GLP Compliance in Digital Pathology

Curtis Adams Ph.D.
Sr. Product Manager – Life Sciences
curtis@aperio.com

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Agenda

- General Considerations
  - **G**eneral **L**aboratory **P**ractices
    - history
    - agencies
    - guidelines
    - observations
  - Comprehensive Solution to Regulatory Guidelines
    - instrument qualification
    - software validation
- Advantages for Compliance

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History of GLP

- GLP Regulations describe the minimal standards for conducting nonclinical laboratory studies the support applications for research or marketing permits for products regulated by FDA or EPA such as **human drugs**, food additives, medical devices, biological products, and pesticide products.

- Origins: GLP regulatory mandate was first promulgated in 1978 by the US-FDA and published in the Federal Register 43 FR 59985-60020. Since then the Organisation for Economic Co-operation and Development (OECD) helped promulgate it to many countries to place in their national regulations.

OECD Member Countries

- Australia
- Austria
- Belgium
- Canada
- Czech Republic
- Denmark
- Finland
- France
- Germany
- Greece
- Hungary
- Iceland
- Ireland
- Italy
- Japan
- S. Korea
- Luxembourg
- Mexico
- Netherlands
- New Zealand
- Norway
- Poland
- Portugal
- Slovak Republic
- Spain
- Sweden
- Switzerland
- Turkey
- United Kingdom
- United States

Alphabet soup of regulations


GLP (21 CFR § 58)

ERES (21 CFR § 11)

GCP (21 CFR § 312, etc)

GMP (21 CFR §210 and 211)

Compliance Policy Guides

Guidances for Industry


OECD Principles of Good Laboratory Practice

Guidance Documents

ERES (Annex 11, "Computerised Systems")

USP <1058>

ISPE GAMP 4 and 5

HIPAA (45 CFR § 160 and 164)

Q9 (Quality Risk Management)

Q10 (Quality System)

E6 (GCP)

E7-E11 (Clinical Trials)


GLP (MHLW Ordinance No. 21)

GCP (Ordinances and Notifications)

ERES (PFSB Notification 0401022)

Overview of ERES and predicate GLP and GCP requirements

Stated or Implied Requirements from ERES regulations, GLP, and GCP **Requirement**	**USA 21 CFR Part 11** "Electronic Records; Electronic Signatures"	**EU Annex 11** "Computerized Systems"	**Japan PFSB Notification**, "Use of Electromagnetic Records and Electronic Signatures…"	**Predicate GLP and GCP** regulations (USA, EU, JP)
Risk management system must be in place		➳		
Instruments, software and systems must be validated	➳	➳	➳	➳
System components must be inventoried		➳		➳
Equipment must be adequately tested, calibrated, and standardized	➳	➳	➳	➳
System generates accurate and complete copies of records for inspection	➳		➳	
Records must be protected	➳	➳	➳	
System access must be limited	➳	➳	➳	
System must identify who created records	➳	➳	➳	➳
Audit trails must track who created/changed/deleted records	➳	➳	➳	➳
Authority checks must be in place	➳	➳	➳	
Device / terminal checks must be in place	➳			
Additional controls must be placed on open systems	➳			
Electronic signature manifestations indicate who / when / why	➳	➳	➳	
Electronic signature irrevocably linked to record	➳	➳	➳	
Electronic signature components and controls are enforced	➳	➳	➳	
System alerts of bad login and bad e-sig attempts	➳	➳		
Data backups are taking place routinely		➳	➳	➳

Why CFR Section 21?

- ***Code Of Federal Regulations* (CFR)**
- The final regulations published in the *Federal Register* (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the *CFR*. The *CFR* is divided into 50 titles which represent broad areas subject to Federal regulations. The FDA's portion of the *CFR* interprets the *Federal Food, Drug and Cosmetic Act* and related statutes. Section 21 of the *CFR* contains all regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.

Source: FDA U.S. Food and Drug Administration

CFR 21 part 58 – General Laboratory Practices

Sec. 58.1 Scope.

(a) This part prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, animal food additives, **human and animal drugs**, medical devices for human use, biological products, and electronic products. Compliance with this part is intended to assure the quality and integrity of the safety data filed pursuant to sections 406, 408, 409, 502, 503, 505, 506, 510, 512-516, 518-520, 721, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33779, Sept. 4, 1987; 64 FR 399, Jan. 5, 1999]

CRF 21 part 58.3(k) definitions

(k)*Raw data* means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), **the exact copy or exact transcript may be substituted for the original source as raw data.** *Raw data* may include photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.

Source:
Source: U.S. Food and Drug Administration

Required SOPs

- Sec. 58.81 Standard operating procedures. (a) A testing facility shall have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study. All deviations in a study from standard operating procedures shall be authorized by the study director and shall be documented in the raw data. Significant changes in established standard operating procedures shall be properly authorized in writing by management.
- (b) Standard operating procedures shall be established for, but not limited to, the following:
- (1) Animal room preparation.
- (2) Animal care.
- (3) Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles.
- (4) Test system observations.
- (5) Laboratory tests.
- (6) Handling of animals found moribund or dead during study.
- (7) Necropsy of animals or postmortem examination of animals.
- (8) Collection and identification of specimens.
- (9) **Histopathology.**
- (10) Data handling, storage, and retrieval.
- (11) Maintenance and calibration of equipment.
- (12) Transfer, proper placement, and identification of animals.
- (c) Each laboratory area shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed. Published literature may be used as a supplement to standard operating procedures.
- (d) A historical file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained.
- [43 FR 60013, Dec. 22, 1978, as amended at 52 FR 33780, Sept. 4, 1987]

Source: FDA U.S. Food and Drug Administration

Comprehensive Approach :
Raw data: digital slide or glass slide?

Interpretations of virtual images have been repeatedly shown to be as accurate as interpreting glass slides...

Histopathology 2007, 50, 266-173

A randomized controlled trial of the diagnostic accuracy of internet based telepathology compared with conventional microscopy

P. Furness

"No significant difference in diagnostic accuracy could be detected between the diagnoses proffered on the basis of virtual slides and conventional slides

Histopathology 2002, 41, 91-109

Telepathology: current status and future prospects in diagnostic histopathology

S. S. Cross, T. Dennis & R. D. Start

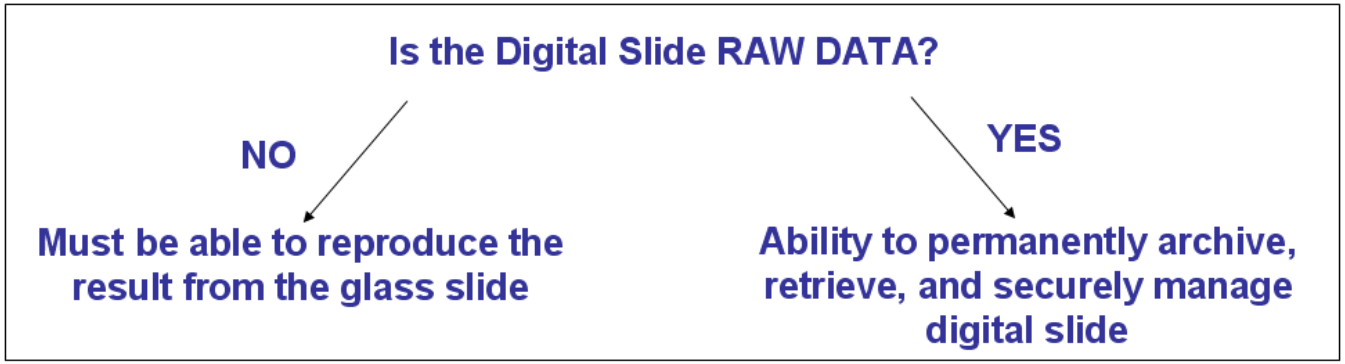
"The review concludes that all the necessary technology for telepathology is available and there is strong published evidence for a diagnostic accuracy comparable with glass slide diagnosis..."

Aperio's FDA clearances

... which makes the raw data (image files) and metadata (annotations and processing) subject to ERES controls

Comprehensive Approach:
Raw data: digital slide or glass slide?

- Electronic revolution: ERES, EHR, ERSR, etc
- Logical solution to regulatory requirements



- Electronic records enable integration across databases with inherent security, tracking, archiving/retrieval and back-ups.

(Further detail in *Toxicologic Pathology* 2007, 450-455, D. Tuomari et al, "Society of Toxicologic Pathology Position Paper on Pathology Image Data: Compliance with 21 CFR Parts 58 and 11")

Society of Toxicologic Pathology conclusions

The Society of Toxicologic Pathology recommends that images used for data generation (e.g., the basis of a diagnosis or morphometric analysis) are raw data, and in contrast, that images not used for data generation are illustrative images that are not raw data. Based on current technologies and practices, any image used for data generation, becomes raw data at the time of data generation and at that time an image print or the electronic image record must be authenticated by specific annotation indicating when and who used that image for data generation, and also that image raw data must be archived.

