

Digital Pathology Panel Meeting: Background Briefing

The Goals for the Panel Meeting

The FDA is sponsoring this 2-day Advisory Panel meeting on Digital Pathology Whole Slide Imaging (WSI) to gather expert information for how to ensure that the current standards of safety and effectiveness of routine surgical pathology will not be compromised if digital WSI is used as a substitute for the conventional light microscope. For over 100 years, the reference method for the diagnosis of cancer and many other critical clinical conditions has been by histopathology using the conventional light microscopy. This process and medical practice is known as surgical pathology in the United States.

Digital pathology is the use of computer technology to convert analog microscopic images into digital images that are similar to digital photography. Digital WSIs do not replace the glass microscope slide. The glass microscope has to be prepared just like with the light microscope and is the source of the information to be digitized. However, there are many functions that digital WSIs offer that are not possible with light microscope examinations. These include the integrating the workflow of the pathologist with the electronic medical record, retrieval of previous biopsy images using the computer, split screen comparison of 2 or more images from the same case or different cases, ability to use WSI data for computer-assisted image analysis and manipulation, transmission of digital images to the patient's electronic chart, the internet and other links, and so forth.

Digital whole slide imaging (WSI) refers to digitizing the image of the entire tissue specimen on a routine 1 X 3 inch glass microscopic slide. Various magnifications are employed; typically, the image is captured through a 20X microscope objective. Once the whole slide image is digitized, it can be displayed on high resolution computer screens. The display can be at 20X magnification (equivalent to 200X on a conventional microscope), or at lower magnification such as 4X (equivalent to 40X on a conventional microscope). It is possible to electronically blow up the 20X digital picture to the equivalent of 40X (400X on a conventional microscope), but the resolving power will be limited to that of the original 20X optical image of the tissue specimen. This is same well known relationship of optical and electronic image enlargement in consumer digital cameras.

FDA hopes to gather information about how to evaluate and compare the performance characteristics of both the light microscope--the reference method--and the digital WSI method. As background for the panel discussions, there will be presentations to cover the principles of light microscopy and the possible criteria and studies for analyzing the accuracy and reproducibility of the diagnostic performance of pathologists using the light microscope for examination of human tissue specimens, the principles of digital

WSI, and the criteria and studies for the evaluation of the diagnostic accuracy and reproducibility of pathologists using digital WSI for examination of human tissue specimens. There will be a discussion of the objective and subjective aspects of reading direct images from a microscope and from a digital screen.

FDA follows the Code of Federal Regulation 21 CFR 860.7 for ensuring the safety and effectiveness of regulated medical devices. (See below for copy of the regulation) FDA believes the first requirement for adoption of digital whole slide imaging will be the maintenance of the diagnostic accuracy and reproducibility of current surgical pathology diagnostic performance using the conventional light microscope --- the current reference method for the diagnosis of cancer and other histopathological entities.

Currently, there are many manufacturers selling different models of digital WSI systems for applications including telepathology, i.e., sending digital images to other locations for review, displaying images for teaching and medical conferences, and using WSI as a platform for computer aided diagnosis and manipulation. FDA has cleared several digital WSI imaging systems for limited uses such as examination of immunohistochemistry (IHC) staining reactions.

FDA has not cleared or approved digital WSI for routine surgical pathology diagnosis to replace surgical pathology using conventional light microscopy.

FDA requests that the expert panel help define what are known benefits and limitations that would be involved in substitution of digital WSI for the conventional light microscope for some or all of routine surgical pathology practice. FDA requests recommendations for any further investigations that should be done to validate digital WSI as a substitute for all or some of routine surgical pathology by conventional light microscopy.

Details of Issues to Address

The tissue specimen and slide

-FDA seeks information about whether there are special requirements for processing the tissue specimen for acceptable digital pathology that may be different from the requirements for conventional light microscopy. These topics include preservation of the tissue, thickness of the microscopic section, staining of the section, and the specifications for the coverslip.

