Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Division of Molecular Genetics and Pathology at 301-796-6179 and Nicholas Anderson at 301-796-4310 or nicholas.anderson@fda.hhs.gov or Aldo Badano at 301-796-2534 or aldo.badano@fda.hhs.gov.

U.S. Department of Health and Human Services
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

Summary of Comments on ucm435355 - including comments from ICC Review.pdf

Page: 1

Author: CRevie Subject: Highlight   Date: 17/03/2015 08:18:54 Z
Comments due before 26th May

Author: CRevie Subject: Highlight   Date: 17/03/2015 08:19:11 Z

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1400053 to identify the guidance you are requesting.

Table of Contents

106

107

Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

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 ***This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

I.   Introduction

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

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

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Page: 5

Author: CRevie   Subject: Highlight   Date: 27/04/2015 07:16:34
General comments:

PH: It would be helpful to indicate which section of standards mentioned are appropriate.

CR: In some cases the standards cannot be applied 'as written' and in such cases it would be helpful to indicate that some modification may be necessary.

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.

155

II.   Background

157

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.

178

III. Scope

180

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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Author: CRevie Subject: Highlight   Date: 27/04/2015 07:17:02

MC: The contents of this guidance document seem to be aimed towards brightfield microscopy and does not provide guidance for fluorescence imaging. Should the scope indicate this limitation?

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.
193

194 **IV. Policy**

195

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.

198

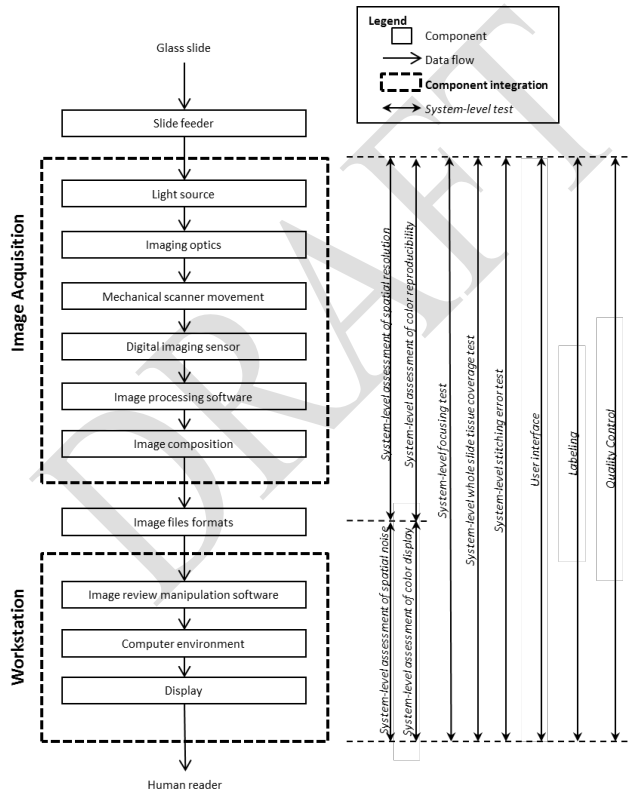199   **IV(A). Description and Test Methods for Each Component**

200

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

214

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

223

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

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**
235

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

275

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

277

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 - Configuration of the slide feed mechanism (a physical description of the
281   equipment)
282   - Slide configuration (physical description of the slide (i.e., custom or
283   commercial off-the-shelf))
284   - Number of slides in queue (carrier)
285   - Class of automation (e.g., robotics, pneumatics, etc.)
286 - User interaction
287   - Hardware (e.g., loading of slides into carrier)
288   - Software (e.g., does the system recognize the number of slides or is this
289   specified by the user)
290   - Feedback (e.g., alarms, notifications, etc.)
291   - Failure Mode and Effects Analysis (FMEA) (including severity,
292   likelihood, mitigations, etc.)
293

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

295

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

297

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:
301 - Lamp
302   - Bulb type (e.g., halogen, xenon arc, LED)
303   - Manufacturer and model
304   - Wattage
305   - Spectral power distribution or color temperature
306   - Expected lifetime
307   - Output adjustment control (electrical/electronic/mechanical)
308   - Optical filter(s)
309   - Type (e.g., heat blocking, polarization, neutral density, diffusing)
310   - Manufacturer and model
311   - Expected intensity variation (coefficient of variation (CV) as a percentage)
312   - Over the duration of scanning a single slide
313   - Over the course of a single workday
314   - Expected spectral variation
315   - Over the duration of scanning a single slide
316   - Over the course of a single workday
317   - Over the lifetime of the device

Author: CRevieSubject: Highlight Date: 12/03/2015 14:21:13 Z
Color temperature does not seem to be sufficient here and spectral power distribution is strongly recommended.

