Medical Imaging Working Group

BenQ HQ
No. 16 Ji-Hu Road,
Nei-Hu District
Taipei, Taiwan
4 May 2016

Craig Revie, MIWG chair, opened the meeting at 14:00 and after self-introductions and a sound check for remote participants, introduced the agenda [see attached] as follows:

1. Medical photography best practices white paper
2. iccMAX applied to medical displays
3. FDA guidance for whole-slide imaging
4. Review of MIWG comments on FDA draft guidance on displays
5. Action item review

1. Medical photography best practices white paper

Phil Green reviewed changes to the document on behalf of John Penczek who was unable to attend the meeting. In discussion since the Munich meeting, it had been proposed that the goal of the paper should be to describe how to obtain output-referred colorimetry, rather than accuracy relative to the scene originals. The meeting supported this approach, and with putting complex material in an annex as proposed by Dr Penczek. It was agreed that the goal should be to have a complete document, reviewed by the group in advance of the next meeting in San Diego. Yves Vander Haeghen agreed to complete outstanding sections assigned to him, and also to provide a poster on camera calibration and a document on a camera calibration research project, for posting on the ICC web site. It was also agreed to post 'before and after' images, provided by Dr Vander Haeghen, on the ICC web site as motivation for the guidelines.

2. iccMAX applied to medical displays

Dr Max Derhak introduced the topic of using iccMAX for medical displays [see attached]. One goal was to define a profile which provided for calibration to GSDF. This could be done as a DeviceLink profile, in both grayscale and RGB. Dr Derhak showed examples in XML. The advantage of the iccMAX approach was better accuracy, together with the possibility of passing in ambient luminance as an environment variable.

The meeting discussed the need for an ICS in this area. A high-level ICS could describe approaches for two classes of display, both primary and secondary. Bai, Derhak, Nagashima-san, Kimpe agreed to discuss an ICS for GSDF and report back to a future MIWG meeting.

3. FDA guidance for whole-slide imaging

Mr Revie reported on the FDA guidance document on whole-slide imaging [see attached], which had been published by FDA with MIWG comments. He felt it had been a useful activity, and asked the meeting whether there might be value in providing a suggested assessment procedure for each of the (colour related) items in the document. Dr Olsen noted that the document did a good job of listing what to test, but more work was needed on reproducibility.

Dr Vander Haeghen proposed that an output-referred encoding of a microscope image be used as reference, as it was easier to make comparisons on display. This method would give the appearance under a standard illuminant, and would also be useful for data exchange.

Currently the FDA document has a pointer to the ICC web site www.color.org. A useful task would be to define the list of items for guidance, which could be posted on the ICC web site. Olsen, Vander Haeghen, Revie, Chang, Badano and Green agreed to do this.

Mr Revie noted that further comments can still be made to the FDA, and proposed that the document be posted on the ICC web site with the colour-related sections highlighted.

4. Review of MIWG comments on FDA draft guidance on displays

Craig Revie summarised the MIWG comments on the draft FDA displays guidance document. Comments had been submitted to FDA on April 18. A longer draft also showed the discussion in MIWG. It was agreed to post both versions in the Displays area of the MIWG web site.

It was also reported that an item had been added to the ICC FAQ on evaluating display profiles. This will be expanded as an activity in the Profile Assessment Working Group.

5. Action item review

Mr Revie presented the list of action items from previous meetings [see attached].
MIWG-15-30 Make assessment targets available to the group (Kimpe). Phil Green and Craig Revie agreed to check the context for this action.
MIWG-15-34 Provide input on calibration errors using different types of training sets (Holm/Walowit). It was agreed to close this item. Phil Green undertook to provide available data.
MIWG-16-01 Send Petri plate imaging guidelines for review by MIWG. This had been done and comments were invited.
MIWG-16-07 Provide further input on medical photography guidelines and workflow figure to Dr Penczek (Hung). This remained open – Dr Hung agreed to discuss with Dr Penczek.

The meeting closed at 16:30.

Action items

MIWG-2016-10 Provide poster on camera calibration (Vander Haeghen)

MIWG-2016-11 Provide document on camera calibration research project for MIWG web site (Vander Haeghen)

MIWG-2016-12 Discuss ICS for GSDF and report back to MIWG (Bai, Derhak, Nagashima-san, Kimpe)

MIWG-2016-13 Compile list of items for information and guidance for FDA WSI guidance document and post on MIWG web site (Olsen, Vander Haeghen, Revie, Chang, Badano and Green)

MIWG-2016-14 Post FDA WSI guidelines document with colour sections highlighted on MIWG web site (Green)

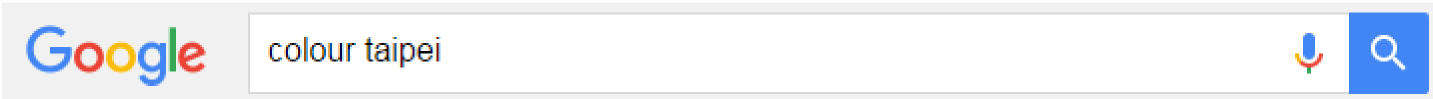
MIWG-2016-15 Post working and submitted versions of the MIWG-commented FDA Displays guidance document in the Displays area of the MIWG web site (Green).

MIWG-2016-16 Post ‘before’ and ‘after’ images provided by Dr Vander Haeghen, showing the effect of calibration, on the Photography area of the MIWG web site (Green).