Source: ***Toxicologic Pathology*** **2007, 450-455, D. Tuomari et al, "Society of Toxicologic Pathology Position Paper on Pathology Image Data: Compliance with 21 CFR Parts 58 and 11**

Form FDA 483 – Inspectional Observations

- Disclaimer – Form FDA 438 contains the observations of the inspector and does not necessarily "represent a final Agency determination regarding your compliance".

- FDA 483 observations should listed in order of significance and may include previous observations that have not been corrected.

- Only those observations directly linked to a violation of regulations are typically included. Suggestions, guidance or other comments are typically not included.

- FDA publishes select 483's on their website:

http://www.fda.gov/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/default.htm

Consequences of not validating GLP lab systems

FDA inspection observations have included:

- “Software... has not been fully validated for its intended use according to an established protocol. Electronic records are used, but they do not meet requirements to ensure that they are trustworthy, reliable, and generally equivalent to paper records”
- “There was a failure to check for accuracy of the inputs to and outputs from the TotalChrom Data Acquisition System, which is used to run your firm’s HPLC instruments ...”

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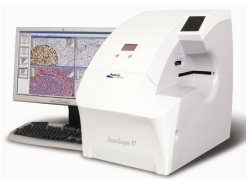
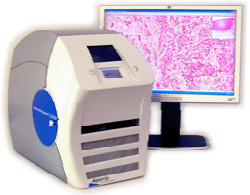
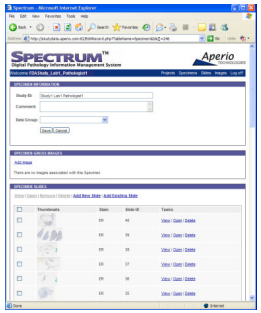
Digital Pathology Components

Slide scanners to digitize whole slides at typical study volumes





Secure data repository for storage, retrieval, analysis, plotting, reporting, archiving, etc



On-site services for GLP validation, international multisite integration etc

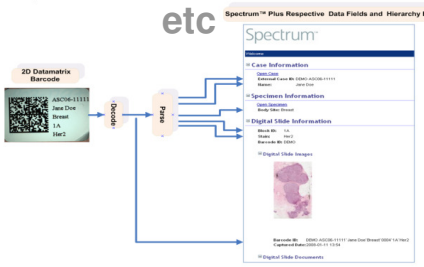
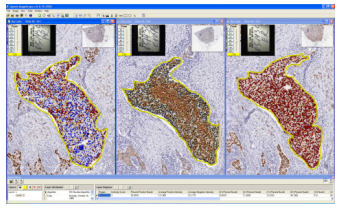
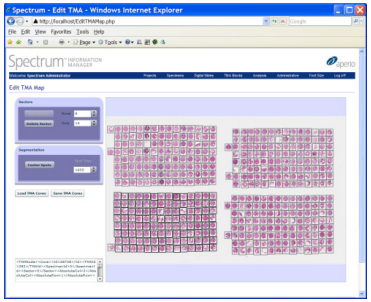


Image analysis for whole slide, automated, objective data



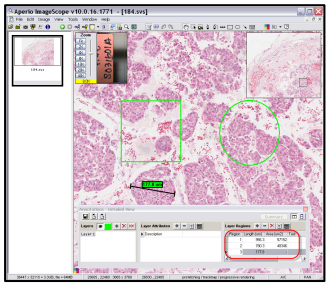
Tissue Microarray Lab for biomarker discovery



Qualification vs Validation

- Qualification : the verification that an instrument is performing under predetermined specifications.

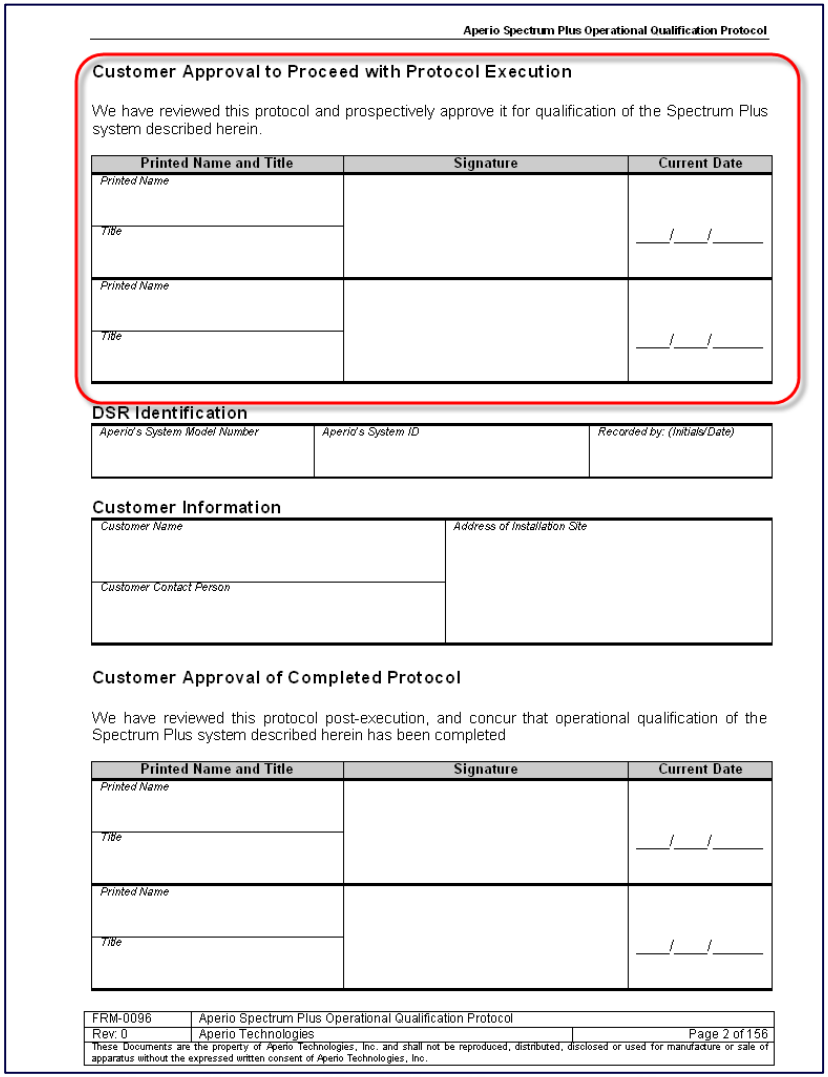
- Validation: the process of evaluating the performance of a specific measuring procedure and checking that the performance meets certain preset criteria.



Definitions: IQ, OQ, and PQ

	Definition	Examples
IQ	**INSTALLATION QUALIFICATION:** ***Documented verification that system components and support systems have been installed correctly and completely****, in accordance with manufacturer and customer requirements, government regulations, and industry standards.*	• Correct equipment has been received in an undamaged condition, • All connections among instruments, computers, servers, and network are connected correctly, • Computers have correct CPU and memory, • Correct OS and software titles installed
OQ	**OPERATIONAL QUALIFICATION:** ***Documented verification that system components operate properly*** *in accordance with manufacturer and customer requirements, government regulations, and industry standards. OQ establishes confidence that the components are capable of consistently operating within the established limits and tolerances required by the systems they support.*	• General system operations function correctly, • Audit trails capture correct information, • Electronic signatures are rendered correctly, • Security roles grant or restrict the correct permissions, • Users without credentials cannot log into system
PQ	**PERFORMANCE QUALIFICATION:** ***Documented verification that the total system performs as intended****. Performance qualification establishes confidence that the system as a whole is capable of consistently performing within established limits.*	• Customer can go through typical laboratory workflow, • Customer's worst-case load scenario doesn't overwhelm server(s).

General guidelines regarding IQ, OQ, and PQ documentation



Aperio Spectrum Plus Operational Qualification Protocol

Customer Approval to Proceed with Protocol Execution

We have reviewed this protocol and prospectively approve it for qualification of the Spectrum Plus system described herein.