Author: CRevieSubject: Highlight Date: 27/04/2015 07:18:43
Consider recommending a standard way to measure and report this.

PG: Spectral RMS is a widely used measure which would be appropriate for this.

318   o   Capability of tracking intensity and spectral degradation with lifetime
319 • Condenser
320   o   Illumination format (e.g., Kohler, critical)
321   o   Manufacturer and model
322   o   Numerical aperture
323   o   Focal length
324   o   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.
338
339   **IV(A)(3).   Imaging Optics**
340
341   **IV(A)(3)(a).   Description**
342
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:
347 • Ray-trace from slide (object plane) to digital image sensor (image plane)
348 • Microscope objective
349   o   Manufacturer
350   o   Type (e.g., Plan, Plan APO)
351   o   Magnification
352   o   Numerical aperture (NA)
353   o   Focal length
354   o   Working distance
355 • Auxiliary lens(es)
356   o   Manufacturer
357   o   Lens type
358   o   Focal length
359 • Magnification of imaging optics, per ISO 8039:1997 *Optics and optical*
360 *instruments — Microscopes — Magnification*
361

Page: 10

T Author: CRevie Subject: Highlight   Date: 27/04/2015 07:19:24
VB: It would be better to measure this at the sensor rather than at the slide plane.

T Author: CRevie Subject: Highlight   Date: 30/04/2015 07:27:46
AO: Sensor sensitivity is often beyond this range.

PH: ISO 17321-1: 2012 uses 380-730 (shall), 360-830 (should) for requirements for spectral measurements.

T Author: CRevie Subject: Highlight   Date: 27/04/2015 07:21:11
PG: spectral radiance would be better for this measurement.

T Author: CRevie Subject: Highlight   Date: 27/04/2015 07:21:43
This standard has been revised twice since 1997 and the updated version is ISO 8039:2014. The 1997 version is no longer available.

This may be a problem as the scope has changed and the new scope may not be appropriate.

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   o Stage size
386   o Stage manufacturer and model number
387   o Stage material (e.g., anodized aluminum)
388   o Single multi-axis or multiple stacked linear stages (manufacturer and
389   model number)
390   o Type of guides or ways (e.g., bearings)
391   o 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   o Movement resolution for XY-axes
395   o Movement in Z-axis
396   o Speed range
397   o Travel distance
398   o Maximum scanning area
399   o Localization and reading of bar code labels
400   • Control of movement of the stage
401   o Open or closed loop operation
402   o Positional accuracy (calibration) and repeatability
403   ▪ Lost motion compensation (e.g., backlash)
404   o Physical control (e.g., joystick) for single-slide, non-batch mode

405   o 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.)
411

412   **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.*

418

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

420

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

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   o Number and dimensions of pixels
430   o Design of color filter array
431   Configuration of color filter array
432   Spectral transmittance of color filter mask
433   • Responsivity specifications
434   o Quantum efficiency versus wavelength
435   o Linearity
436   o Spatial uniformity
437   • Noise specifications
438   o Dark current level (electrons per second)
439   o 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)

442

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

444

445   Sponsors should conduct the following tests in conformance with the corresponding
446   International Standards, if applicable:

447

Page: 12

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
456 **IV(A)(6)(a). Description**
457
458 Image processing software refers to the software components of the camera. It includes
459 control algorithms for image capture and processing algorithms for raw data conversion
460 into the digital image file. Sponsors should provide the following information and
461 specifications, if applicable:
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
472 See the guidance entitled "*Guidance for the Content of Premarket Submissions for*
473 *Software Contained in Medical Devices*"
474 (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocument
475 s/ucm089543.htm) for the information that should be provided.
476
477 **IV(A)(7). Image Composition**
478
479 **IV(A)(7)(a). Description**
480
481 Image composition is a step present in systems that produce whole slide images as
482 opposed to individual fields of view. Whole slide scanning is typically performed in
483 accordance with the positioning of a stage that moves in submicron steps. At each
484 location of the stage movement, an image of the field of view is acquired. Images can be
485 acquired with a degree of overlapping (redundancy) between them to avoid gaps in data
486 collection. Images can also be acquired at different depths of focus followed by the
487 application of focusing algorithms. At the end of this process, all acquired images are
488 combined (stitched) together to create a composite high resolution image. There are a
489 number of features that can affect this process, and they are listed below. Sponsors
490 should provide a description of these features, if applicable:
491 • Scanning method

T Author: CRevie   Subject: Highlight   Date: 23/03/2015 11:21:30 Z
Probably an error in the guidance document as there was no 2003 revision. Probably this should be ISO 15739:2013.