ICC Medical Imaging Working Group

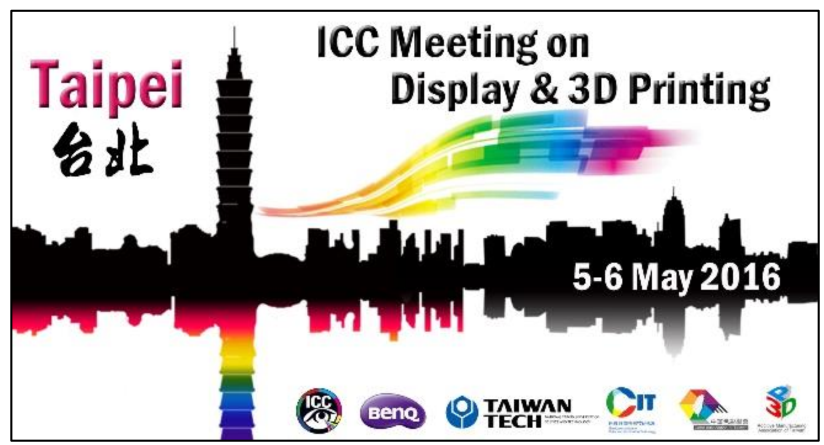
Taipei

4th May 2016

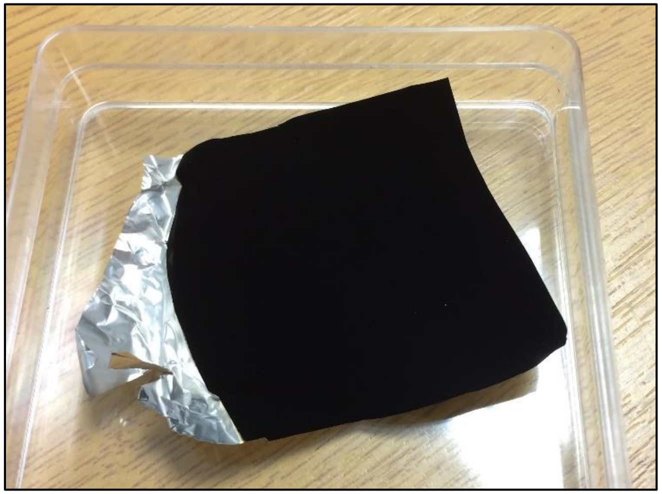

Google
colour taipei


玩彩格旅店
Color Fun Inn


台新金控
THE COLOR RUN.
TheColorRun.tw


Taipei
台北
ICC Meeting on
Display & 3D Printing
5-6 May 2016
ICC
BenQ
TAIWAN TECH

BlackPoint compensation rethink…
…introducing Vantablack



Vertically **A**ligned **N**ano**T**ube **A**rrays

Reflectance measurements

	UV-to-near IR	Near-to-mid IR	Mid-to-far IR
Wavelength, µm	0.2-2	2–20	25–200
Incident angle, °	8	5	10
Reflection	Hemispherical-directional	Hemispherical-directional	Specular
Reference	White reflectance standard	Gold mirror	Aluminum mirror
Average reflectance	0.0160	0.0097	0.0017
Standard deviation	0.0048	0.0041	0.0027