Printed Name and Title	Signature	Current Date
Printed Name *Title*		____/____/_____
Printed Name *Title*		____/____/_____

DSR Identification

Aperio's System Model Number	*Aperio's System ID*	*Recorded by: (Initials/Date)*

Customer Information

Customer Name *Customer Contact Person*	*Address of Installation Site*

Customer Approval of Completed Protocol

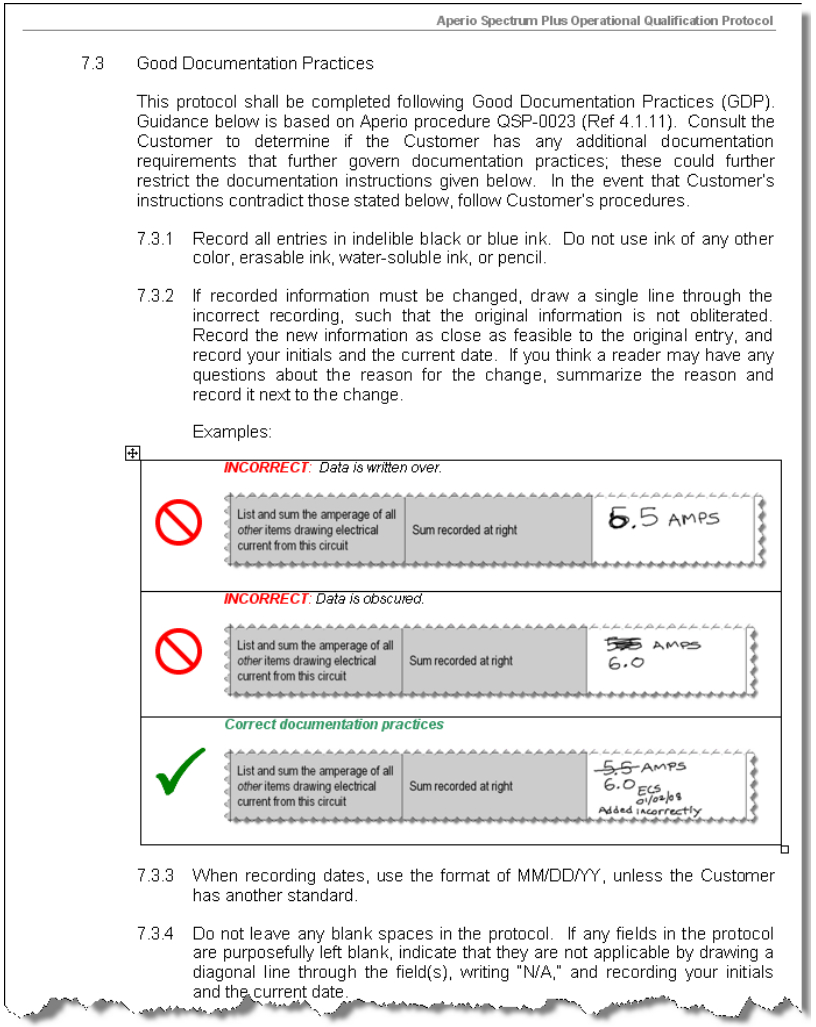
We have reviewed this protocol post-execution, and concur that operational qualification of the Spectrum Plus system described herein has been completed

Printed Name and Title	Signature	Current Date
Printed Name *Title*		____/____/_____
Printed Name *Title*		____/____/_____

- Protocols must be prospectively prepared
- Protocols must be approved before being executed

General guidelines regarding IQ, OQ, and PQ documentation

- Protocols must be completed using good documentation practices, and documentation must occur at time of validation execution



Aperio Spectrum Plus Operational Qualification Protocol

7.3 Good Documentation Practices

This protocol shall be completed following Good Documentation Practices (GDP). Guidance below is based on Aperio procedure QSP-0023 (Ref 4.1.11). Consult the Customer to determine if the Customer has any additional documentation requirements that further govern documentation practices; these could further restrict the documentation instructions given below. In the event that Customer's instructions contradict those stated below, follow Customer's procedures.

7.3.1 Record all entries in indelible black or blue ink. Do not use ink of any other color, erasable ink, water-soluble ink, or pencil.

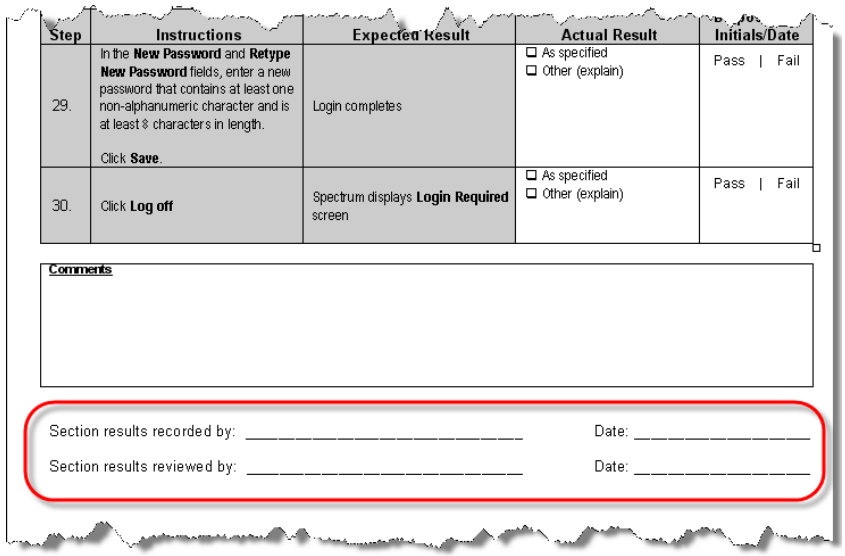
7.3.2 If recorded information must be changed, draw a single line through the incorrect recording, such that the original information is not obliterated. Record the new information as close as feasible to the original entry, and record your initials and the current date. If you think a reader may have any questions about the reason for the change, summarize the reason and record it next to the change.

Examples:

7.3.3 When recording dates, use the format of MM/DD/YY, unless the Customer has another standard.

7.3.4 Do not leave any blank spaces in the protocol. If any fields in the protocol are purposefully left blank, indicate that they are not applicable by drawing a diagonal line through the field(s), writing "N/A," and recording your initials and the current date.

General guidelines regarding IQ, OQ, and PQ documentation

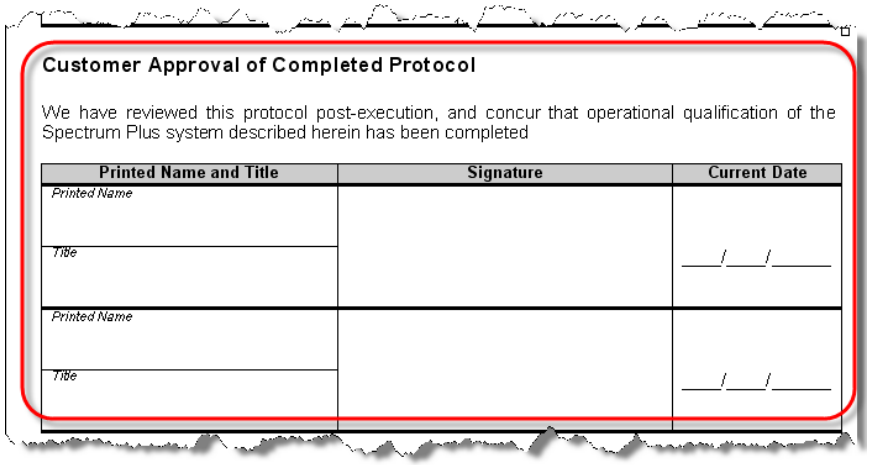


Step	Instructions	Expected Result	Actual Result	Initials/Date
29.	In the **New Password** and **Retype New Password** fields, enter a new password that contains at least one non-alphanumeric character and is at least 8 characters in length. Click **Save**.	Login completes	☐ As specified ☐ Other (explain)	Pass | Fail
30.	Click **Log off**	Spectrum displays **Login Required** screen	☐ As specified ☐ Other (explain)	Pass | Fail

Comments

Section results recorded by: _____ Date: _____

Section results reviewed by: _____ Date: _____



Customer Approval of Completed Protocol

We have reviewed this protocol post-execution, and concur that operational qualification of the Spectrum Plus system described herein has been completed

Printed Name and Title	Signature	Current Date
Printed Name *Title*		___/___/_____
Printed Name *Title*		___/___/_____

- Results must be independently reviewed:
  - On a per-section basis
  - At conclusion of execution