Establishing the diagnostic content of current reference method, the conventional light microscope

- Establishing the head-to-head diagnostic performance of digital pathology images with features that constitute the normal and abnormal tissues and cells

- known and unknown effects of finding and not finding one or more features to the diagnosis of a representative spectrum of pathological entities
 - cancer invasion of basement membrane
 - cytoplasmic vacuoles
 - cross striations in sarcoma cytoplasm
 - microcalcification in breast tissue
 - gram-stain and other chemical stained organisms
 - immunohistochemistry
 - chromagen in situ hybridization (CISH)

- What microscopic features require documentation of performance?
 - Different magnifications, i.e., 4, 20, 40X objectives?
 - Single focal planes vs the z-axis range with light microscope
 - Color fidelity (as perceived by pathologist)
 - Surgical pathology relies on hematoxylin and eosin (H&E) stain, but special stains are frequently employed
 - How is digital image perceived color compared to the expected color palette of the light microscope?
 - What is the current practice with light microscope used in average pathology practice vs the ideal of a research microscope with LED light source, etc.?
 - What is the benchmark for the specification of the digital imaging system? Ideal or average quality? How is this specification described for the pathologist?

Benefits of digital pathology (We have no evidence that digital pathology improves the diagnostic accuracy. Could it improve reproducibility?)

- Allows for telepathology
- Workflow
- Easier to pull up previous surgical pathology material to compare with current specimens
- Digitized images for chart
- Platform for computer assisted image analysis

Limitations of Digital WSI

- Glass slides will always have to be prepared and the expense will not be dispensed with.
- Glass slides consist of an actual sample of the patient specimen and are not just an image of the real specimen.
- Glass slides can be retrieved for molecular pathology procedures

Risk-Benefit Analysis of digital WSI

- Risk benefit analysis of substitution of digital imaging for light microscope used in surgical pathology diagnostic applications
- Harm of decreased diagnostic accuracy and reproducibility
- Likelihood of the harm
 - possible on any type of surgical pathology specimens
 - only likely for certain specimens
 - o high magnification required
 - hematopathology
 - cytopathology

Design of studies to answer the concerns about digital pathology

Pre-clinical

- Establishing the physics of the optical image of the light microscope
- Establishing the physics image from digital microscopy
- Establishing the psycho-neurological factors involved in image recognition and perception
 - o the light image
 - o the digital image

Clinical

- Optimal material to challenge the head-to-head comparison of manual light microscopy to digital pathology diagnostic performance
- Pathologists
 - o experts
 - o average
 - o with and without training for digital images
- Type of normal and pathological material
- Ideally prepared slides
- “average” range of prepared slides
- Clinical study designs to compare the diagnostic performance of conventional light microscopy to digital WSI on actual patient specimens

21 CFR 860.7 Determination of safety and effectiveness (of medical devices)

[Code of Federal Regulations]
[Title 21, Volume 8]
[Revised as of April 1, 2008]
[CITE: 21CFR860.7]



TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES

[PART 860 -- MEDICAL DEVICE CLASSIFICATION PROCEDURES](#)

Subpart A--General

Sec. 860.7 Determination of safety and effectiveness.

(a) The classification panels, in reviewing evidence concerning the safety and effectiveness of a device and in preparing advice to the Commissioner, and the Commissioner, in making determinations concerning the safety and effectiveness of a device, will apply the rules in this section.

(b) In determining the safety and effectiveness of a device for purposes of classification, establishment of performance standards for class II devices, and premarket approval of class III devices, the Commissioner and the classification panels will consider the following, among other relevant factors:

(1) The persons for whose use the device is represented or intended;

(2) The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other

intended conditions of use;

(3) The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and

(4) The reliability of the device.

(c)(1) Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate the safety and effectiveness of a device, the agency relies upon only valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective. After considering the nature of the device and the rules in this section, the Commissioner will determine whether the evidence submitted or otherwise available to the Commissioner is valid scientific evidence for the purpose of determining the safety or effectiveness of a particular device and whether the available evidence, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the device is safe and effective for its conditions of use.