BBC video

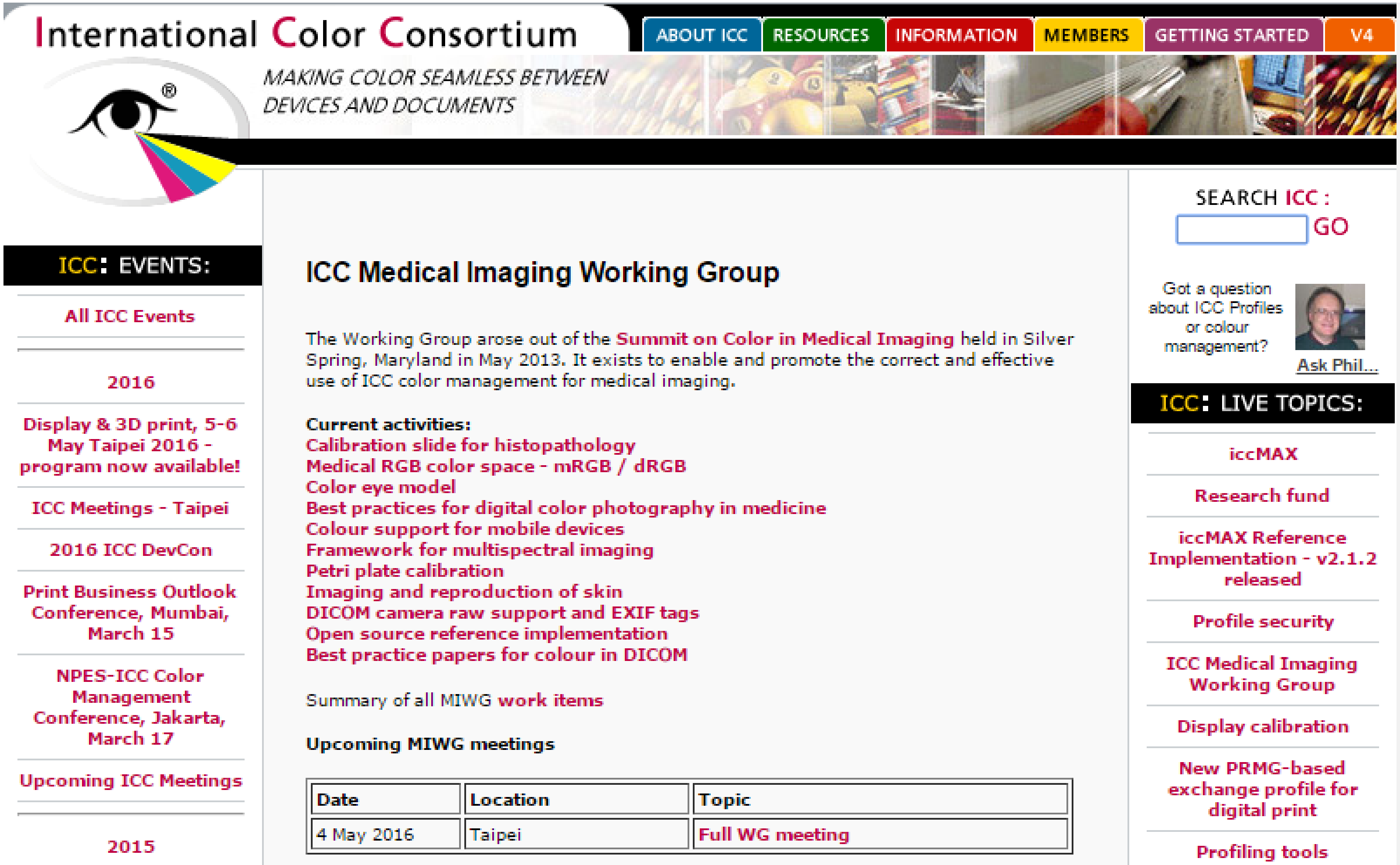
https://youtu.be/xuRTbGsVI0M

details available from

www.surreynanosystems.com

International Color Consortium

ICC MIWG ICC web page



International Color Consortium

ABOUT ICC | RESOURCES | INFORMATION | MEMBERS | GETTING STARTED | V4

MAKING COLOR SEAMLESS BETWEEN DEVICES AND DOCUMENTS

ICC: EVENTS:

All ICC Events

2016

Display & 3D print, 5-6 May Taipei 2016 - program now available!

ICC Meetings - Taipei

2016 ICC DevCon

Print Business Outlook Conference, Mumbai, March 15

NPES-ICC Color Management Conference, Jakarta, March 17

Upcoming ICC Meetings

2015

ICC Medical Imaging Working Group

The Working Group arose out of the **Summit on Color in Medical Imaging** held in Silver Spring, Maryland in May 2013. It exists to enable and promote the correct and effective use of ICC color management for medical imaging.

Current activities:

Calibration slide for histopathology
Medical RGB color space - mRGB / dRGB
Color eye model
Best practices for digital color photography in medicine
Colour support for mobile devices
Framework for multispectral imaging
Petri plate calibration
Imaging and reproduction of skin
DICOM camera raw support and EXIF tags
Open source reference implementation
Best practice papers for colour in DICOM

Summary of all MIWG **work items**

Upcoming MIWG meetings

Date	Location	Topic
4 May 2016	Taipei	Full WG meeting

SEARCH ICC : GO

Got a question about ICC Profiles or colour management?

Ask Phil...

ICC: LIVE TOPICS:

iccMAX

Research fund

iccMAX Reference Implementation - v2.1.2 released

Profile security

ICC Medical Imaging Working Group

Display calibration

New PRMG-based exchange profile for digital print

Profiling tools

ICC MIWG Working group meeting

Wednesday 4th May, 14:00-16:30

iccMAX applied to medical displays	Max Derhak
Medical photography best practices white paper	**Phil Green / John Penczek**
FDA Guidance for Whole Slide Imaging	Craig Revie
Review of MIWG comments on FDA draft guidance on displays	Craig Revie
Action items review	Craig Revie

FDA guidance for whole slide imaging

- **Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices guidance published April 20th 2016**
- **About FDA Guidance Documents**
  - — Guidance documents represent FDA's current thinking on a topic. They do not create or confer any rights for or on any person and do 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.
- **Commenting on Guidance Documents**
  - — …you can comment on any guidance at any time (see 21 CFR 10.115(g)(5))…

- Version of WSI guidance with colour-specific elements highlighted

Review of MIWG comments on FDA draft guidance on displays

- **Draft guidance reviewed by MIWG members on 13th April 2016**
  - comments submitted for FDA review on 18th April 2016
  - tracking number 1k0-8p68-23jv (This comment was received in Regulations.gov but is not yet posted)
- **Draft showing discussion**
- **Comments as submitted to FDA**

- **ICC recommendations for display calibration**
  - ICC FAQ covered input and output profiles and we have added a separate recommendation for display profiles which can be referenced from other documents

Action items review

No	Activity	Action	Date	Owner	Status
MIWG-16-02	Displays	Edit WP44 and circulate for review by end February	16-02-2016	Kimpe / Bai / Revie	Open -> Close
MIWG-16-04	Displays	Circulate draft recommendation on display devices for radiology to members	16-02-2016	Revie	Open -> Close
MIWG-16-05	Displays	Provide comments on draft recommendations on display devices for radiology to Revie	16-02-2016	Martin / Nagashima-san / Bai / Kimpe / Pescatore / Vogh	Open -> Close
MIWG-16-03	Displays	Circulate revised WP44 for member review ending before next steering committee meeting	16-02-2016	Green	Open -> Close

Action items review

No	Activity	Action	Date	Owner	Status
MIWG-14-16	MIWG	Include recommendation on white surface to be included in scene in medical photography guidelines	03-03-2014	Penczek, Green	Open
MIWG-15-30	Displays	Make assessment targets available to group	13-10-2015	Kimpe	Open
MIWG-15-34	WSI	Provide input on calibration errors using different types of training sets	13-10-2015	Holm / Walowit	Open -> Close + new action for PG
MIWG-16-01	Petri plate	Send Petri plate imaging guidelines for review by MIWG	16-02-2016	Pescatore	Open -> Close
MIWG-14-29	Opthalmology	Provide paper on Phase 1 results for publication on ICC web site	19-06-2014	Sisson	Open -> Close
MIWG-16-06	Photography	Consider providing annex for white paper on medical photography describing some basic steps that can be taken in situations where full guidelines cannot be followed	16-02-2016	Penczek	Open
MIWG-16-07	Photography	Provide further input on medical photography guidelines and workflow figure to Penczek	16-02-2016	Hung	Open

Implementing GSDF profiles using iccMAX

Max Derhak

Grayscale Standard Display Function

- **Medical imaging profiles display images that are based upon steps of Just Noticeable Differences (JND's)**
  - —Defined by Grayscale Standard Display Function GSDF mapping Luminance to JND
- **Effective number of JNDs of a display is determined by both the max and min luminance of display in combination with ambient luminance**
  - —Relationship defined by GSDF
- **Monitor profile needs to convert from JND steps to device drive values**
  - —No intermediate PCS value needed

iccMAX based GSDF profiles

- **Measure luminance of display in dark environment from lowest to highest drive values**
- **Determine inverse function ($out=f_i(L)$) from illuminance to drive values**
  - Save as 1-D sampled curve transform in profile that is indexed by absolute luminance
- **Use GSDF (defined as 1-D sampled curve) to determine JND_{min} and JND_{max} values for monitor**
  - Based upon brightest and darkest measurements plus ambient luminance
  - Ambient luminance is provided as CMM environment variable in iccMAX to calc 'env ' operator

