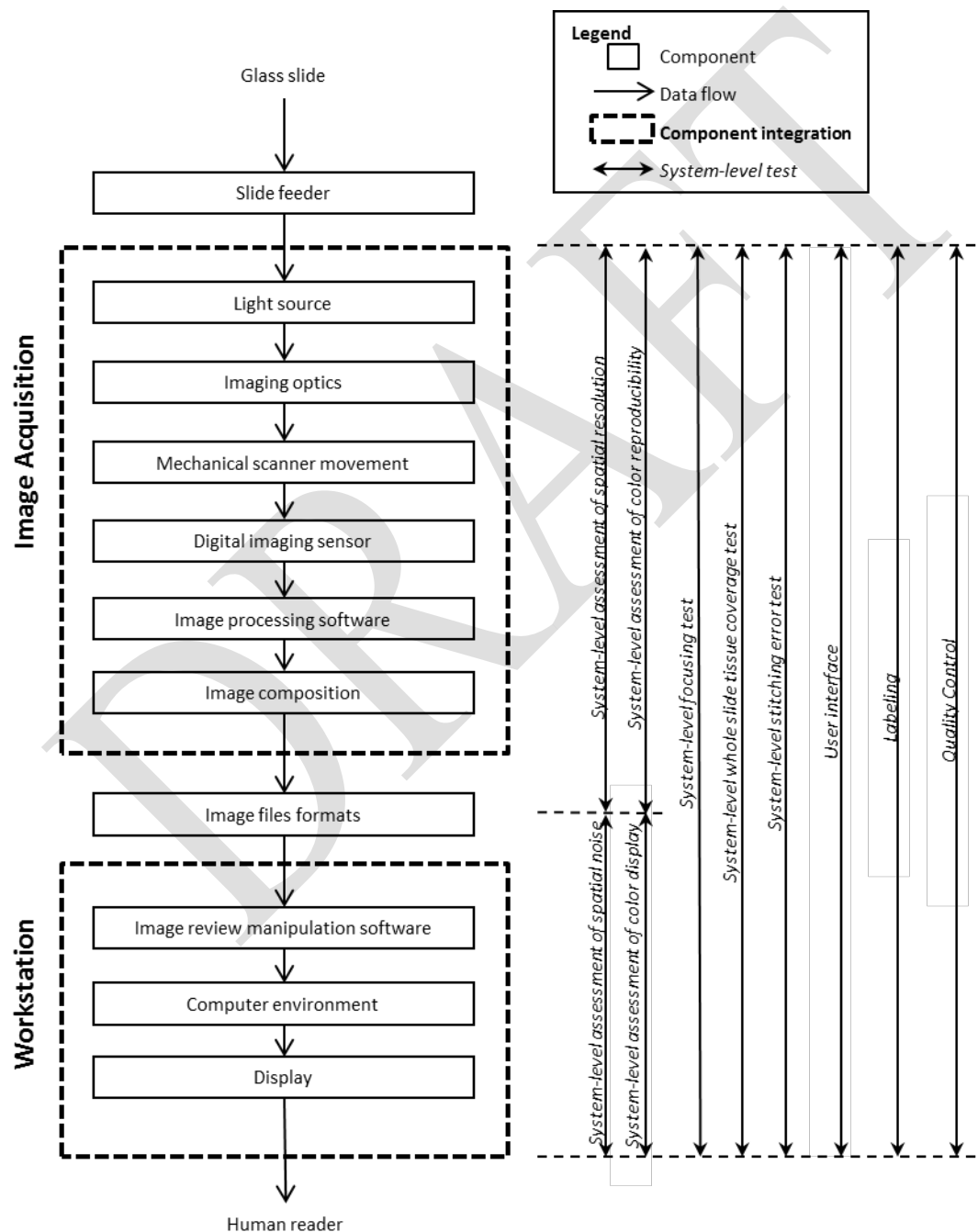
Sponsors should provide a block diagram of the components found in the WSI system in the premarket submission. A chart indicating the relationship among the components and the test methods utilized for the specific system characterization should also be provided. Diagram 1 on the following page is offered as an example block diagram of typical

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228 components found in current WSI systems. The components of a particular WSI system  
229 might not include all of those listed in the diagram or may include additional  
230 components. Sponsors are encouraged to provide additional diagrams, illustrations, and  
231 photographs of their devices as part of their submissions.

232  
233 **Diagram 1: Example block diagram of typical components found in current WSI**  
234 **systems**





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### 274 **IV(A)(1). Slide Feeder**

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#### **IV(A)(1)(a). Description**

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278 The slide feeder is the mechanism(s) used to introduce the slide(s) to the scanner. For the  
279 slide feeder, sponsors should provide the following information, if applicable:

280

281

- Configuration of the slide feed mechanism (a physical description of the equipment)
  - Slide configuration (physical description of the slide (i.e., custom or commercial off-the-shelf))
  - Number of slides in queue (carrier)
  - Class of automation (e.g., robotics, pneumatics, etc.)
- User interaction
  - Hardware (e.g., loading of slides into carrier)
  - Software (e.g., does the system recognize the number of slides or is this specified by the user)
  - Feedback (e.g., alarms, notifications, etc.)
  - Failure Mode and Effects Analysis (FMEA) (including severity, likelihood, mitigations, etc.)