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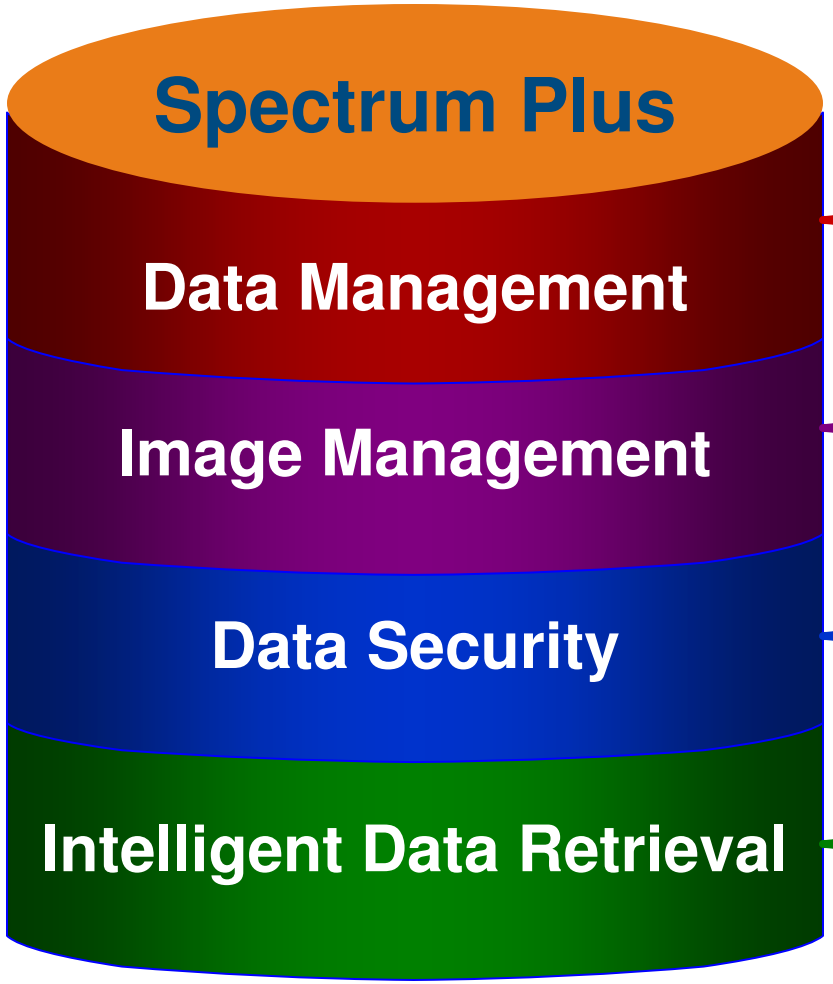
Data Repository/Viewer Validation



- Meta-data
- Image Data
- Results

- Digital Slides
- Gross Images
- Fluorescent images

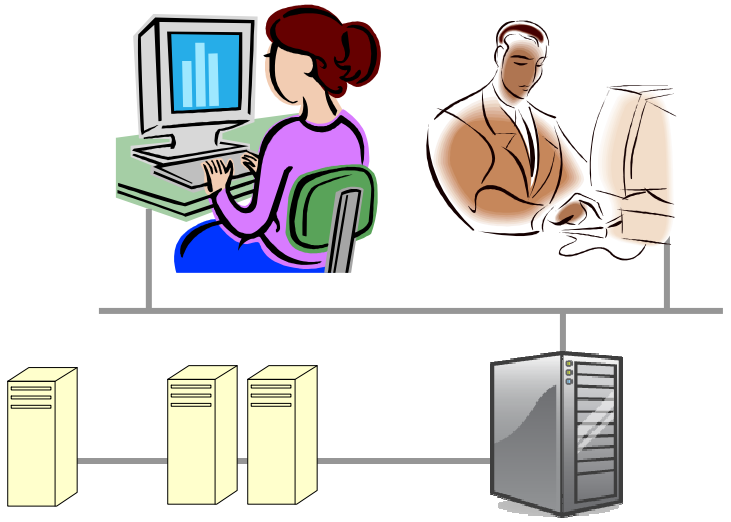
- Named users with passwords
- User defined data access
- Audit Trails and E-signatures

- Organize data based on application
- Image retrieval based on Data search
- Integration with LIMS systems

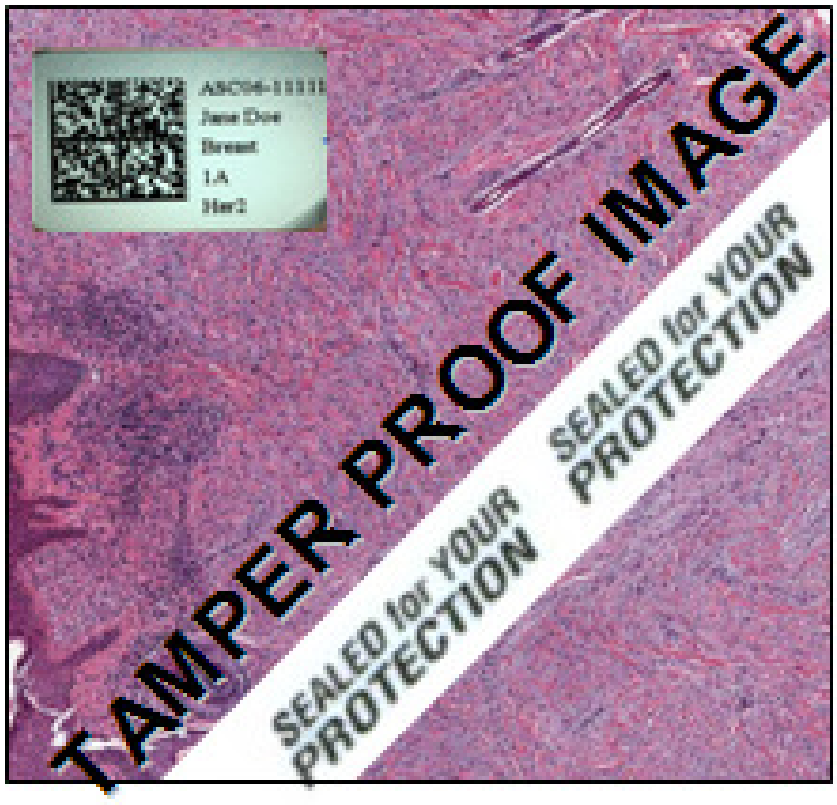
Processing Architecture

Technical challenges around Entire Slide Processing

- **Processing of huge Digital Images**
  e.g. 15mm x 15mm specimen scanned at 20X yields an image with 30,000 x 30,000 pixels or 2.7 GB of data (~60MB compressed JPEG2000 file)
- **Server-Side Processing**
  analysis runs server-side
- **Distributed Computing**



Securing the Digital Slide



- Raw data image files are stored in a secured folder in the DSR
- A checksum is calculated for each image file
- If corruption or alteration of the image occurs, Spectrum Plus will display an error message and will not open the slide

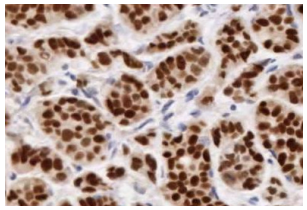
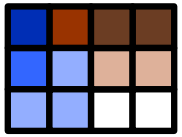
Managing Images and Data

Digital Pathology Information System

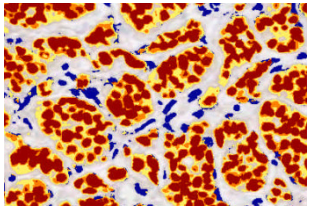
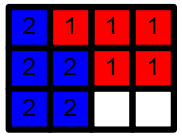
- Server storage, Web based access
- Customizable organization of images and information
- Supports many image types
- Software Integration
- Access Security
- Archiving & Retrieval
- User roles and permissions
- Remote viewing, collaborations, virtual review boards, etc
- Slide metadata
  - LIS Interface
  - Barcodes

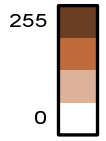
Image Analysis

You use Stains to highlight Features
e.g. - Cell Compartments
(nuclei, membrane, cytoplasm)
- Protein expressions

Multi-Color Images with RGB Color Pixels (Picture Elements)
Pixels of different Colors (Stains)

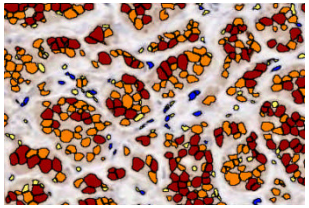


Where and how much staining is there?

Classify Pixels by Color (Stain)

Measure Pixel (Stain) Intensities

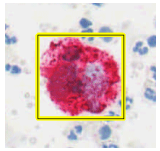
Where and how many objects are there?
e.g. - Tumor Cells