(2) Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. Such information may be considered, however, in identifying a device the safety and effectiveness of which is questionable.

(d)(1) There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

(2) Among the types of evidence that may be required, when appropriate, to determine that there is reasonable assurance that a device is safe are investigations using laboratory animals, investigations involving human subjects, and nonclinical

investigations including in vitro studies.

(e)(1) There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

(2) The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations, as defined in paragraph (f) of this section, unless the Commissioner authorizes reliance upon other valid scientific evidence which the Commissioner has determined is sufficient evidence from which to determine the effectiveness of a device, even in the absence of well-controlled investigations. The Commissioner may make such a determination where the requirement of well-controlled investigations in paragraph (f) of this section is not reasonably applicable to the device.

(f) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of a well-controlled clinical investigation. They provide the basis for the Commissioner's determination whether there is reasonable assurance that a device is effective based upon well-controlled investigations and are also useful in assessing the weight to be given to other valid scientific evidence permitted under this section.

(1) The plan or protocol for the study and the report of the results of a well-controlled investigation shall include the following:

(i) A clear statement of the objectives of the study;

(ii) A method of selection of the subjects that:

(a) Provides adequate assurance that the subjects are suitable for the purposes of the study, provides diagnostic criteria of the condition to be treated or diagnosed, provides confirmatory laboratory tests where appropriate and, in the case of a device to prevent a disease or condition, provides evidence of susceptibility and exposure to the condition against which prophylaxis is desired;

(b) Assigns the subjects to test groups, if used, in such a way as to minimize any possible bias;

(c) Assures comparability between test groups and any control groups of pertinent variables such as sex, severity or duration of the disease, and use of therapy other than

the test device;

(iii) An explanation of the methods of observation and recording of results utilized, including the variables measured, quantitation, assessment of any subject's response, and steps taken to minimize any possible bias of subjects and observers;

(iv) A comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be specified and an explanation provided of the methods employed to minimize any possible bias of the observers and analysts of the data. Level and methods of "blinding," if appropriate and used, are to be documented. Generally, four types of comparisons are recognized:

(a)*No treatments.* Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients;

(b)*Placebo control.* Where there may be a placebo effect with the use of a device, comparison of the results of use of the device with an ineffective device used under conditions designed to resemble the conditions of use under investigation as far as possible;

(c)*Active treatment control.* Where an effective regimen of therapy may be used for comparison, e.g., the condition being treated is such that the use of a placebo or the withholding of treatment would be inappropriate or contrary to the interest of the patient;

(d)*Historical control.* In certain circumstances, such as those involving diseases with high and predictable mortality or signs and symptoms of predictable duration or severity, or in the case of prophylaxis where morbidity is predictable, the results of use of the device may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations who received no treatment or who followed an established effective regimen (therapeutic, diagnostic, prophylactic).

(v) A summary of the methods of analysis and an evaluation of the data derived from the study, including any appropriate statistical methods utilized.

(2) To insure the reliability of the results of an investigation, a well-controlled investigation shall involve the use of a test device that is standardized in its composition or design and performance.

(g)(1) It is the responsibility of each manufacturer and importer of a device to assure

that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into class III.

(2) The Commissioner may require that a manufacturer, importer, or distributor make reports or provide other information bearing on the classification of a device and indicating whether there is reasonable assurance of the safety and effectiveness of the device or whether it is adulterated or misbranded under the act.

(3) A requirement for a report or other information under this paragraph will comply with section 519 of the act. Accordingly, the requirement will state the reason or purpose for such request; will describe the required report or information as clearly as possible; will not be imposed on a manufacturer, importer, or distributor of a classified device that has been exempted from such a requirement in accordance with 860.95; will prescribe the time for compliance with the requirement; and will prescribe the form and manner in which the report or information is to be provided.

(4) Required information that has been submitted previously to the Center for Devices and Radiological Health need not be resubmitted, but may be incorporated by reference.

[43 FR 32993, July 28, 1978, as amended at 53 FR 11253, Apr. 6, 1988]