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### **IV(A)(2). Light Source**

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#### **IV(A)(2)(a). Description**

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298 The light source, including the light guide, generates and delivers light to the slide being  
299 imaged. The two major components are the lamp and condenser. For the light source,  
300 sponsors should provide the following information and specifications, if applicable:

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- Lamp
  - Bulb type (e.g., halogen, xenon arc, LED)
  - Manufacturer and model
  - Wattage
  - Spectral power distribution or color temperature
  - Expected lifetime
  - Output adjustment control (electrical/electronic/mechanical)
  - Optical filter(s)
    - Type (e.g., heat blocking, polarization, neutral density, diffusing)
  - Manufacturer and model
  - Expected intensity variation (coefficient of variation (CV) as a percentage)
    - Over the duration of scanning a single slide
    - Over the course of a single workday
  - Expected spectral variation
    - Over the duration of scanning a single slide
    - Over the course of a single workday
    - Over the lifetime of the device

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- 318 ○ Capability of tracking intensity and spectral degradation with lifetime
- 319 ● Condenser
- 320 ○ Illumination format (e.g., Kohler, critical)
- 321 ○ Manufacturer and model
- 322 ○ Numerical aperture
- 323 ○ Focal length
- 324 ○ Working distance

325

326

### **IV(A)(2)(b). Test Method**

327

328 The following steps should be used to measure the spectral distribution of light incident  
329 on the slide. Position the input of a calibrated spectrometer or monochromator at the  
330 plane where the slide would be placed, centered on the illumination spot from the  
331 condenser. If desired, the light can be coupled into the spectrometer via light guide (e.g.,  
332 fiber optic cable) or an integrating sphere. The measurement aperture should be at least  
333 as large as the anticipated field of view on the slide at the lowest magnification of the  
334 imaging optics. The wavelength accuracy and relative spectral efficiency of the  
335 spectrometer or monochromator in the wavelength range of 400-700 nm should be  
336 calibrated prior to measurements and reported. Plots of the measured spectrum in  
337 radiometric units (i.e., irradiance in  $W/cm^2/nm$  or similar) should be provided.

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### **IV(A)(3). Imaging Optics**

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#### **IV(A)(3)(a). Description**

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343 The imaging optics comprises the microscope objective and auxiliary lens(es) (e.g., tube  
344 lens), which optically transmit an image of the tissue from the slide to the digital image  
345 sensor. Sponsors should provide the following information and specifications, if  
346 applicable:

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- Ray-trace from slide (object plane) to digital image sensor (image plane)
- Microscope objective
  - Manufacturer
  - Type (e.g., Plan, Plan APO)
  - Magnification
  - Numerical aperture (NA)
  - Focal length
  - Working distance
- Auxiliary lens(es)
  - Manufacturer
  - Lens type
  - Focal length
- Magnification of imaging optics, per ISO 8039:1997 *Optics and optical instruments — Microscopes — Magnification*

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### 362 **IV(A)(3)(b). Test Methods**

363

364 Sponsors should conduct the following tests in conformance with the International  
365 Standards, if applicable:

- 366 • Relative irradiance of imaging optics at image plane per ISO 13653:1996 *Optics*  
367 *and optical instruments – General optical test methods - Measurement of relative*  
368 *irradiance in the image field*
- 369 • Distortion per ISO 9039:2008 *Optics and photonics — Quality evaluation of*  
370 *optical systems —Determination of distortion*
- 371 • Chromatic aberrations per ISO 15795:2002 *Optics and optical instruments —*  
372 *Quality evaluation of optical systems — Assessing the image quality degradation*  
373 *due to chromatic aberrations*

374

### 375 **IV(A)(4). Mechanical Scanner Movement**

376

#### 377 **IV(A)(4)(a). Description**

378

379 The mechanical scanner addresses the physical characteristics of the stage upon which  
380 the glass slide is affixed. The key components include stage configuration, movement,  
381 and control. This information is relevant whether it is only the stage that is moving and  
382 the optics are stationary, or if there is movement on all axes. For the mechanical scanner,  
383 sponsors should provide the following information and specifications, if applicable:

- 384 • Configuration of the stage (a physical description of the stage)
  - 385 ○ Stage size
  - 386 ○ Stage manufacturer and model number
  - 387 ○ Stage material (e.g., anodized aluminum)
  - 388 ○ Single multi-axis or multiple stacked linear stages (manufacturer and  
389 model number)
  - 390 ○ Type of guides or ways (e.g., bearings)
  - 391 ○ Sample retention mechanism (slide holder)
- 392 • Method of movement of the stage (e.g., stepper motor, servomotor, piezomotor,  
393 etc., coupled with belt, ball-screw, lead-screw, etc.)
  - 394 ○ Movement resolution for XY-axes
  - 395 ○ Movement in Z-axis
  - 396 ○ Speed range
  - 397 ○ Travel distance
  - 398 ○ Maximum scanning area
  - 399 ○ Localization and reading of bar code labels
- 400 • Control of movement of the stage
  - 401 ○ Open or closed loop operation
  - 402 ○ Positional accuracy (calibration) and repeatability
    - 403 ■ Lost motion compensation (e.g., backlash)
  - 404 ○ Physical control (e.g., joystick) for single-slide, non-batch mode

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- 405 ○ Selection of area to be scanned (in accordance to image composition
- 406 software)
- 407     ▪ whole slide
- 408     ▪ automatically determined area with tissue content
- 409 ● Failure Mode and Effects Analysis (FMEA) (including severity, likelihood,
- 410 mitigations, etc.)