492   o Single objective or multiple miniature objectives in an array pattern
493   o Scanning pattern: square matrix acquisition (tiling), line scanning, etc.
494   o Overlap between scanned regions
495   o 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   o 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
506   **IV(A)(7)(b).**   **Test Methods**
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
515   **IV(A)(8).**   **Image Files Formats**
516
517   **IV(A)(8)(a).**   **Description**
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   o Single file with multi-resolution information (pyramidal organization)
535   o Stack of files at different magnifications

536
537 **IV(A)(9).   Image Review Manipulation Software**
538
539   **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
563 s/ucm089543.htm) for additional information on this subject.
564
565 **IV(A)(10).   Computer Environment**
566
567   **IV(A)(10)(a).   Description**
568
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:
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)

11

T Author: CRevieSubject: Highlight   Date: 27/04/2015 07:25:07

MF: indicate interpolation method used by graphics card.

T Author: CRevieSubject: Highlight   Date: 27/04/2015 07:25:17

TK: An individual display-specific profile would be better and should be listed as a preferred option here.

579   • Display interface (e.g., DVI or DisplayPort)
580

581   **IV(A)(11).   Display**
582

583   **IV(A)(11)(a).   Description**
584

585   Display refers to the optoelectronic device that converts the digital image signals in the
586   RGB space into optical image signals for the human reader. For the display, sponsors
587   should provide the following information and specifications, if applicable:
588   • Complete description of the entire display system, including the display device,
589   display controller or graphics card, and software for the control of display
590   functions, calibration, and image manipulation
591   • Display technology
592   • Physical size of the display available for image visualization
593   • Backlight type for liquid crystal displays
594   • Pixel array, pitch and pattern
595   • Sub-pixel and color driving techniques
596   • Video bandwidth
597   • On-Screen Display (OSD) controls
598   • Ambient light sensing
599   • Touch screen technology
600   • Color calibration tools and method for color management
601   • QC procedures
602

603   **IV(A)(11)(b).   Test Methods**
604

605   • On-Screen Display settings of the testing conditions should be specified,
606   including:
607   o Input signal (e.g., sRGB or AdobeRGB)
608   o Brightness setting (e.g., 95%)
609   o White point setting (e.g., 6500K)
610   o Color channel settings (e.g., Red=100%, Green=95%, Blue=100%)
611   • Characterization metrics related to image quality should be provided, including
612   the following items:
613   o Luminance range
614   o Grayscale resolution, including luminance mapping or gamma response
615   analysis
616   o Luminance and color coordinates of primaries
617   o Gray tracking (e.g., AAPM TG196)
618   o Additivity of primaries
619   • Physical characterization tests should be performed, including:
620   o Bidirectional reflection
621   o Pixel fill factor
622   o Pixel defects (count and map)

12

Page: 16

Author: CRevie Subject: Highlight   Date: 27/04/2015 07:24:57
MF: probably inappropriate for the type of displays used for WSI.
TK: replace with frame rate.

Author: CRevie Subject: Highlight   Date: 27/04/2015 07:28:26
CR: The ICC has a variety of resources that could be useful for this. Consider adding a bibliographic reference to the ICC Web Site.

TK: add a section ICC Profile for display including version, accuracy,generic/specific etc.

Author: CRevie Subject: Highlight   Date: 30/04/2015 07:22:28
TK: replace by (e.g. 95% or 250 cd/m²)

Author: CRevie Subject: Highlight   Date: 27/04/2015 07:28:25
MF: Align terminology with IEC 62563 display standards, for example 'luminance response' rather than 'luminance mapping'

MF: Add luminance uniformity

TK: spatial colour uniformity (IEC 62563-1), colour gamut of display, for example according to IDMS standard, Display aging and provisions to compensate (how frequently, etc),

Author: CRevie Subject: Highlight   Date: 30/04/2015 07:23:36
TK: recommend replacing by "Luminance and color coordinates of primaries in function of driving level"
TK: consider also requesting perceptual linearity of these primaries (eg. expressed as deltaE2000 steps) similar to JND/step for DICOM GSDF.