Identify Objects by Color, Shape, & Size

Measure Object (Stain) Intensities


How much staining is there on different objects?
e.g. - Cell Compartments



Validation:
Comprehensive, Detailed, Documented

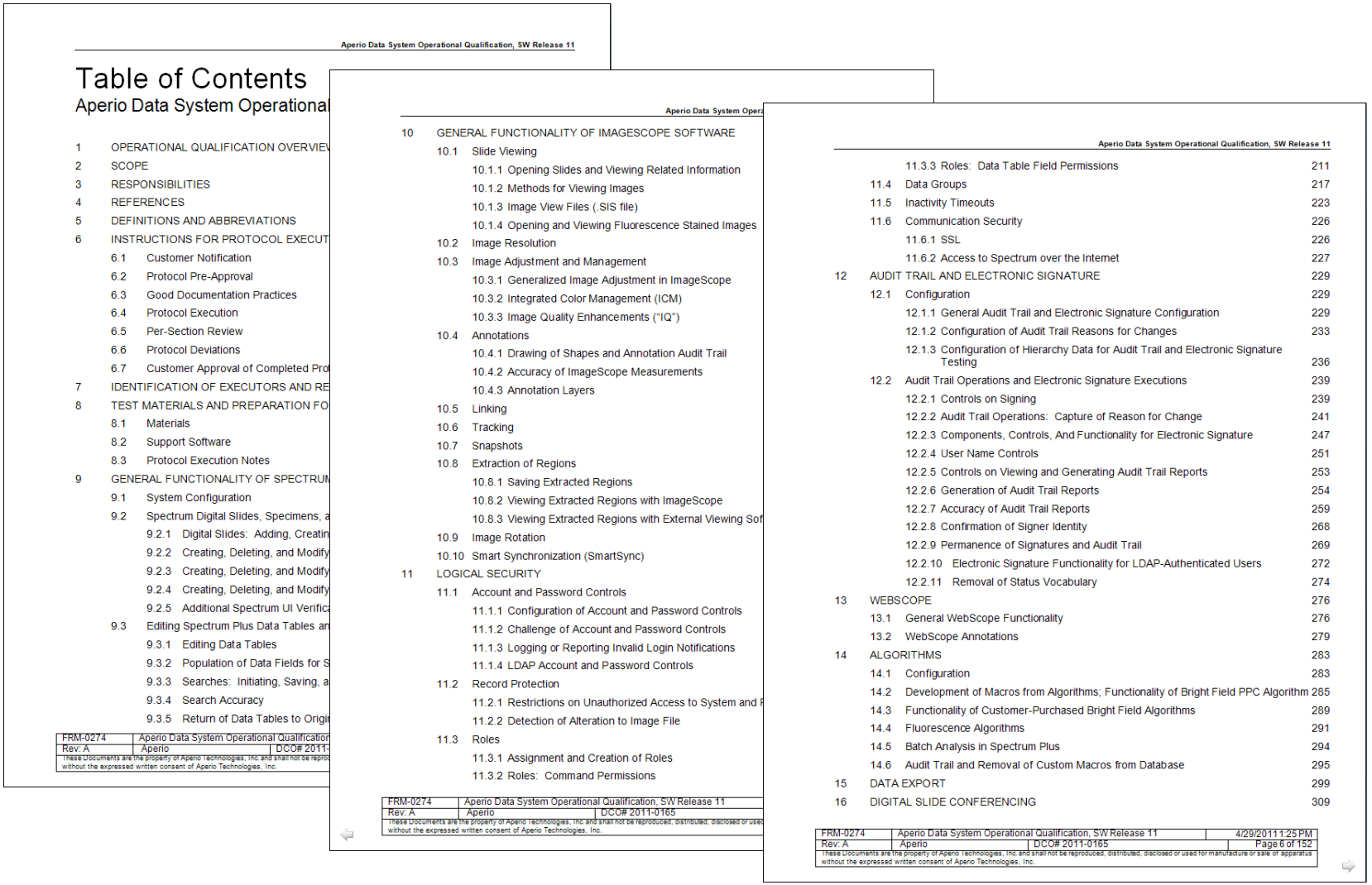


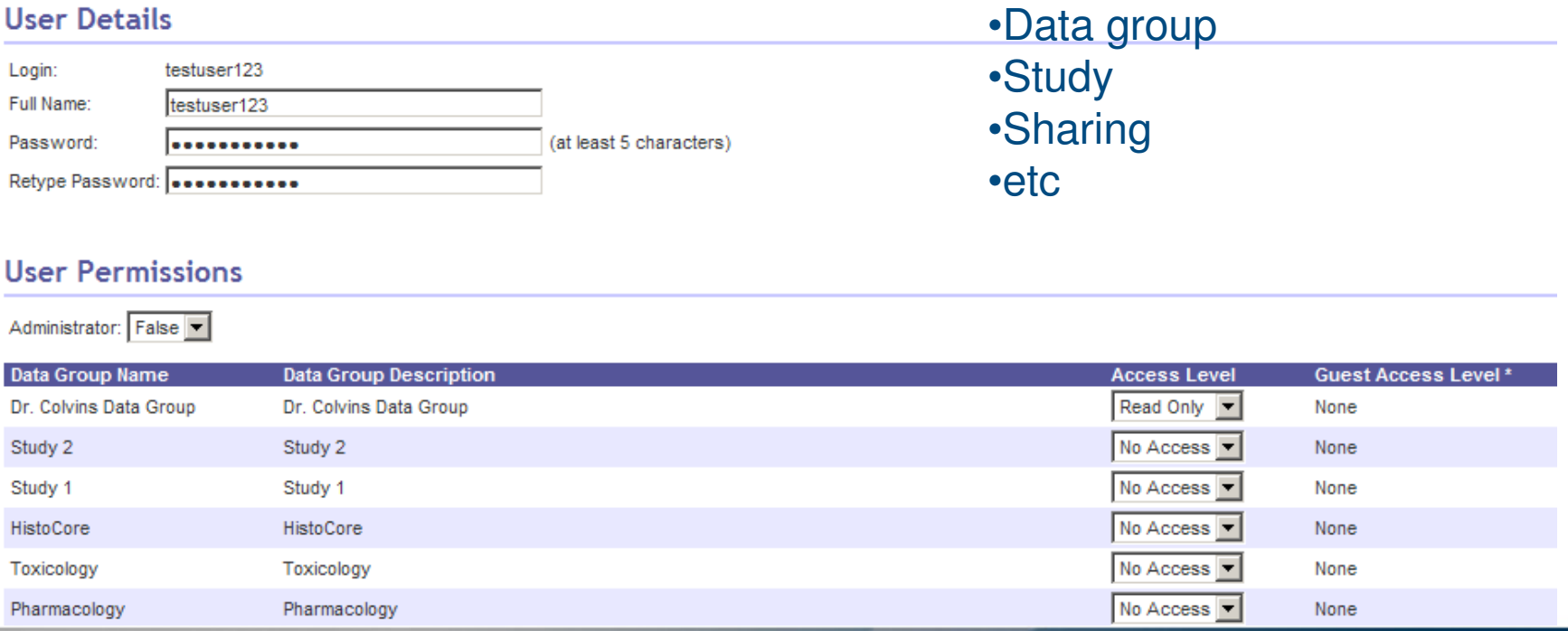
Table of Contents

Aperio Data System Operational

Role-Based Security

- Administration control
- Logon required
- Password protected

- Role based permissions
  - Read/write
  - Data entry
  - Editing
  - Status changes
  - Data group
  - Study
  - Sharing
  - etc



User Details

Login: testuser123

Full Name: testuser123

Password: ••••••••••• (at least 5 characters)