### **IV(A)(4)(b). Test Method**

413  
414 Sponsors should demonstrate the mechanical performance of the stage with respect to  
415 positional repeatability and accuracy on all relevant axes, in accordance with ISO 230-  
416 2:2006 Test code for machine tools—Part 2: *Determination of accuracy and*  
417 *repeatability of positioning numerically controlled axes.*

### **IV(A)(5). Digital Imaging Sensor**

#### **IV(A)(5)(a). Description**

420  
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422  
423 The digital image sensor is an array of photosensitive elements (pixels) that convert the  
424 optical signals of the slide to digital signals, which consist of a set of values  
425 corresponding to the brightness and color at each point in the optical image. Please  
426 provide the following information and specifications:

- 427 ● Sensor type (e.g., CMOS, CCD) and manufacturer
- 428 ● Pixel information/specifications
  - 429 ○ Number and dimensions of pixels
  - 430 ○ Design of color filter array
    - 431     ▪ Configuration of color filter array
    - 432     ▪ Spectral transmittance of color filter mask
- 433 ● Responsivity specifications
  - 434 ○ Quantum efficiency versus wavelength
  - 435 ○ Linearity
  - 436 ○ Spatial uniformity
- 437 ● Noise specifications
  - 438 ○ Dark current level (electrons per second)
  - 439 ○ Read noise (electrons)
- 440 ● Readout rate (e.g., pixels per second, frames per second)
- 441 ● Digital output format (e.g., bits per pixel, bits per color channel)

#### **IV(A)(5)(b). Test Methods**

442  
443  
444 Sponsors should conduct the following tests in conformance with the corresponding  
445 International Standards, if applicable:  
446  
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- 448 • Opto-electronic conversion function per ISO 14524:2009 *Photography —*  
449 *Electronic still-picture cameras — Methods for measuring optoelectronic*  
450 *conversion functions (OECFs)*  
451 • Noise measurements per ISO 15739:2003 *Photography — Electronic still-picture*  
452 *imaging — Noise measurements*  
453

454 **IV(A)(6). Image Processing Software**

455 **IV(A)(6)(a). Description**

456 Image processing software refers to the software components of the camera. It includes  
457 control algorithms for image capture and processing algorithms for raw data conversion  
458 into the digital image file. Sponsors should provide the following information and  
459 specifications, if applicable:  
460

- 461
- 462 • Exposure control
  - 463 • White balance
  - 464 • Color correction
  - 465 • Sub-sampling
  - 466 • Pixel-offset correction
  - 467 • Pixel-gain or flat-field correction
  - 468 • Pixel-defect correction
- 469

470 **IV(A)(6)(b). Resources**

471 See the guidance entitled “*Guidance for the Content of Premarket Submissions for*  
472 *Software Contained in Medical Devices*”  
473 ([http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocument](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm)  
474 [s/ucm089543.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm)) for the information that should be provided.  
475  
476

477 **IV(A)(7). Image Composition**

478 **IV(A)(7)(a). Description**

479 Image composition is a step present in systems that produce whole slide images as  
480 opposed to individual fields of view. Whole slide scanning is typically performed in  
481 accordance with the positioning of a stage that moves in submicron steps. At each  
482 location of the stage movement, an image of the field of view is acquired. Images can be  
483 acquired with a degree of overlapping (redundancy) between them to avoid gaps in data  
484 collection. Images can also be acquired at different depths of focus followed by the  
485 application of focusing algorithms. At the end of this process, all acquired images are  
486 combined (stitched) together to create a composite high resolution image. There are a  
487 number of features that can affect this process, and they are listed below. Sponsors  
488 should provide a description of these features, if applicable:  
489

- 490
- 491 • Scanning method

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- 492 ○ Single objective or multiple miniature objectives in an array pattern
- 493 ○ Scanning pattern: square matrix acquisition (tiling), line scanning, etc.
- 494 ○ Overlap between scanned regions
- 495 ○ Merging algorithms that stitch the aligned images together into a
- 496 composite image file. Such algorithms may employ functions to align
- 497 adjacent fields of view in accordance to the scanning pattern, overlap, etc.
- 498 ○ Automatic background correction functions to eliminate the effect of non-
- 499 uniformities in the microscope's illumination and image merging
- 500 procedure. These non-uniformities if not corrected might create visible
- 501 borders (seams and stitch lines) between the adjacent fields of view.
- 502 • Scanning speed: time to scan the whole slide. This time is dependent on selected
- 503 magnification, and the amount of tissue on the glass slide.
- 504 • Number of planes at the Z-axis to be digitized (stack depth)
- 505

#### **IV(A)(7)(b). Test Methods**

506  
507  
508 Testing for image composition can be performed on a system level using special  
509 calibration slides (such as grid patterns) that can test for line uniformity and focus  
510 quality. Sponsors should provide the following outputs for these tests, if applicable:

- 511 • Images of digitized calibration slides
- 512 • Analysis of focus quality metrics
- 513 • Analysis of coverage of the image acquisition for the entire tissue slide
- 514

#### **IV(A)(8). Image Files Formats**

##### **IV(A)(8)(a). Description**

515  
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518  
519 The final result from image acquisition can be a whole slide image consisting of a stack  
520 of all acquired fields of view and magnifications during WSI. The complete digitized  
521 image file usually occupies between 1-20 gigabytes of storage space depending on the  
522 sample and the magnification of the objective lens used. Images can then be stored in a  
523 number of ways and formats. Sponsors should provide the following information:

- 524 • Compression method (e.g., the wavelet-based JPEG2000 compression standard or
- 525 TIFF)
- 526 • Compression ratio: ratio of uncompressed to compressed file size
- 527 • Compression type: lossless or lossy compression
- 528 • File format: can be formats easily accessible with public domain software such as
- 529 JPEG or TIFF, or can be proprietary formats only accessible with specific vendor
- 530 viewers. The file format depends on the file organization and related use.
- 531 • For systems that interact with DICOM-compliant software and hardware,
- 532 sponsors should provide a DICOM compatibility report.
- 533 • File organization:
  - 534 ○ Single file with multi-resolution information (pyramidal organization)
  - 535 ○ Stack of files at different magnifications