Grayscale Profile Link Application

- **Convert input value to scaled JND of montior**
  - JND = in*(JNDmax-JNDmin)+JNDmin
- **Convert JND to luminance using inverse GSDF (in 1-D curve table)**
  - $L = GSDF^{-1}(JND)$
- **Subtract ambient luminance**
  - $L = L - L_{ambient}$
- **Determine output display drive value**
  - $out=f_i(L)$
- **Check that maximum input results in maximum output (to avoid floating point roundoff errors)**

RGB based GDSF profiles

- **Measure RGB channels from dark to bright**
- **Determine adjustments to get balanced grayscale (store as 1-d sampled curves)**
  - outR=balR(inR), outG=balG(inG), outB=balB(inB)
- **Apply same procedure as for Grayscale displays to JND_{min} and JND_{max} values for monitor**
  - Based upon brightest and darkest measurements plus ambient luminance
  - Ambient luminance is provided as CMM environment variable in iccMAX to calc ‘env ‘ operator

RGB Profile Link Application

- **For each RGB channel apply Grayscale JND correction**
- **Apply RGB balancing curves**

GSDF with iccMAX vs ICC.1

- **iccMAX utilizes calc element**
  - Interpolation based on log(L) rather than L improves accuracy of GSDF curve interpolation
    - Can possibly implement as direct math function
  - CMM environment value allows ambient luminance to be passed in to determine effective JND levels
  - Sub-element calc functions can be utilized in RGB case
- **ICC.1**
  - Limited transform options reduce accuracy of GSDF curve estimation
  - Need separate profile for every ambient luminance level with separate selection of profile to use

Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on: April 20, 2016

The draft of this document was issued on February 25, 2015

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

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to http://www.regulations.gov . Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number [FDA-2015-D-0230]. Comments may not be acted upon by the Agency until the document is next revised or updated.

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.

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Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

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. FDA regulates WSI system manufacturers to help ensure that the images intended for clinical uses are reasonably safe and effective for such purposes. Essential to the regulation of these systems is the understanding of the technical performance of the WSI system and the components in the imaging chain, from image acquisition to image display and their effect on pathologist's diagnostic performance and workflow. Prior to performing non-technical analytical studies (i.e., those using clinical samples) and clinical studies to evaluate a digital imaging system's performance, the manufacturer should first determine the technical characteristics that are relevant to such performance for its intended use and determine any possible limitations that might affect its safety and effectiveness. This guidance provides recommendations for the assessment of technical characteristics of a WSI device.

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

II. Background

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

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

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

III. Scope

This document provides guidance regarding only the technical performance assessment of WSI systems for regulatory evaluation. WSI systems are defined here as those consisting of (a) an image acquisition subsystem that converts the content of a glass slide into a digital image file, and (b) a workstation environment for viewing the digital images. If not otherwise specified, the term "image" in the context of whole slide imaging refers to a pyramid structure consisting of multiple images at different resolutions. The baseline image has the highest resolution. This guidance is applicable for surgical pathology tasks performed in the anatomic pathology laboratory. It is intended to provide recommendations to industry and FDA staff regarding only the technical performance assessment data needed for the regulatory evaluation of a WSI device. This document is not meant to provide guidance for special stain techniques or fluorescence imaging or for the non-technical analytical studies (utilizing clinical samples) or pivotal clinical studies necessary to support safety and effectiveness, nor does this guidance alone suffice to demonstrate safety and effectiveness of WSI systems. Interpretation of WSI images on mobile platforms is beyond the scope of this guidance.

IV. Policy

The following subsections of this section describe the technical performance assessment data FDA believes will facilitate the regulatory evaluation of a WSI device.

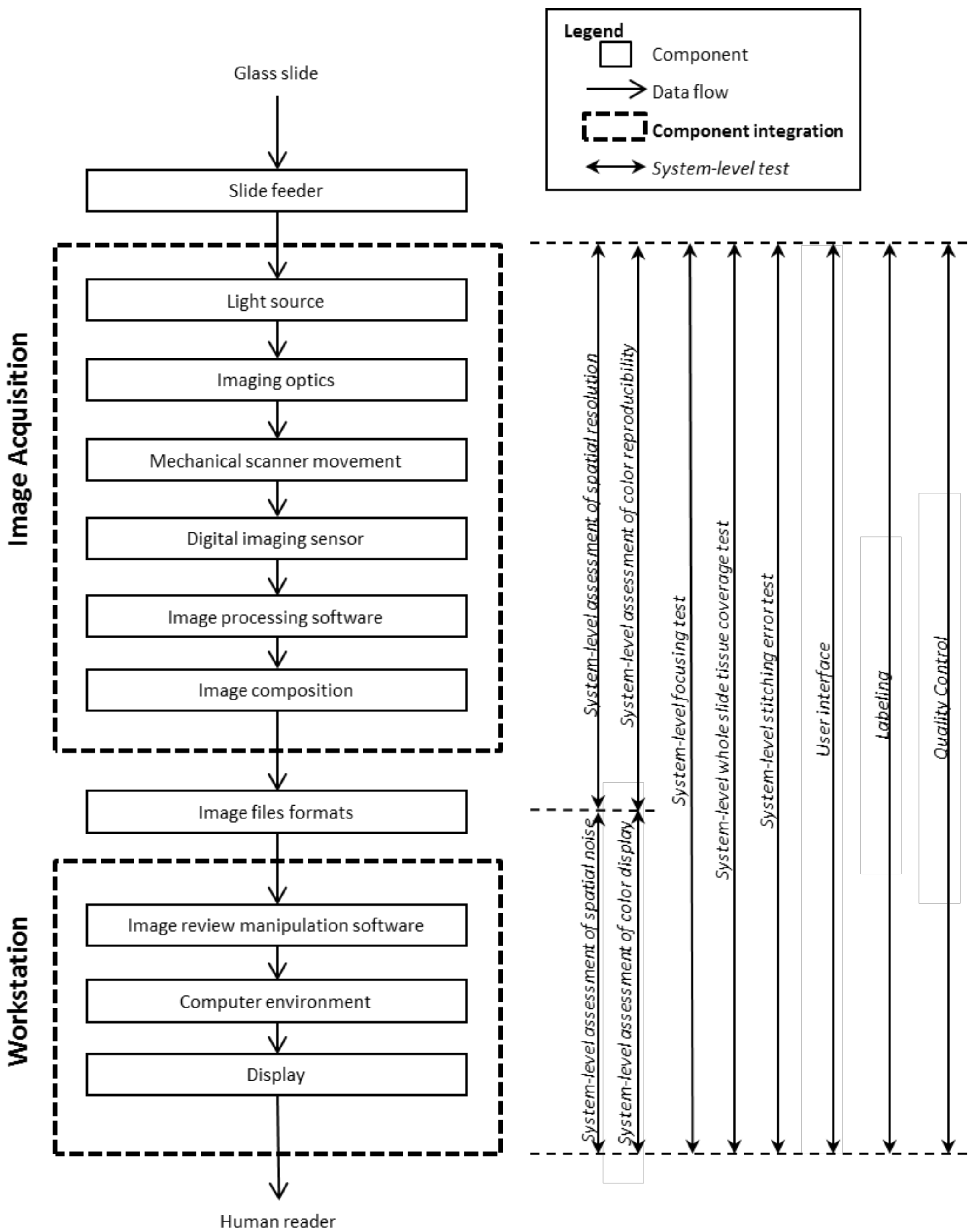
IV(A). Description and Test Methods for Each Component