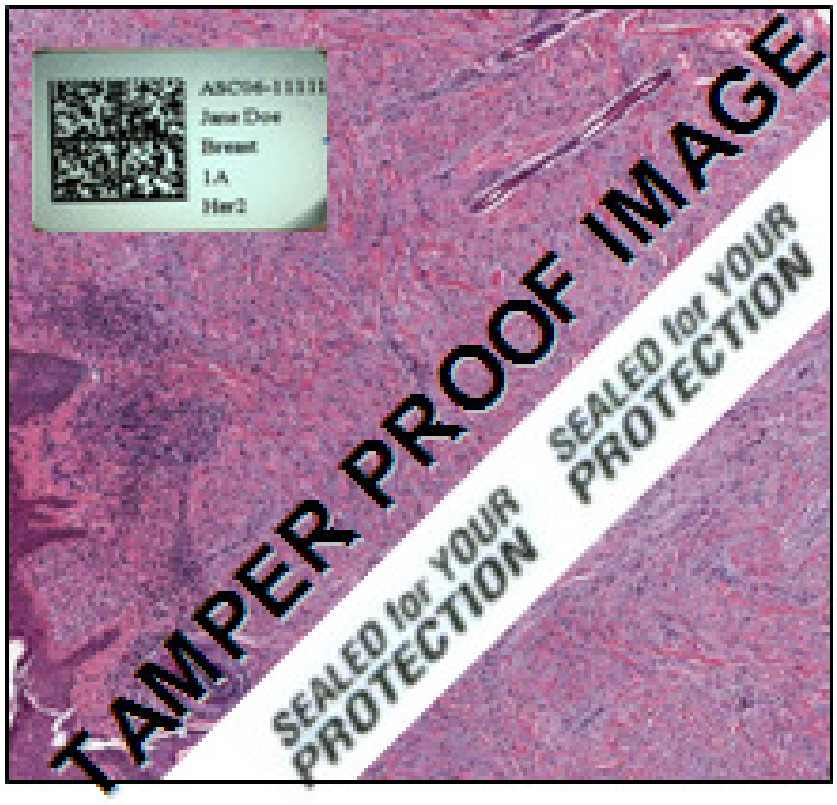
Retype Password: •••••••••••

User Permissions

Administrator: False

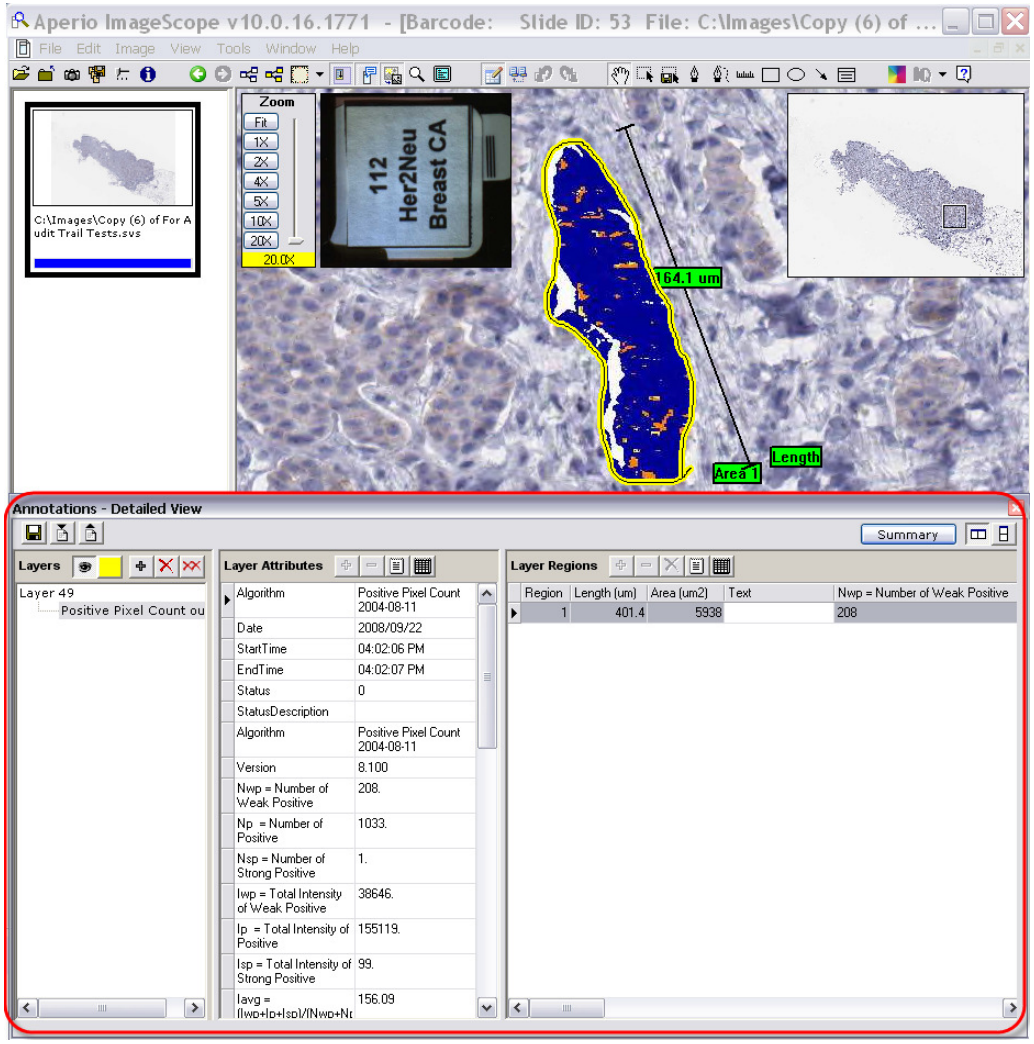
Data Group Name	Data Group Description	Access Level	Guest Access Level *
Dr. Colvins Data Group	Dr. Colvins Data Group	Read Only	None
Study 2	Study 2	No Access	None
Study 1	Study 1	No Access	None
HistoCore	HistoCore	No Access	None
Toxicology	Toxicology	No Access	None
Pharmacology	Pharmacology	No Access	None

Securing the Digital Slide



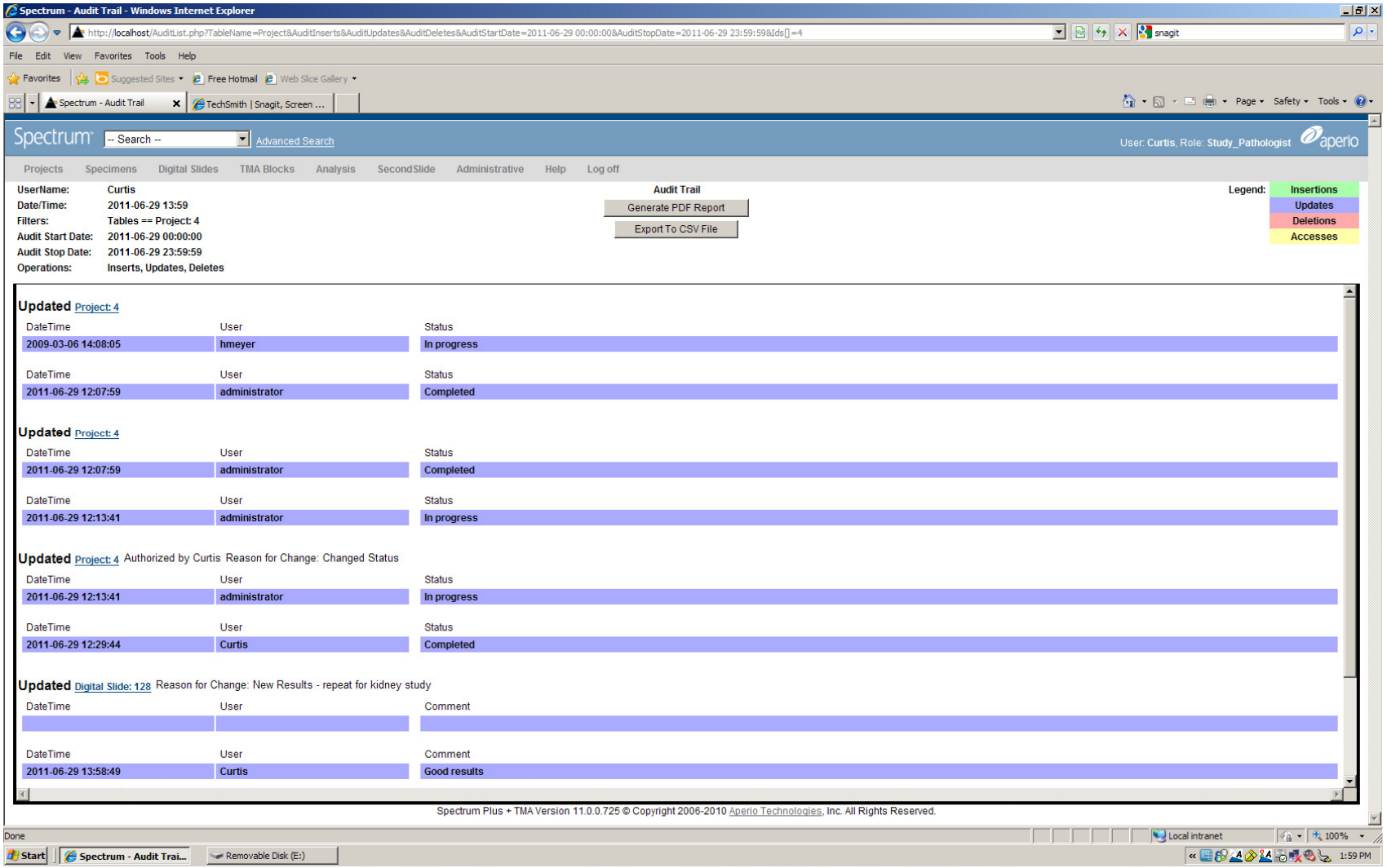
- Raw data image files are stored in a secured folder in the DSR
- A checksum is calculated for each image file
- If corruption or alteration of the image occurs, Spectrum Plus will display an error message and will not open the slide