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### **IV(A)(9). Image Review Manipulation Software**

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#### **IV(A)(9)(a). Description**

540

541 For the image review manipulation software, sponsors should provide the following  
542 information, if applicable:

- 543 • Continuous panning (moving in x-y space) and pre-fetching (buffering adjacent  
544 images to speed up panning time)
- 545 • Continuous zooming (magnification)
- 546 • Discrete Z-axis displacement
- 547 • Ability to compare multiple slides simultaneously on multiple windows
- 548 • Ability to perform annotations
- 549 • Image enhancement such as sharpening functions
- 550 • Color manipulation, including color profile, white balance, color histogram  
551 manipulation, and color filters
- 552 • Annotation tools
- 553 • Tracking of visited areas and annotations
- 554 • Digital bookmarks (revisit selected regions of interest)
- 555 • Virtual “multihead microscope” (this is when multiple pathologists  
556 simultaneously review the same areas remotely)

557

558

#### **IV(A)(9)(b). Resources**

559

560 See the guidance entitled “*Guidance for the Content of Premarket Submissions for*  
561 *Software Contained in Medical Devices*”

562 ([http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocument](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm)  
563 [s/ucm089543.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm)) for additional information on this subject.

564

565

### **IV(A)(10). Computer Environment**

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#### **IV(A)(10)(a). Description**

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569 Computer environment refers to the workstation, including both hardware and software  
570 components, that retrieves the digital image file and drives the display for the user to  
571 review the images. Sponsors should provide the following information and  
572 specifications, if applicable:

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- 573 • Computer hardware (e.g., PC or Mac)
- 574 • Operating system (e.g., Win7 32-bit, OSX 10.6, or Linux/Ubuntu 11.10 32-bit)
- 575 • Graphics card (e.g., nVidia GeForce GTX 5x0 PCI Express x16)
- 576 • Graphics card driver (e.g., nVidia GeForce driver 285.63)
- 577 • Color management settings (e.g., ICS or WCS)
- 578 • Color profile (e.g., sRGB IEC61966-2.1)

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- 579 • Display interface (e.g., DVI or DisplayPort)  
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581

### **IV(A)(11). Display**

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#### **IV(A)(11)(a). Description**

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586 Display refers to the optoelectronic device that converts the digital image signals in the  
587 RGB space into optical image signals for the human reader. For the display, sponsors  
588 should provide the following information and specifications, if applicable:

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#### **IV(A)(11)(b). Test Methods**

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- On-Screen Display settings of the testing conditions should be specified, including:
  - Input signal (e.g., sRGB or AdobeRGB)
  - Brightness setting (e.g., 95%)
  - White point setting (e.g., 6500K)
  - Color channel settings (e.g., Red=100%, Green=95%, Blue=100%)
- Characterization metrics related to image quality should be provided, including the following items:
  - Luminance range
  - Grayscale resolution, including luminance mapping or gamma response analysis
  - Luminance and color coordinates of primaries
  - Gray tracking (e.g., AAPM TG196)
  - Additivity of primaries
- Physical characterization tests should be performed, including:
  - Bidirectional reflection
  - Pixel fill factor
  - Pixel defects (count and map)



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- 623 ○ Veiling glare (small-spot)
- 624 ○ Chromaticity
- 625 ○ Spatial resolution
- 626 ○ Spatial noise
- 627 ○ Backlight modulation
- 628 ○ Rise and fall time constants
- 629 ○ Luminance stability
- 630 ○ Angular color response

631

### **IV(A)(11)(c). Resources**

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633  
634 Those interested in learning more about these types of display considerations should  
635 consider reading:

- 636 • The guidance entitled “*Guidance for Industry and FDA Staff: Display Accessories*  
637 *for Full-Field Digital Mammography Systems-Premarket Notification (510(k))*  
638 *Submissions*”  
639 ([http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceD](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107549.htm)  
640 [ocuments/ucm107549.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107549.htm)).

641

- 642 • E. Samei, A. Badano, D. Chakraborty, K. Compton, C. Cornelius, K. Corrigan,  
643 M. J. Flynn, B. Hemminger, N. Hangiandreou, J. Johnson, M. Moxley, W.  
644 Pavlicek, H. Roehrig, L. Rutz, J. Shepard, R. Uzenoff, J. Wang, and C. Willis,  
645 *Assessment of display performance for medical imaging systems, Draft Report of*  
646 *the American Association of Physicists in Medicine (AAPM) Task Group 18,*  
647 *Technical Report, AAPM (October 2002).*

648

- 649 • *Gray Tracking in Medical Color Displays - A report of the AAPM Task Group*  
650 *196*

651

- 652 • IEC 62563-1:2009, *Medical electrical equipment – Medical image display*  
653 *systems – Part 1: Evaluation methods*

654

- 655 • Amendment 1 to IEC 62563-1: *Medical image display systems – Part 1:*  
656 *Evaluation methods*

657

### **IV(B). System-level Assessment**

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659  
660 This subsection details the test methods at the system level that should be included in the  
661 technical performance assessment of a WSI device. In this guidance, *system* refers to a  
662 series of consecutive components in the imaging chain with clearly defined, measurable  
663 input and output. For example, a system-level test can be designed for the image  
664 acquisition subsystem, the image display subsystem, or a combination of both. The goal  
665 of system-level tests is to assess the composite performance of a series of consecutive  
666 components in the imaging chain. System-level tests should be conducted when the

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667 component-level tests are either unfeasible or unable to capture the interplay between  
668 components.