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

Diagram 1: Example block diagram of typical components found in current WSI systems



IV(A)(1). Slide Feeder

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

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

- 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.)

IV(A)(2). Light Source

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

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

- Lamp
  - Bulb type (e.g., halogen, xenon arc, LED)
  - Manufacturer and model
  - Wattage
  - Spectral power distribution
  - 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)
    - Over the duration of scanning a single slide
    - Over the course of a single workday
    - Over the lifetime of the device
  - Expected spectral variation
    - Over the duration of scanning a single slide
    - Over the course of a single workday
    - Over the lifetime of the device
  - Capability of tracking intensity and spectral degradation with lifetime

- Condenser
    - Illumination format (e.g., Kohler, critical)
    - Manufacturer and model
    - Numerical aperture
    - Focal length
    - Working distance

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

The following steps should be used to measure the spectral distribution of light incident on the slide. Position the input of a calibrated spectrometer or monochromator at the plane where the slide would be placed, centered on the illumination spot from the condenser. If desired, the light can be coupled into the spectrometer via light guide (e.g., fiber optic cable) or an integrating sphere. The measurement aperture should be at least as large as the anticipated field of view on the slide at the lowest magnification of the imaging optics. The wavelength accuracy and relative spectral efficiency of the spectrometer or monochromator in the wavelength range of 360-830 nm should be calibrated prior to measurements and reported. Plots of the measured spectrum with at least 10 nm spectral resolution should be provided, using radiometric units (e.g., spectral irradiance in $W/cm^2/nm$, spectral radiance in $W/sr/cm^2/nm$).

IV(A)(3). Imaging Optics

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

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

- Optical schematic with all optical elements identified from slide (object plane) to digital image sensor (image plane)
- Microscope objective
    - Manufacturer
    - Type
    - Magnification
    - Numerical aperture (NA)
    - Focal length
    - Working distance
- Auxiliary lens(es)
    - Manufacturer
    - Lens type
    - Focal length
- Magnification of imaging optics: ISO 8039:2014 *Optics and optical instruments — Microscopes — Magnification*

IV(A)(3)(b). Test Methods

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

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

IV(A)(4). Mechanical Scanner Movement

IV(A)(4)(a). Description

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

- Configuration of the stage (a physical description of the stage)
  - Stage size
  - Stage manufacturer and model number
  - Stage material (e.g., anodized aluminum)
  - Single multi-axis or multiple stacked linear stages (manufacturer and model number)
  - Type of guides or ways (e.g., bearings)
  - Sample retention mechanism (slide holder)
- Method of movement of the stage (e.g., stepper motor, servomotor, piezomotor, etc., coupled with belt, ball-screw, lead-screw, etc.)
  - Movement resolution for XY-axes
  - Movement in Z-axis
  - Speed range
  - Travel distance
  - Maximum scanning area
  - Localization and reading of bar code labels
- Control of movement of the stage
  - Open or closed loop operation
  - Positional accuracy (calibration) and repeatability
    - Lost motion compensation (e.g., backlash)
  - Physical control (e.g., joystick) for single-slide, non-batch mode
  - Selection of area to be scanned (in accordance to image composition software)
    - whole slide

- automatically determined area with tissue content

- Failure Mode and Effects Analysis (FMEA) (including severity, likelihood, mitigations, etc.)

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

Sponsors should demonstrate the mechanical performance of the stage with respect to positional repeatability and accuracy on all relevant axes, in accordance with ISO 230-2:2014 Test code for machine tools—Part 2: *Determination of accuracy and repeatability of positioning numerically controlled axes.*

IV(A)(5). Digital Imaging Sensor

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

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

- Sensor type (e.g., CMOS, CCD) and manufacturer
- Pixel information/specifications
  - Number and dimensions of pixels
  - Design of color filter array
    - Configuration of color filter array
    - Spectral transmittance of color filter mask
- Responsivity specifications
  - Relative response versus wavelength
  - Linearity
  - Spatial uniformity
- Noise specifications
  - Dark current level (electrons per second)
  - Read noise (electrons)
- Readout rate (e.g., pixels per second, frames per second)
- Digital output format (e.g., bits per pixel, bits per color channel)

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

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

- Opto-electronic conversion function per ISO 14524:2009 *Photography — Electronic still-picture cameras — Methods for measuring optoelectronic conversion functions (OECFs)*
- Noise measurements per ISO 15739:2013 *Photography — Electronic still-picture imaging — Noise measurements*

IV(A)(6). Image Processing Software

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

Image processing software refers to the embedded software components of the image acquisition device. It typically includes control algorithms for image capture and processing algorithms for raw data conversion into the digital image file. Sponsors should provide the following information and specifications, if applicable:

- Exposure control
- White balance
- Color correction
- Sub-sampling
- Pixel-offset correction
- Pixel-gain or flat-field correction
- Pixel-defect correction

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

See the guidance entitled "*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm) for the information that should be provided.