623   o   Veiling glare (small-spot)
624   o   Chromaticity
625   o   Spatial resolution
626   o   Spatial noise
627   o   Backlight modulation
628   o   Rise and fall time constants
629   o   Luminance stability
630   o   Angular color response
631
632   **IV(A)(11)(c).**   **Resources**
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
640   ocuments/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

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

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, measureable
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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Page: 17

T Author: CRevieSubject: Highlight   Date: 30/04/2015 07:25:26
TK: related to "Chromaticity", I believe this refers to gray tracking behavior? (chromaticity in function of drive level?)?

T Author: CRevieSubject: Highlight   Date: 30/04/2015 07:25:56
TK: consider replacing by "Spatial noise (both luminance and color component)"

T Author: CRevieSubject: Highlight   Date: 30/04/2015 07:26:14
TK: consider replacing by "short and long term luminance and color stability"

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.
683
684 **Diagram 2: Framework of a typical system-level test.**
685
686
687
688
689
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691
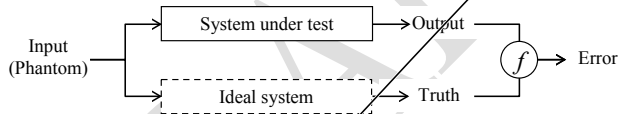
692 **IV(B)(1).   Color Reproducibility**
693
694 **IV(B)(1)(a).   Description**
695
696 Color reproducibility is one of the key characteristics of a WSI system and cannot be
697 evaluated at the component level. The goal of this system-level test is to measure the
698 color differences between the input 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.
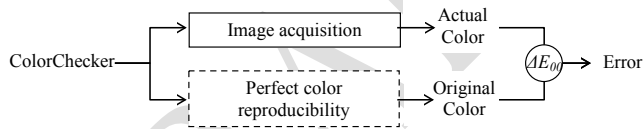700
701 **IV(B)(1)(b).   Test Methods**
702
703 The following test is recommended for examining the color reproducibility of the image
704 acquisition phase (i.e., from slide to digital image file).
705 • Input color patches: Use transparent test patterns consisting of colors similar to
706   the Gretag Macbeth ColorChecker (24 colors) or X-rite Digital ColorChecker SG
707   (140 colors). Notice that both color targets consist of a ramp of gray shades for
708   assessing the tone reproduction curve.

709   • Ground truth:
710   o Measure the color coordinates of each color patch in CIEXYZ with a
711   colorimeter or a spectroradiometer
712   o Repeat the same measurement for the reference white
713   o Calculate the CIELAB values
714   • Output digital image file:
715   o Each pixel consists of the red, green, and blue (RGB) values in a default
716   color space such as the sRGB or AdobeRGB
717   o Convert the RGB values into CIEXYZ based on the default color space
718   o Convert the CIEXYZ values into the CIELAB color space
719   o Choose a region of interest with at least 100 pixels and calculate the
720   average CIELAB value
721   • Calculate the color differences between the measured color coordinates of the
722   patches at the input (ground truth) and the output color coordinates calculated as
723   describe in the previous paragraphs with the delta-E 2000 formula
724
725   **Diagram 3: Framework of the system-level color reproducibility test.**
726
727
728
729
730
731
732
733

734 The following test is recommended for examining the color reproducibility of the image
735 display phase (i.e., from digital image file to display). The goal is to calculate the color
736 differences between the input RGB values in the image file and the output color stimuli
737 on the display.
738   • Input color patches: Select a set of representative colors such as the Gretag
739   Macbeth ColorChecker (24 colors) or X-rite Digital ColorChecker SG (140
740   colors). A ramp of gray shades can be used for assessing the gamma
741   characteristics.
742   • Ground truth:
743   o Obtain the CIELAB values of each color patch
744   • Output color stimuli:
745   o For each color patch, convert the CIELAB values into the device RGB
746   space based on the color profile or the default color space of the
747   workstation, which includes the image review manipulation software,
748   computer environment, and display
749   o Create an image file that consists of the color patches
750   o Show the image with the workstation
751   o Use a colorimeter or a spectroradiometer to measure the color coordinates
752   of each color patch and record the color coordinates in CIEXYZ
753   o Repeat the same measurement for the white point (255,255,255)

Page: 19

Author: CRevie Subject: Highlight Date: 27/04/2015 07:29:33
CR: A reference illuminant must be selected to perform this measurement. It is not clear what this reference illuminant should be in the case of whole slide imaging (could be actual illuminant, Illuminant E, D50 or similar).