669

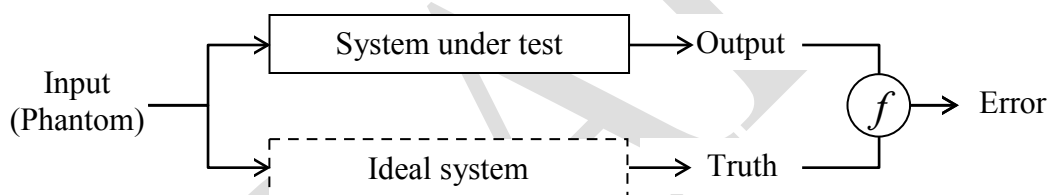
670 The common framework of the system-level tests described in this section is to compare  
671 the system under test with an ideal system based on the same input, and then report the  
672 difference between their outputs quantitatively. Designing such a system-level test  
673 typically involves the following steps: (1) define the scope of the system and its input and  
674 output, (2) define the input, which in most cases is a test target or phantom, (3) measure  
675 the input to establish the ground truth that would be generated by an ideal system, (4)  
676 measure the output of the system under test, and (5) calculate the errors between the truth  
677 and the output with a quantitative metric. The framework of a typical system-level test is  
678 shown in Diagram 2. Notice that the *ideal system* is a hypothetical device that generates  
679 the perfect output with respect to the objective of the test such as color or focus. The  
680 purpose of the ideal system is to define the intended behavior of the system under test.  
681 The ideal system does not need to be implemented. Instead, the ideal system should be  
682 simulated by a test method that establishes the truth of the input phantom.

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**Diagram 2: Framework of a typical system-level test.**



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### 692 **IV(B)(1). Color Reproducibility**

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#### 694 **IV(B)(1)(a). Description**

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696 Color reproducibility is one of the key characteristics of a WSI system and cannot be  
697 evaluated at the component level. The goal of this system-level test is to measure the  
698 color differences between the input color stimuli and the output digital image file. This  
699 test also evaluates the tone reproduction curve (i.e., gamma curve) of the WSI system.

700

#### 701 **IV(B)(1)(b). Test Methods**

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703 The following test is recommended for examining the color reproducibility of the image  
704 acquisition phase (i.e., from slide to digital image file).

705

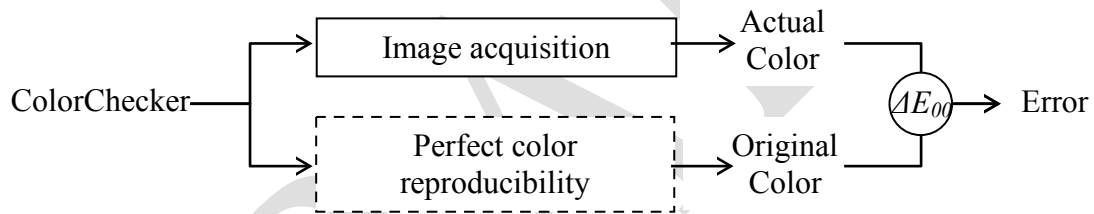
- 706 • Input color patches: Use transparent test patterns consisting of colors similar to  
707 the Gretag Macth ColorChecker (24 colors) or X-rite Digital ColorChecker SG  
708 (140 colors). Notice that both color targets consist of a ramp of gray shades for  
assessing the tone reproduction curve.

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- 709
- Ground truth:
    - Measure the color coordinates of each color patch in CIEXYZ with a colorimeter or a spectroradiometer
    - Repeat the same measurement for the reference white
    - Calculate the CIELAB values
  - 714 • Output digital image file:
    - Each pixel consists of the red, green, and blue (RGB) values in a default color space such as the sRGB or AdobeRGB
    - Convert the RGB values into CIEXYZ based on the default color space
    - Convert the CIEXYZ values into the CIELAB color space
    - Choose a region of interest with at least 100 pixels and calculate the average CIELAB value
  - 721 • Calculate the color differences between the measured color coordinates of the patches at the input (ground truth) and the output color coordinates calculated as describe in the previous paragraphs with the delta-E 2000 formula
- 722
- 723
- 724

725 **Diagram 3: Framework of the system-level color reproducibility test.**



734 The following test is recommended for examining the color reproducibility of the image display phase (i.e., from digital image file to display). The goal is to calculate the color differences between the input RGB values in the image file and the output color stimuli on the display.

- 735
- 736
- 737
- 738 • Input color patches: Select a set of representative colors such as the Gretag Macbeth ColorChecker (24 colors) or X-rite Digital ColorChecker SG (140 colors). A ramp of gray shades can be used for assessing the gamma characteristics.
  - 742 • Ground truth:
    - 743 ○ Obtain the CIELAB values of each color patch
  - 744 • Output color stimuli:
    - 745 ○ For each color patch, convert the CIELAB values into the device RGB space based on the color profile or the default color space of the workstation, which includes the image review manipulation software, computer environment, and display
    - 747 ○ Create an image file that consists of the color patches
    - 749 ○ Show the image with the workstation
    - 751 ○ Use a colorimeter or a spectroradiometer to measure the color coordinates of each color patch and record the color coordinates in CIEXYZ
    - 752 ○ Repeat the same measurement for the white point (255,255,255)
    - 753

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- 754           ○ Calculate the CIELAB values  
755       • Calculate the color differences between the measured color coordinates of the  
756       patches at the input (ground truth) and the output color stimuli with the delta-E  
757       2000 formula  
758

### **IV(B)(1)(c). Resources**

- 759 A useful reference on the subject of color reproducibility is  
760  
761       • Roy S. Berns, *Billmeyer and Saltzman's Principles of Color Technology*, 3<sup>rd</sup> ed.  
762       *John Wiley and Sons, Inc., New York, 2000.*  
763  
764  
765