Audit Trails



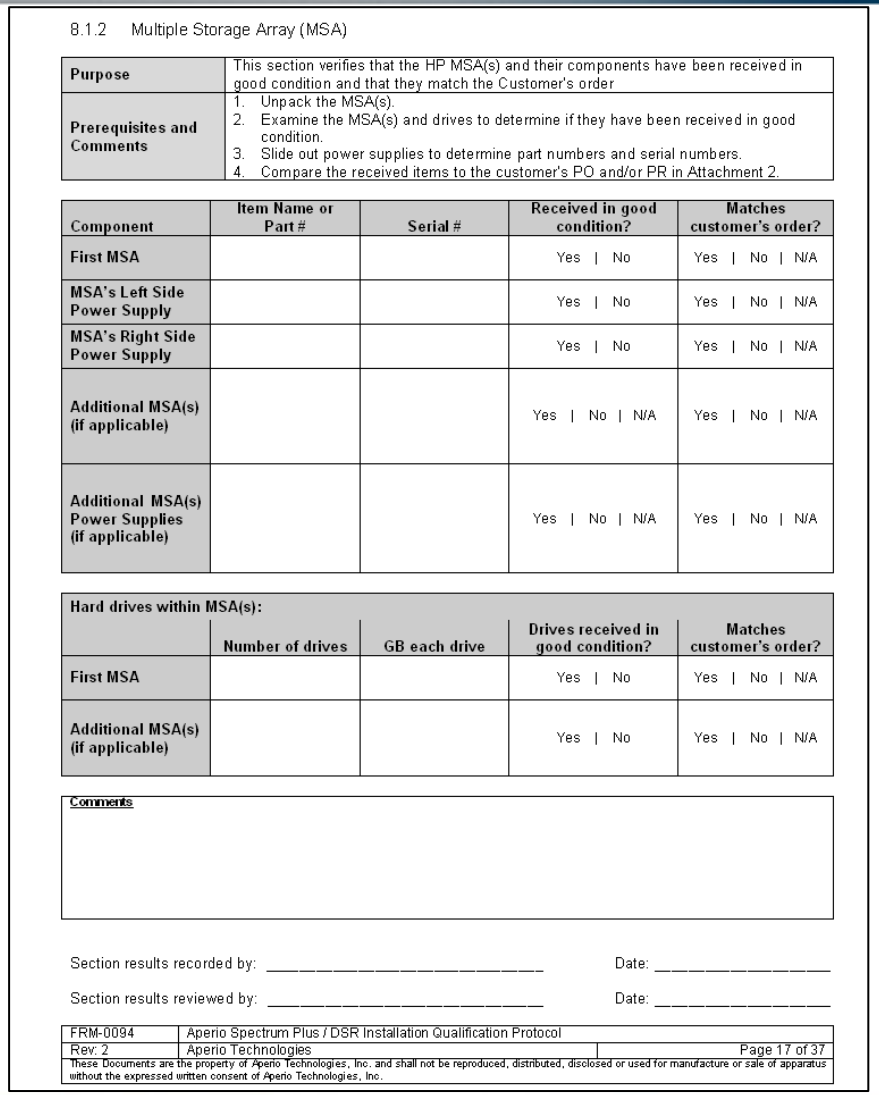
- Unlike the raw data image files, metadata can and will change as slides are annotated, reviewed, and processed.
- Metadata is maintained in a secure database where it cannot be manipulated from outside the Spectrum Plus application
- Changes to metadata are tracked in secure audit trail
- Critical data changes require reason for change and electronic signature

Audit Trails



Example protocol content: Spectrum Plus / DSR

- Equipment inventory (correct server and drive array received in good condition?)
- Site prepared?
- Server has correct components in place (CPU, RAM, network cards, etc.)?
- Connectivity complete?
- All software installed and configured correctly?



8.1.2 Multiple Storage Array (MSA)

Purpose	This section verifies that the HP MSA(s) and their components have been received in good condition and that they match the Customer's order
Prerequisites and Comments	1. Unpack the MSA(s). 2. Examine the MSA(s) and drives to determine if they have been received in good condition. 3. Slide out power supplies to determine part numbers and serial numbers. 4. Compare the received items to the customer's PO and/or PR in Attachment 2.

Component	Item Name or Part #	Serial #	Received in good condition?	Matches customer's order?
First MSA			Yes | No	Yes | No | N/A
MSA's Left Side Power Supply			Yes | No	Yes | No | N/A
MSA's Right Side Power Supply			Yes | No	Yes | No | N/A
Additional MSA(s) (if applicable)			Yes | No | N/A	Yes | No | N/A
Additional MSA(s) Power Supplies (if applicable)			Yes | No | N/A	Yes | No | N/A

Hard drives within MSA(s):	Number of drives	GB each drive	Drives received in good condition?	Matches customer's order?
First MSA			Yes | No	Yes | No | N/A
Additional MSA(s) (if applicable)			Yes | No	Yes | No | N/A

Comments

Section results recorded by: _____ Date: _____

Section results reviewed by: _____ Date: _____

Protocol content: Spectrum Plus / DSR

- General functionality of Spectrum Plus and the DSR
  - Creating, deleting, and modifying database objects, comments,
  - Attaching documents,
  - Database search and query functions.
- General functionality of ImageScope software
  - Annotation of slides; audit trail capture of changes,
  - Image adjustment, linking, tracking, extraction, etc,
  - Drawing of shapes and accuracy of linear and area measurement.
- Algorithms
- WebScope application
  - General functionality
  - Annotations in WebScope and audit trail
- Data export
- Digital slide conferencing
- Reporting
- Image file and database backup and restore
- GLP Archive utility*

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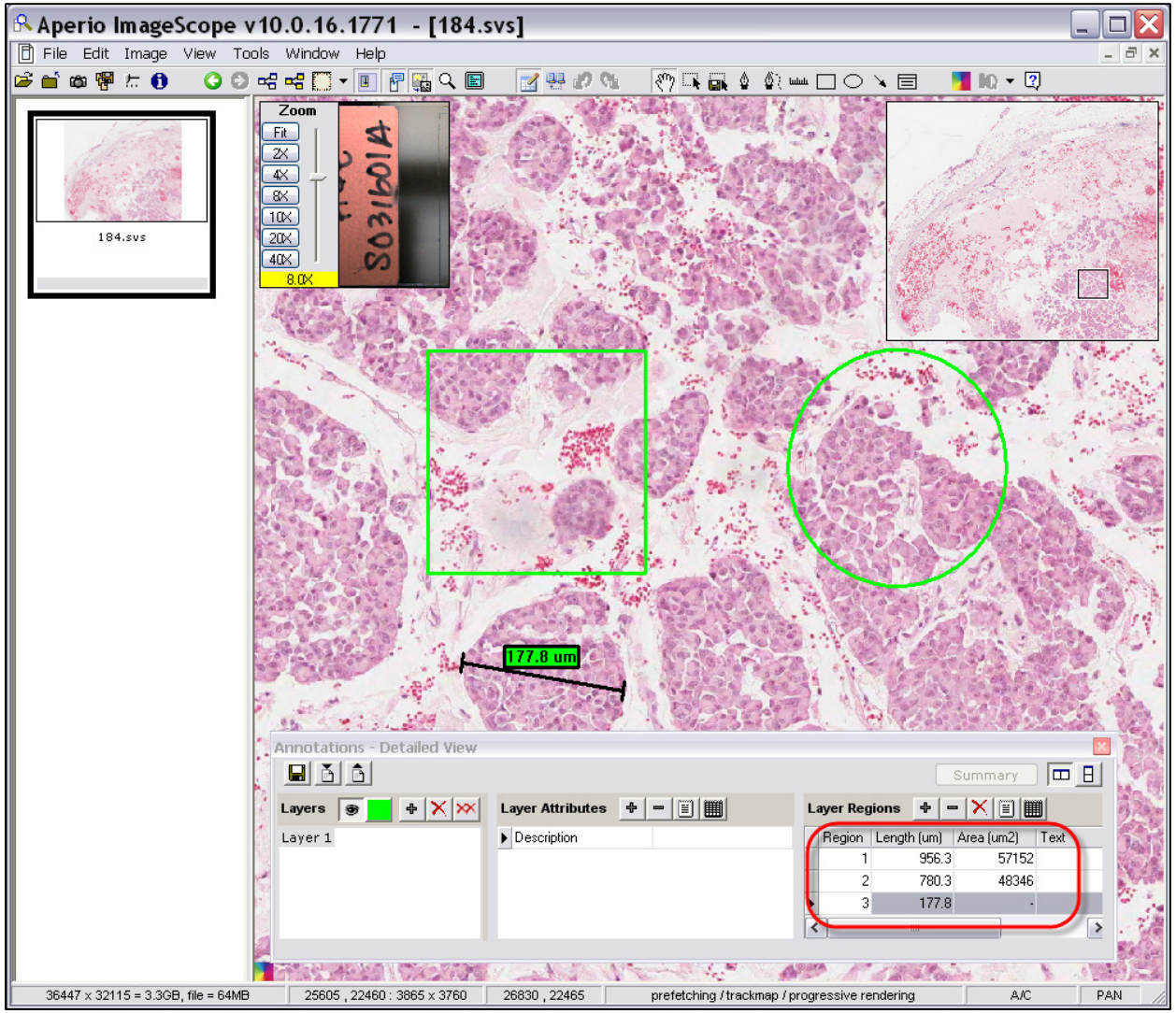
- Image file and database backup and restore
- GLP Archive utility*