Author: CRevie Subject: Highlight Date: 27/04/2015 07:32:27
CR: A reference illuminant must be selected to perform this measurement (see previous comment).

It is not clear what should be used for the reference white, for example lamp, clear slide etc. or whether headroom should be included.

Author: CRevie Subject: Highlight Date: 12/03/2015 15:03:14 Z
Perhaps more usefully described by an ICC Profile for the capture system.

Author: CRevie Subject: Highlight Date: 12/03/2015 15:03:17 Z
Perhaps more usefully described by an ICC Profile for the capture system.

Author: CRevie Subject: Highlight Date: 23/03/2015 11:12:59 Z
The preferred form is 'CIEDE2000' and not 'delta-E 2000'.

More importantly using this as a measure could be very misleading. Compare, for example one system where all of the 'error vectors' are pointing in arbitrary directions with a second system with the same average CIEDE2000 value but where the error vectors are coherent (for example represent saturation of color).

Author: CRevie Subject: Highlight Date: 27/04/2015 07:33:29
CR: This section is not clear, for example what is the 'device RGB space' referred to? Is the image being created here intended to be in the same space as the images being captured?

CR: It would be better to reference a standard color target such as ISO 12640 S6 and using the ICC Profile that defines the image color space.

Author: CRevie Subject: Highlight Date: 27/04/2015 07:34:24
Color management of some kind will be needed here. Consider providing a description of the two options commonly used: (a) display calibration to sRGB or similar for all displays and (b) on-the-fly ICC Color Management for each display.

Author: CRevie Subject: Highlight Date: 27/04/2015 07:34:44
This white point is very likely to be different from the reference while of the capture system.

Consider making some recommendations for each white point and to describe how the difference should be accommodated in the assessment of color accuracy.

754   o   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
759   **IV(B)(1)(c).**   **Resources**
760
761 A useful reference on the subject of color reproducibility is
762   •   Roy S. Berns, *Billmeyer and Saltzman's Principles of Color Technology, 3rd ed.*
763   *John Wiley and Sons, Inc., New York, 2000.*
764
765
766   **IV(B)(2).**   **Spatial Resolution**
767
768   **IV(B)(2)(a).**   **Description**
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
774   **IV(B)(2)(b).**   **Test Methods**
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/GuidanceDocument
786 s/ucm107549.htm) is recommended for assessing noise, as evidenced by pixel signal-to-
787 noise ratio, of the image display phase.
788
789   **IV(B)(3).**   **Focusing Test**
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.

Page: 20

[T] Author: CRevieSubject: Highlight   Date: 27/04/2015 07:35:09
The preferred form is 'CIEDE2000' and not 'delta-E 2000'.

[T] Author: CRevieSubject: Highlight   Date: 30/04/2015 07:29:56
JP: for spatial resolution (section IV (B) (2) shall we not refer to the ISO 12233 : 2014 "Photography -- Electronic still picture imaging -- Resolution and spatial frequency responses" ?

[T] Author: CRevieSubject: Highlight   Date: 23/03/2015 11:22:36 Z
Probably an error in the guidance document and should be ISO 15529:2007. This has been replaced by ISO 15529:2010and the 2007 version is not available.

798
799 - Data demonstrating that the focus quality is acceptable, even in the presence of
800   uneven tissue, should be provided. Such data with proper justification could be
801   derived from a phantom study, from clinical data, or both in a complementary
802   fashion. The technology of phantom construction for testing focus is under
803   development and this guidance will be updated as such technologies become
804   available. Sponsors could attempt to build their own phantoms for testing depth
805   of focus for their device. Alternatively, sponsors could provide experimental data
806   using clinical tissue slides. Sampling of cases for such an experiment should be
807   enriched for uneven tissue cases within a range representative of typical
808   laboratory output. Alternative approaches for assessing the focus quality of a
809   WSI will be considered along with proper justification. In addition, the following
810   specifications should be provided, if applicable:
811   - o Focus method: auto-focus for high-throughput or user-operated focus
812   points
813   - o Instructions for the selection of manual focus points (if applicable),
814   including number of focus points and location in relation to a tissue
815   sample
816   - o Metrics used to evaluate focusing and description of methods to extract
817   them
818   - o Methods for constructing focus map from sample focus points
819
820 **Diagram 4: Framework of the system-level focusing test.**
821
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824
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826
827
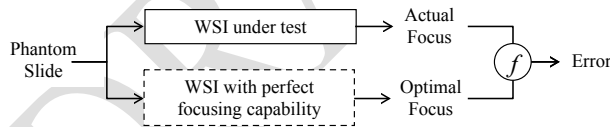
828
829
830 **IV(B)(4). Whole Slide Tissue Coverage**
831
832 **IV(B)(4)(a). Description**
833
834 During the scan phase, WSI systems usually skip blank areas where tissue is absent in
835 order to reduce scan time and file size. The purpose of the whole slide tissue coverage
836 test is to demonstrate that all of the tissue specimen on the glass slide is included in the
837 digital image file.
838
839 **IV(B)(4)(b). Test Method**
840
841 Sponsors should include a test that demonstrates the completeness of the tissue coverage.
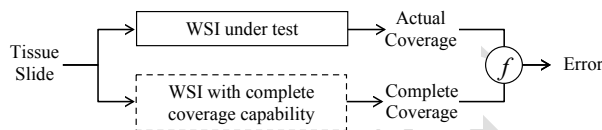842 Sponsors should describe the test method and include the following items:

17

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**
849
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856
857 **IV(B)(5).   Stitching Error**
858
859   **IV(B)(5)(a).   Description**
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
870   **IV(B)(5)(b).   Test Methods**
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   o 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   o 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**
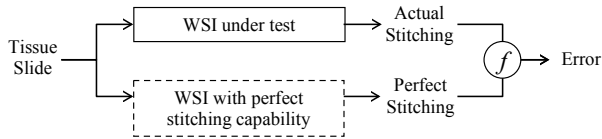886

887
888
889　Tissue
890　Slide
891
892
893
894

895 **IV(C). User Interface**

896
897　　**IV(C)(1).   Description**

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　　　　o Software menu options (e.g., scanning parameters)
906　　　　o Physical controls (e.g., clips on the slide feeder)
907　　　　o Connectors and connections (e.g., cables connecting system components)
908　　● Information presented to the user through
909　　　　o Visual displays (e.g., scanned image, software menus)
910　　　　o Sounds (e.g., tone played when scanning completed)
911　　　　o Instructions (e.g., software users' manual)
912　　　　o Labels
913
914　　**IV(C)(2).   Test Methods**

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

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 **Table 1: Items a Human Factors/Usability Validation Test Report Should Include**
947

Section	Contents
1	Intended device users, uses, use environments, and training • Intended user population(s) and critical differences in capabilities between multiple user populations • Intended uses and operational contexts of use • Use environments and key considerations • Training intended for users and provided to test participants
2	Device user interface • Graphical depiction (drawing or photograph) of device user interface • Verbal description of device user interface
3	Summary of known use problems • Known problems with previous models • Known problems with similar devices • Design modifications implemented in response to user difficulties
4	User task selection, characterization and prioritization • Risk analysis methods

	• Use-related hazardous situation and risk summary • Critical tasks identified and included in HFE/UE validation tests
5	Summary of formative evaluations • Evaluation methods • Key results and design modifications implemented • Key findings that informed the HFE/UE validation testing protocol
6	Validation testing • Rationale for test type selected (i.e., simulated use or clinical evaluation) • Number and type of test participants and rationale for how they represent the intended user populations • Test goals, critical tasks and use scenarios studied • Technique for capturing unanticipated use errors • Definition of performance failures • Test results: Number of device uses, success and failure occurrences • Subjective assessment by test participants of any critical task failures and difficulties • Description and analysis of all task failures, implications for additional risk mitigation
7	Conclusion A statement to the effect that "The <device name/model> has been found to be reasonably safe and effective for the intended users, uses and use environments" should be included under the following conditions: • The methods and results described in the preceding sections support this conclusion. • 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.

948

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
955 **IV(C)(3). Resources**
956
957 FDA recognizes standards published by national and international organizations that
958 apply human factors engineering/usability engineering (HFE/UE) principles to device
959 design and testing. The recognized standards listed below provide suggestions on
960 conducting an analysis of use-related hazards and a human factors/usability validation
961 test to assess the safety and effectiveness of the final device design.
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 o 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/Guid
978 anceDocuments/ucm089543.htm). This guidance document provides
979 recommendations to industry regarding premarket submissions for
980 software devices, including stand-alone software applications and
981 hardware-based devices that incorporate software. It includes test
982 methods to assure that the software conforms to the needs of the user and
983 to check for proper operation of the software in its actual or simulated use
984 environment.
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

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).
1011 o 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).
1020 o 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).
1026 o 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

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