### **IV(B)(2). Spatial Resolution**

#### **IV(B)(2)(a). Description**

766  
767  
768  
769  
770 Spatial resolution is another key characteristic of a WSI system. The goal of this system-  
771 level test is to evaluate the composite optical performance of all components in the image  
772 acquisition phase (i.e., from slide to digital image file).  
773

#### **IV(B)(2)(b). Test Methods**

- 774  
775  
776 The following test is recommended for assessing spatial resolution of the image  
777 acquisition phase:  
778       • Modulation transfer function per ISO 15229:2007 *Optics and photonics —*  
779       *Optical transfer function — Principles of measurement of modulation transfer*  
780       *function (MTF) of sampled imaging systems.*  
781

782 The test in the guidance entitled “*Guidance for Industry and FDA Staff: Display*  
783 *Accessories for Full-Field Digital Mammography Systems-Premarket Notification*  
784 *(510(k) Submissions)*”  
785 (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107549.htm>) is recommended for assessing noise, as evidenced by pixel signal-to-  
786 noise ratio, of the image display phase.  
787  
788

### **IV(B)(3). Focusing Test**

- 789  
790  
791       • The quality of focus in WSI can be affected by a number of inter-related factors,  
792       including the scanning method and approaches for constructing a focus map. Due  
793       to a trade-off between the number of focus points and the overall speed of the  
794       scanning process, focusing is typically based on a sample of focus points,  
795       determined automatically (auto-focus) or manually by the user. Since tissue can  
796       have uneven depth, auto-focus algorithms are needed to detect and adjust for  
797       different depths of focus.

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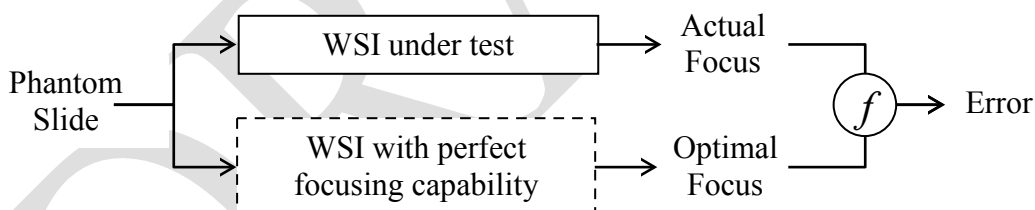
840

841

842

- Data demonstrating that the focus quality is acceptable, even in the presence of uneven tissue, should be provided. Such data with proper justification could be derived from a phantom study, from clinical data, or both in a complementary fashion. The technology of phantom construction for testing focus is under development and this guidance will be updated as such technologies become available. Sponsors could attempt to build their own phantoms for testing depth of focus for their device. Alternatively, sponsors could provide experimental data using clinical tissue slides. Sampling of cases for such an experiment should be enriched for uneven tissue cases within a range representative of typical laboratory output. Alternative approaches for assessing the focus quality of a WSI will be considered along with proper justification. In addition, the following specifications should be provided, if applicable:
  - Focus method: auto-focus for high-throughput or user-operated focus points
  - Instructions for the selection of manual focus points (if applicable), including number of focus points and location in relation to a tissue sample
  - Metrics used to evaluate focusing and description of methods to extract them
  - Methods for constructing focus map from sample focus points

**Diagram 4: Framework of the system-level focusing test.**



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### **IV(B)(4). Whole Slide Tissue Coverage**

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#### **IV(B)(4)(a). Description**

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During the scan phase, WSI systems usually skip blank areas where tissue is absent in order to reduce scan time and file size. The purpose of the whole slide tissue coverage test is to demonstrate that all of the tissue specimen on the glass slide is included in the digital image file.

#### **IV(B)(4)(b). Test Method**

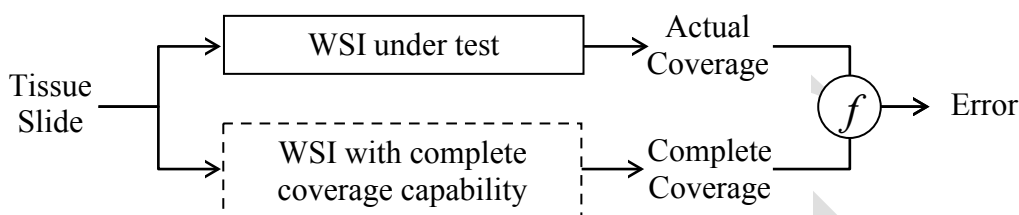
Sponsors should include a test that demonstrates the completeness of the tissue coverage. Sponsors should describe the test method and include the following items:

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- 843 • Selection of the input tissue slide
- 844 • How to determine the complete coverage of the input tissue slide
- 845 • How to measure the actual coverage of the WSI output
- 846 • Calculate the ratio of the actual to complete coverage

847  
848 **Diagram 5: Framework of the system-level whole slide tissue coverage test**



### 857 **IV(B)(5). Stitching Error**

#### 858 **IV(B)(5)(a). Description**

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860  
861 Stitching is the technique that enables a WSI system to combine thousands of sub-images  
862 into a single whole-slide image. Although during the scanning process a certain amount  
863 of overlapping between adjacent sub-images is maintained for alignment purposes,  
864 successful stitching relies on the texture present in the overlapped area. When the  
865 stitching algorithm fails to align two sub-images seamlessly, the error may or may not be  
866 perceivable by the human reader depending on whether noticeable stitching artifacts are  
867 generated. Therefore, a system-level test should be conducted when assessing the  
868 stitching quality of the WSI system.