IV(A)(7). Image Composition

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

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

- Scanning method
    - Single objective or multiple miniature objectives in an array pattern
    - Scanning pattern: square matrix acquisition (tiling), line scanning, etc.
    - Overlap between scanned regions
    - Merging algorithms that stitch the aligned images together into a composite image file. Such algorithms may employ functions to align adjacent fields of view in accordance to the scanning pattern, overlap, etc.

    - Automatic background correction functions to eliminate the effect of non-uniformities in the microscope's illumination and image merging procedure. These non-uniformities if not corrected might create visible borders (seams and stitch lines) between the adjacent fields of view.
- Scanning speed: time to scan the whole slide. This time is dependent on selected magnification, and the amount of tissue on the glass slide.
- Number of planes at the Z-axis to be digitized (stack depth)

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

Testing for image composition can be performed on a system level using special calibration slides (such as grid patterns) that can test for line uniformity and focus quality. Sponsors should provide the following outputs for these tests, if applicable:
- Images of digitized calibration slides
- Analysis of focus quality metrics
- Analysis of coverage of the image acquisition for the entire tissue slide

IV(A)(8). Image Files Formats

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

The final result from image acquisition can be a whole slide image consisting of a stack of all acquired fields of view and magnifications during WSI. The complete digitized image file usually occupies between 1-20 gigabytes of storage space depending on the sample and the magnification of the objective lens used. Images can then be stored in a number of ways and formats. Sponsors should provide the following information:
- Compression method (e.g., the wavelet-based JPEG2000 compression standard or TIFF)
- Compression ratio: ratio of uncompressed to compressed file size. This metric should be provided along with descriptive information on the data it was measured from, since compression ratio is dependent on the content of the data applied to.
- Compression type: lossless or lossy compression
- File format: can be formats easily accessible with public domain software such as JPEG or TIFF, or can be proprietary formats only accessible with specific vendor viewers. The file format depends on the file organization and related use.
- For systems that interact with DICOM-compliant software and hardware, sponsors should provide a DICOM compatibility report.
- File organization:
    - Single file with multi-resolution information (pyramidal organization)
    - Stack of files at different magnifications

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

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

For the image review manipulation software, sponsors should provide the following information, describing software features, if applicable.

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

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

See the guidance entitled "*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm) for additional information on this subject.

IV(A)(10). Computer Environment

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

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

- Computer hardware
- Operating system
- Graphics card
- Graphics card driver
- Color management settings
- Color profile
- Display interface (e.g., DVI or DisplayPort)

IV(A)(11). Display

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

The final stage of a WSI system is the display component that presents the scanned image to the pathologists for reading. Technically, display refers to the optoelectronic device that converts the digital image signals in the RGB space into optical image signals. For the display, sponsors should provide the following information and specifications, if applicable:

- Technological characteristics of the display device (e.g., in-plane switching LCD panel with TFT active-matrix array with fluorescent backlight)
- Physical size of the viewable area and aspect ratio
- For transmissive displays, backlight type and properties including temporal, spatial, and spectral characteristics
- Frame rate and refresh rate
- Pixel array, pitch, pixel aperture ratio and subpixel matrix scheme (e.g., chevron, RGBW)
- Subpixel driving to improve grayscale resolution (e.g., spatial and temporal dithering)
- Supported color spaces
- Display Interface
- User controls of brightness, contrast, gamma, color space, power-saving options, etc. via the on-screen display (OSD) menu
- Ambient light adaptation including the ambient light sensing method, instrumentation, and software tool description
- Touch screen technology including method, functionality, and any calibration or periodical re-tuning requirements
- Color calibration tools (sensor hardware and associated software), color profile, and method for color management
- Frequency and nature of quality-control tests to be performed by the user and/or the physicist with associated action limits.

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

- ***User controls:*** Modes and settings of the display undergoing testing should be specified, including brightness, contrast, gamma, white point, color space, etc. See *2.1 Modified-Performance Modes, IDMS 1.03*.
- ***Spatial resolution:*** Measurements of the transfer of information from the image data to the luminance fields at different spatial frequencies of interest typically done by reporting the modulation transfer function. Non-isotropic resolution properties should be characterized properly by providing two-dimensional measurements or measurements along at least two representative axes. See *7.7 Effective Resolution, IDMS 1.03*.