#### 869 **IV(B)(5)(b). Test Methods**

870  
871  
872 Sponsors should include a test that evaluates the stitching errors and include the  
873 following items:

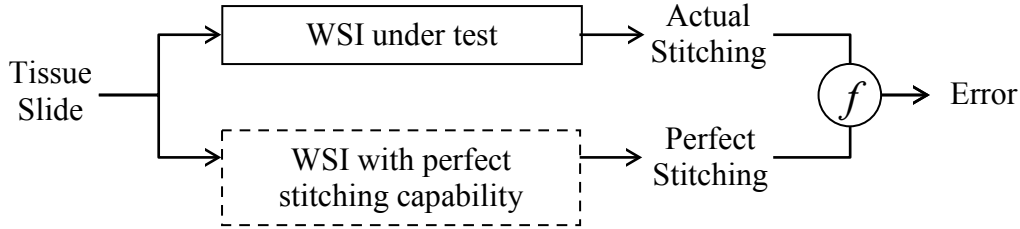
- 874 • Selection of the input tissue slide
- 875 • Method for sampling of the stitching boundaries where stitching errors might  
876 occur
- 877 • How to determine the perfect stitching as the ground truth
  - 878 ○ For example, the region of the stitching boundaries can be re-imaged in  
879 one shot such that there is no stitching artifact.
- 880 • How to evaluate quality of the actual stitching based on the perfect stitching
  - 881 ○ For example, compare the image of stitching boundaries with the perfect  
882 one that does not have stitching artifact. The difference between these two  
883 images can be used as a figure of merit of the stitching quality.

884  
885 **Diagram 6: Framework of the system-level stitching error test**

886

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### IV(C). User Interface

#### IV(C)(1). Description

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896  
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898  
899 The user interface covers all components and accessories of the WSI system with which  
900 users interact while loading the slides and acquiring, manipulating, and reviewing the  
901 images. It also includes preparing the system for use (e.g., unpacking, set up,  
902 calibration), and performing maintenance. Elements of the user interface have been  
903 noted in many of the preceding sections and include two broad categories:

- 904
- Options through which the user operates the WSI system, such as:
    - 905 ○ Software menu options (e.g., scanning parameters)
    - 906 ○ Physical controls (e.g., clips on the slide feeder)
    - 907 ○ Connectors and connections (e.g., cables connecting system components)
  - Information presented to the user through
    - 908 ○ Visual displays (e.g., scanned image, software menus)
    - 909 ○ Sounds (e.g., tone played when scanning completed)
    - 910 ○ Instructions (e.g., software users' manual)
    - 911 ○ Labels
    - 912
- 913

#### IV(C)(2). Test Methods

914  
915  
916 It is recommended that the analysis to identify the use-related hazards of the WSI system  
917 include the consideration of use errors involving failure to acquire, perceive, read,  
918 interpret, and act on information from the WSI system correctly or at all and the harm  
919 that could be caused by such errors. A human factors/usability validation test should be  
920 performed to demonstrate that representative users of the WSI system can perform  
921 essential tasks and those critical to safety effectively and safely under simulated use  
922 conditions.

923  
924 When selecting participants for validation testing, sponsors should carefully consider user  
925 capabilities and expectations that could potentially impact the safe and effective use of  
926 the WSI system. Examples of items that should be considered, if applicable, include  
927 visual acuity and type of vision correction and the impact of expectations formed from  
928 prior experience with other systems (e.g., optical microscope).

929

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930 When selecting the critical tasks to be evaluated, sponsors should incorporate all known  
931 use related errors and problems from similar devices into the validation testing.  
932 Consideration also should be given to whether task performance changes over time, and  
933 if test duration needs to account for user fatigue. Examples might include a user altering  
934 a task sequence in response to fatigue from repetitive image selection and manipulation  
935 with mouse or keyboard.

936  
937 When creating the simulated use conditions for validation testing, special consideration  
938 should be given to the location of the WSI system primary workstation, its components,  
939 their arrangement and how their locations affect user performance. Examples of location  
940 considerations might include multiple monitors, a monitor with sub-optimal display  
941 settings, or glare on a monitor from indoor lighting.

942  
943 A human factors/usability validation test report should generally include the information  
944 found in Table 1.

945  
946  
947

**Table 1: Items a Human Factors/Usability Validation Test Report Should Include**

<b>Section</b>	<b>Contents</b>
<b>1</b>	Intended device users, uses, use environments, and training <ul style="list-style-type: none"><li>• Intended user population(s) and critical differences in capabilities between multiple user populations</li><li>• Intended uses and operational contexts of use</li><li>• Use environments and key considerations</li><li>• Training intended for users and provided to test participants</li></ul>
<b>2</b>	Device user interface <ul style="list-style-type: none"><li>• Graphical depiction (drawing or photograph) of device user interface</li><li>• Verbal description of device user interface</li></ul>
<b>3</b>	Summary of known use problems <ul style="list-style-type: none"><li>• Known problems with previous models</li><li>• Known problems with similar devices</li><li>• Design modifications implemented in response to user difficulties</li></ul>
<b>4</b>	User task selection, characterization and prioritization <ul style="list-style-type: none"><li>• Risk analysis methods</li></ul>