- ***Pixel defects (count and map):*** Measurements (counts) and location of pixel defects. This is typically provided as a tolerance limit. Pixel defects can interfere with the visibility of small details in medical images. See *7.6 Defective Pixels, IDMS 1.03*.
- ***Artifacts:*** Evaluate for image artifacts such as ghosting and/or image sticking from displaying a fixed test pattern for a period of time. See *4.6 Artifacts and Irregularities, IDMS 1.03*.
- ***Temporal response:*** Measurements of the temporal behavior of the display in responding to changes in image values from frame to frame. Since these transitions are typically not symmetric, rise and fall time constants are needed to characterize the system. See *10.2.3 Gray-to-Gray Response Time, IDMS 1.03*.
- ***Maximum and minimum luminance (achievable and recommended):*** Measurements of the maximum and minimum luminance that the device outputs as used in the application under recommended conditions and the achievable values if the device is set to expand the range to the limit. See *2.4 Vantage-Point Suite of Measurement, IDMS 1.03*.
- ***Grayscale:*** Measurements of the mapping between image values and the luminance. See *6.1 Grayscale, IDMS 1.03.*
- ***Luminance uniformity and Mura test:*** Measurements of the uniformity of the luminance across the display screen. See *8.1.2 Sampled Vantage-Point Uniformity and 8.2.3 Mura Analysis, IDMS 1.03*.
- ***Stability of luminance and chromaticity response with temperature and lifetime***
- ***Bidirectional reflection distribution function:*** Measurements of the reflection coefficients of the display device. Specular and diffuse reflection coefficients can be used as surrogates for the full bidirectional reflection distribution function. See *11.12 Diagnostic: Characterizing Hemisphere Uniformity, IDMS 1.03*.
- ***Gray Tracking:*** Chromaticity at different luminance levels as indicated by the color coordinates in an appropriate units system (e.g., CIE *u'v'*). See *AAPM Task Group 196 Report*.
- ***Color scale:*** Color coordinates of primary and secondary colors as a function of the digital driving level and their additivity. See *6. Gray- and Color-Scale Measurement and 5.4 Color-Signal White, IDMS 1.03.*
- ***Color gamut volume:*** See *5.31 Volume-Color-Reproduction Capability, IDMS 1.03*.

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

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

- *IDMS 1.03 - Information Display Measurements Standard Version 1.03, International Committee for Display Metrology, Society for Information Display, www.icdm-sid.org*

- E. Samei, A. Badano, D. Chakraborty, K. Compton, C. Cornelius, K. Corrigan, M. J. Flynn, B. Hemminger, N. Hangiandreou, J. Johnson, M. Moxley, W.

Pavlicek, H. Roehrig, L. Rutz, J. Shepard, R. Uzenoff, J. Wang, and C. Willis, *Assessment of display performance for medical imaging systems, Report of the American Association of Physicists in Medicine (AAPM) Task Group 18*, Technical Report, AAPM (April 2005).

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

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

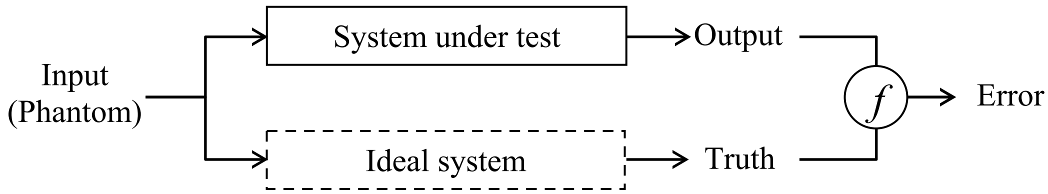
- The guidance entitled "*Guidance for Industry and FDA Staff: Display Accessories for Full-Field Digital Mammography Systems-Premarket Notification (510(k)) Submissions*" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107549.htm).

IV(B). System-level Assessment

This subsection details the test methods at the system level that should be included in the technical performance assessment of a WSI device. In this guidance, *system* refers to a series of consecutive components in the imaging chain with clearly defined, measureable input and output. For example, a system-level test can be designed for the image acquisition subsystem, the image display subsystem, or a combination of both. The goal of system-level tests is to assess the composite performance of a series of consecutive components in the imaging chain. System-level tests should be conducted when the component-level tests are either unfeasible or unable to capture the interplay between components.

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

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



IV(B)(1). Color Reproducibility

IV(B)(1)(a). Description

Color reproducibility is one of the key characteristics of a WSI system. The color characteristics are determined by every component in the imaging chain. Therefore, the color characteristics might be best evaluated at the system level. Color reproducibility indicates the accuracy and precision of the color transformation from the tissue sample on the slide to the image on the display. The colors of the tissue specimen should be accurately and precisely reproduced on the display based on the color reproduction intent, which should be clearly defined and justified by the sponsor.

IV(B)(1)(b). Test Methods

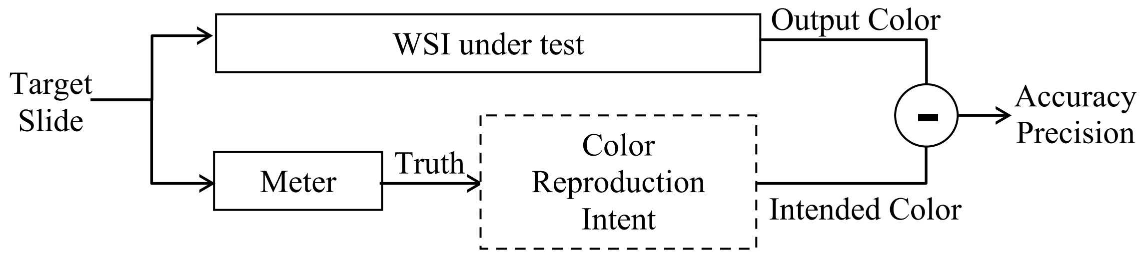
The WSI system should be tested with a target slide. The target slide should contain a set of measurable and representative color patches. Ideally the color patches should have similar spectral characteristics to stained tissue. The color patches should include a grayscale ramp for evaluating the grayscale response. The truth of the color patches should be measured with proper apparatuses separately.

For each color patch, the intended color (i.e., the expected output color based on the color reproduction intent defined by the Sponsor) should be calculated based on the truth of the color patches.

The target slide should be scanned and displayed by the WSI system. The output color of each color patch should be measured from the display.

The three datasets – truth, intended color, and output color – should be compared and analyzed. The sponsor should provide a rationale if the intended color is different from the truth.

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



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

Useful references on the subject of color reproducibility can be found at the International Color Consortium website http://www.color.org.

IV(B)(2). Spatial Resolution

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

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

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

The following test is recommended for assessing spatial resolution of the image acquisition phase:

- Resolution and spatial frequency response: ISO 12233:2014(E) — Photography — Electronic still picture imaging — Resolution and spatial frequency responses.

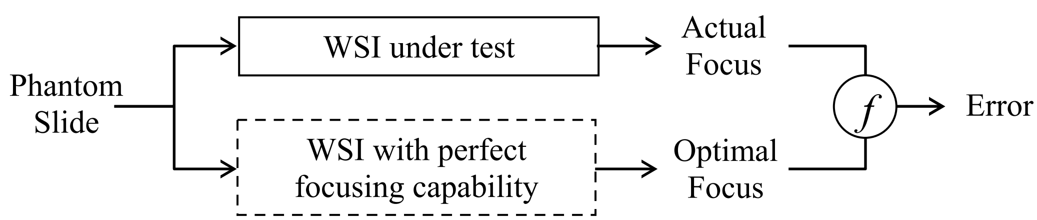
IV(B)(3). Focusing Test

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

- 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.



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

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

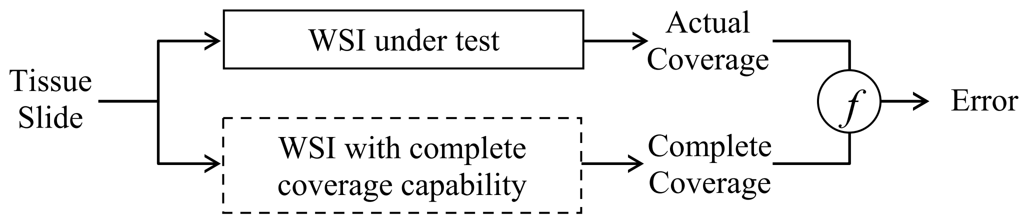
During the scan phase, WSI systems usually skip blank areas where tissue is absent in order to reduce scan time and file size. The purpose of the whole slide tissue coverage test is to demonstrate that all of the tissue specimen on the glass slide is included in the digital image file.

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:

- Selection of the input tissue slide
- How to determine the complete coverage of the input tissue slide
- How to measure the actual coverage of the WSI output
- Calculate the ratio of the actual to complete coverage

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



IV(B)(5). Stitching Error

IV(B)(5)(a). Description

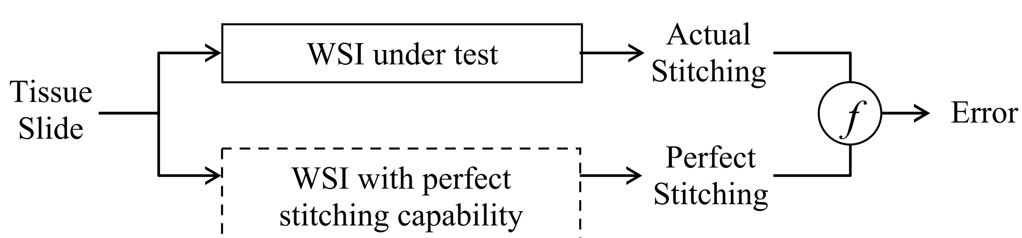
Stitching is the technique that enables a WSI system to combine thousands of sub-images into a single whole-slide image. Although during the scanning process a certain amount of overlapping between adjacent sub-images is maintained for alignment purposes, successful stitching relies on the texture present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

IV(B)(5)(b). Test Methods

Sponsors should include a test that evaluates the stitching errors and include the following items:

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

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



IV(B)(6). Turnaround Time

IV(B)(6)(a). Description

Turnaround time is the time required by the WSI system to execute a particular user operation such as panning/zooming where the software and I/O (input/output) devices retrieve image data, execute the computation, and refresh the image on the display. The turnaround time starts when the user enters a command via a keyboard stroke or a mouse click/movement and finishes when the image is completely updated on the display. Turnaround time is important for a WSI system when fast and repetitive panning operations are performed during a search task, which is delay-free in an optical microscope. Prolonged, unpredictable turnaround time may impact the user's diagnostic performance. The user interface should properly prompt the user when the operation is incomplete and the requested image is not available . The turnaround time may vary greatly depending on the user-requested operation, image content, data size/location, computer workload, display size, etc. The sponsor should report the typical turnaround time as well as the test method and test conditions.

IV(C). User Interface

IV(C)(1). Description

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

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

IV(C)(2). Test Methods

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

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

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

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

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

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

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.

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

IV(C)(3). Resources

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

- ISO 14971:2007, Medical Devices – Application of Risk Management to Medical Devices: Provides systematic process to manage the risks associated with the use of medical devices.
- AAMI/ANSI HE75:2009, *Human Factors Engineering – Design of Medical Devices*: Comprehensive reference of recommended practices related to human factors design principles for medical devices.
- IEC 62366-1:2015, *Medical devices – Application of usability engineering to medical devices:* Describes the process to conduct medical device usability testing and incorporate results into a risk management plan.

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

IV(D). Labeling

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

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

IV(D)(1). Test Methods

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

IV(D)(2). Resources

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

- The guidance entitled "Labeling - Regulatory Requirements for Medical Devices" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM095308.pdf).
    - This publication covers labeling issues that device manufacturers, reconditioners, repackers, and relabelers should consider when a product requires labeling. Labeling includes adequate instructions for use, servicing instructions, adequate warnings against uses that may be dangerous to health, or information that may be necessary for the protection of users.
- The guidance entitled "Device Labeling Guidance #G91-1 (blue book memo)" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081368.htm).
    - This guidance is intended to ensure the adequacy of, and consistency in device labeling information. It is intended for use by industry in preparing device labeling.
- The guidance entitled "Human Factors Principles for Medical Device Labeling" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM095300.pdf).
    - This report presents the principles of instruction, human factors, and cognitive psychology that are involved in designing effective labeling for medical devices.

IV(E). Quality Control

Sponsors should provide information on the quality control procedures, including frequency and testing methods to be performed by the laboratory technologists and/or field engineers with associated quantitative action limits. Discussions of tests for constancy should include discussions of the slide feeder and scanning mechanisms, coverage of the entire tissue slide, the bar code reader, the light source, the imaging sensor device, and the calibrations at the component and system level. A detailed quality control manual should be provided.