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	<ul style="list-style-type: none"><li>• Use-related hazardous situation and risk summary</li><li>• Critical tasks identified and included in HFE/UE validation tests</li></ul>
<b>5</b>	<p>Summary of formative evaluations</p> <ul style="list-style-type: none"><li>• Evaluation methods</li><li>• Key results and design modifications implemented</li><li>• Key findings that informed the HFE/UE validation testing protocol</li></ul>
<b>6</b>	<p>Validation testing</p> <ul style="list-style-type: none"><li>• Rationale for test type selected (i.e., simulated use or clinical evaluation)</li><li>• Number and type of test participants and rationale for how they represent the intended user populations</li><li>• Test goals, critical tasks and use scenarios studied</li><li>• Technique for capturing unanticipated use errors</li><li>• Definition of performance failures</li><li>• Test results: Number of device uses, success and failure occurrences</li><li>• Subjective assessment by test participants of any critical task failures and difficulties</li><li>• Description and analysis of all task failures, implications for additional risk mitigation</li></ul>
<b>7</b>	<p>Conclusion</p> <p>A statement to the effect that “The &lt;device name/model&gt; has been found to be reasonably safe and effective for the intended users, uses and use environments” should be included under the following conditions:</p> <ul style="list-style-type: none"><li>• The methods and results described in the preceding sections support this conclusion.</li><li>• Any residual risk that remains after the validation testing would not be further reduced by modifications of design of the user interface (including any accessories and the Instructions for Use (IFU)), is not needed, and is outweighed by the benefits that may be derived from the device’s use.</li></ul>

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949 Recommended methods for performing a human factors/usability validation test are  
950 described in the resources listed in section IV(C)(3) entitled “Resources” directly below.  
951 The goal of testing is to assure that users can operate the WSI system successfully for the  
952 intended uses without negative clinical consequences to the patient and that potential use  
953 errors or failures have been eliminated or reduced.

954

### **IV(C)(3). Resources**

955

956 FDA recognizes standards published by national and international organizations that  
957 apply human factors engineering/usability engineering (HFE/UE) principles to device  
958 design and testing. The recognized standards listed below provide suggestions on  
959 conducting an analysis of use-related hazards and a human factors/usability validation  
960 test to assess the safety and effectiveness of the final device design.

961

- 962
- 963 • ISO 14971:2007, *Medical Devices – Application of Risk Management to Medical*  
964 *Devices*: Provides systematic process to manage the risks associated with the use  
965 of medical devices.
- 966 • AAMI/ANSI HE75:2009, *Human Factors Engineering – Design of Medical*  
967 *Devices*: Comprehensive reference of recommended practices related to human  
968 factors design principles for medical devices.
- 969 • IEC 62366:2007, *Medical devices – Application of usability engineering to*  
970 *medical devices*: Describes the process to conduct medical device usability testing  
971 and incorporate results into a risk management plan.

972

- 973 ○ In addition, FDA has published guidance with human factors related  
974 recommendations to assist manufacturers and facilitate premarket review.  
975 The guidance entitled “Guidance for the Content of Premarket  
976 Submissions for Software Contained in Medical Devices”  
977 (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm>). This guidance document provides  
978 recommendations to industry regarding premarket submissions for  
979 software devices, including stand-alone software applications and  
980 hardware-based devices that incorporate software. It includes test  
981 methods to assure that the software conforms to the needs of the user and  
982 to check for proper operation of the software in its actual or simulated use  
983 environment.

984

985

986

### **IV(D). Labeling**

987

988 The premarket application must include labeling in sufficient detail to satisfy the  
989 requirements of 21 CFR Part 801 and 21 CFR 809.10. The labeling includes  
990 supplementary information necessary to use and care for the WSI system such as  
991 instruction books or direction sheets and software user manuals.

992

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993 Although instructions, labeling, and training can influence users to use devices safely and  
994 effectively, they should not be the primary strategy used to control risk. Modification of  
995 the user interface design is a more effective approach to mitigate use-related hazards.  
996

### **997 IV(D)(1). Test Methods**

998  
999 It is recommended that studies on labeling and training be conducted separately from  
1000 other human factors/usability validation testing. Human factors/usability validation  
1001 testing should be conducted with the final version of the labeling and related materials.  
1002 Timing and content of training should be consistent with that expected of actual users.  
1003

### **1004 IV(D)(2). Resources**

1005  
1006 FDA has published several guidance documents on labeling to facilitate premarket  
1007 review and assist manufacturers.

- 1008 • The guidance entitled “Labeling - Regulatory Requirements for Medical Devices”  
1009 ([http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/  
1010 GuidanceDocuments/UCM095308.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM095308.pdf)).
  - 1011 ○ This publication covers labeling issues that device manufacturers,  
1012 reconditioners, repackers, and relabelers should consider when a product  
1013 requires labeling. Labeling issues may include adequate instructions for  
1014 use, servicing instructions, adequate warnings against uses that may be  
1015 dangerous to health, or information that may be necessary for the  
1016 protection of users.
- 1017 • The guidance entitled “Device Labeling Guidance #G91-1 (blue book memo)”  
1018 ([http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceD  
1019 ocuments/ucm081368.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081368.htm)).
  - 1020 ○ This guidance is intended to ensure the adequacy of, and consistency in  
1021 device labeling information. It was intended for use by industry in  
1022 preparing device labeling.
- 1023 • The guidance entitled “Human Factors Principles for Medical Device Labeling”  
1024 ([http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/  
1025 GuidanceDocuments/UCM095300.pdf](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM095300.pdf)).
  - 1026 ○ This report presents the principles of instruction, human factors, and  
1027 cognitive psychology that are involved in designing effective labeling for  
1028 medical devices.  
1029

### **1030 IV(E). Quality Control**

1031  
1032 Sponsors should provide information on the quality control procedures, including  
1033 frequency and testing methods to be performed by the laboratory technologists and/or  
1034 field engineers with associated quantitative action limits. Discussions of tests for  
1035 constancy should include discussions of the slide feeder and scanning mechanisms,  
1036 coverage of the entire tissue slide, the bar code reader, the light source, the imaging

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1037 sensor device, and the calibrations at the component and system level. A detailed quality  
1038 control manual should be provided.

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