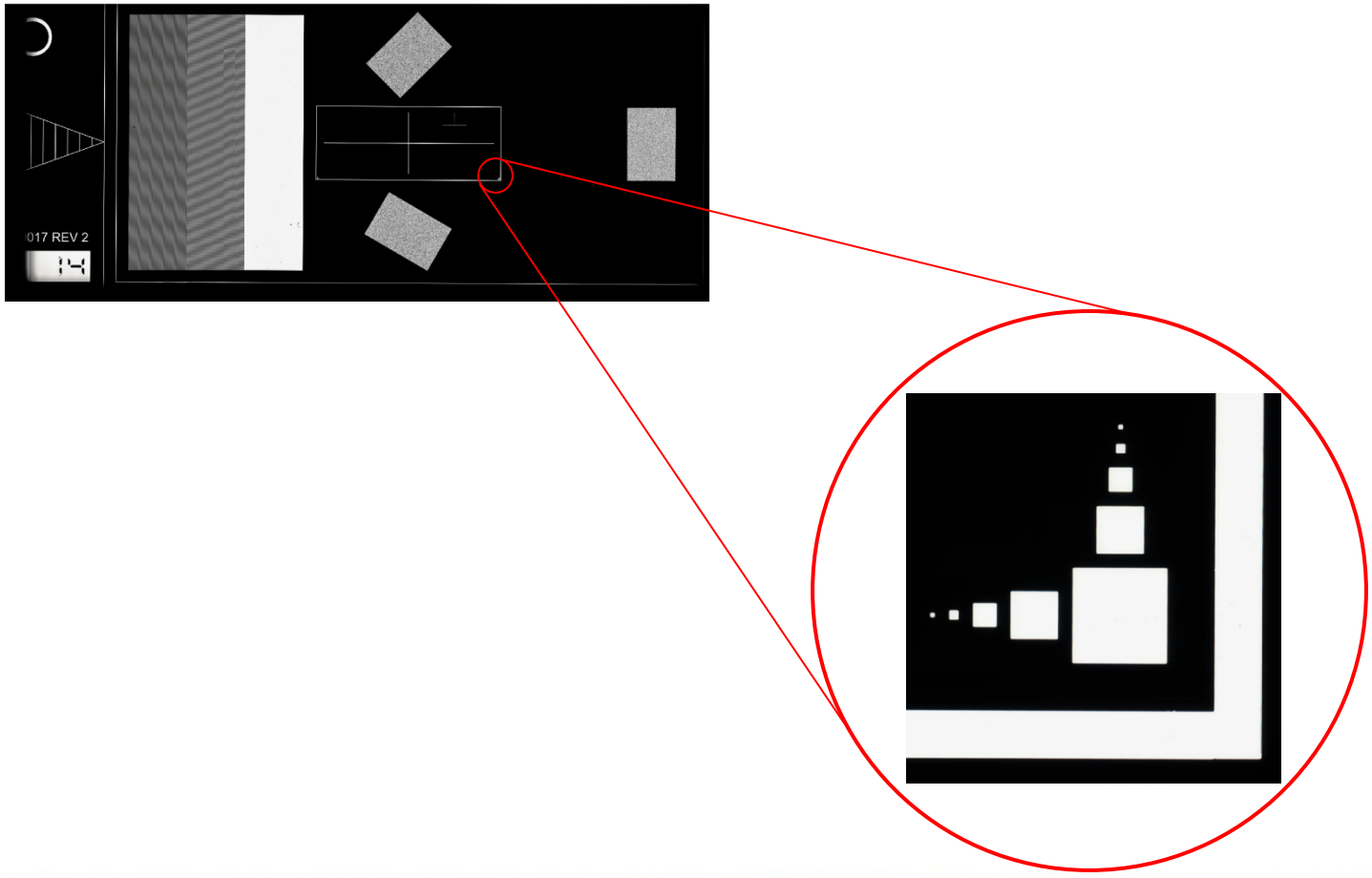
Case Study: Spectrum Plus / DSR
Validation of Linear and Area Measurement



How do we verify that these measurements of length and area are accurate?

Case Study: Spectrum Plus / DSR OQ
Qualification of Linear and Area Measurement

Solution: The NIST-traceable Aperio Calibration Slide



Case Study: Spectrum Plus / DSR OQ Validation of Linear and Area Measurement

Table for Recording Results for Accuracy of ImageScope Measurements

1. ImageScope will report perimeter and circumference in the Length (um) column of the Annotations Layer Regions table.
2. Calculation for Percent Difference is: $\frac{(100 * |\text{Value from Cal. Cert.} - \text{Value from ImageScope}|)}{\text{Value from Cal. Cert.}}$

Object	Dimension	As Indicated on Cal. Cert.	As Calculated from Cal. Cert	As Measured in ImageScope	Percent Difference
Large Rectangle (Nominally 15 mm wide x 6 mm high)	Width			*From Step 11:*	
	Height			*From Step 11:*	
Circle (Nominally 100 um diameter)	Width			*From Step 13:*	
	Circum-ference		**Width x 3.1416 =**	*From Step 13:*	
	Area		**(Width/2)^2 x 3.1416 =**	*From Step 13:*	
Square (Nominally 10 um width)	Width			*From Step 19:*	
Square (Nominally 100 um height)	Height			*From Step 16:*	
	Perimeter		**Height x 4 =**	*From Step 17:*	
	Area		**(Height)^2 =**	*From Step 17:*	

Comments

Presentation of IQ, OQ, PQ Results

SECTIONS AND CONTENTS OF THE SCANSCOPE AND SPECTRUM PLUS VALIDATION BINDER

TITLE PAGE AND INDEX

Contains:

- Description of the subject of the validation,
- Table of contents

Typical Size: 1 or 2 pages

VALIDATION FINAL REPORT

Contains:

- Summary of results from all IQ, OQ, PQ protocols
- Resolutions of any deviations found during protocol executions
- Signatures indicating that equipment is validated

Typical Size: 2 to 8 pages

VALIDATION PROTOCOLS: IQ, OQ, PQ

Contains:

- Completed IQ, OQ, and PQ protocolS
- Signatures indicating that protocols were approved prior to execution
- Signatures indicating that work was reviewed after execution

Typical Size: 20 to 150 pages per protocol

EXHIBITS AND ATTACHMENTS

Contains:

- Printouts and other data generated during protocol execution
- Any supplemental testing required during protocol executions, for example, to further explore and resolve deviations
- Signatures indicating that data was reviewed after execution

Typical Size: 20 to 30 Exhibits of 1 to 10 pages each

Agenda

- General Considerations
  - **G**eneral **L**aboratory **P**ractices
    - history
    - agencies
    - guidelines
    - observations
  - Comprehensive Solution to Regulatory Guidelines
    - instrument qualification
    - software validation
- Advantages for Compliance

Aperio's GLP Compliance Module

Provide a customer-facing IQ/OQ/PQ package to accompany v11 release

- Why?
  - As noted, FDA and international regulatory agencies require qualification of such systems for all pre-clinical and clinical drug development
  - Ease customers' burden with compliance
  - Complements new regulatory-oriented functionality that comes with v11 release
  - Many other system/software manufacturers provide this type of service

Advantages of Using Vendor-Supplied Validation Services

- **Common in GxP laboratories and for GxP information systems.** Examples include:
  - Networked chromatography systems and instrumentation (Agilent, Waters)
  - Laboratory Information Management Systems (SQL*LIMS, LabWare)
  - Electronic Document Management Systems (Livelink EDMS)
- **Advantages of using them:**
  - Vendor has comprehensive test case set that came from the development specifications of the hardware and software
  - Vendor's existing work saves time and cost of developing these on your own

Challenges in a vendor validation package

- Must be comprehensive but not excessive
- Must capture as much commonality as possible among various customer deployments
- Must assist with showing that other regulations are satisfied (e.g., ERES, HIPAA, CLIA, GCP, GMP, etc)

Digital Pathology Benefits for GLP

- **Archive** –breakage, photo-bleaching, oxidizing, loss, recovery, duplication, etc
- **Annotations** – Identify exact tumor mass/cell/organelle analyzed w/ scoring
- **Data Quality** – Objective data, blind studies, Image Analysis confirmation
- **Tracking** – All access, annotations, notes, image analyses, scoring, reports, etc are time/date stamped, tracked, electronically signed……..
- **Retrospective Analysis** – Raw image is always available for subsequent studies (review, new application, improved methods, new algorithms, etc)
- **Only practical method** to store fluorescent data
- **FDA submissions** – digital images easier to sort, search, transport, store, retrieve specific annotations and analyses

Acknowledgements

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- Mark Wrenn
- Kush Kapila
- Dr. Kate Lillard
- Jackie Gogue

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- Erik Staley, Valicom Inc.

References

- FDA regulations:
  - 21 CFR § 11 *Electronic Records; Electronic Signatures* ("Part 11")
  - 21 CFR § 58, *Good Laboratory Practice for Nonclinical Laboratory Studies*
  - 21 CFR § 312, *Investigational New Drug Application* (Good Clinical Practices)
  - 21 CFR § 820 *Quality System Regulation* (medical devices and diagnostics)
  - 45 CFR § 160, 164, Standards for Privacy of Individually Identifiable Health Information (HIPAA)
- FDA Warning Letters: http://www.fda.gov/foi/warning.htm
- FDA and industry guidances
  - ICH, *Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance*
  - FDA Compliance Program Guidance Manual 7348.808, *Bioresearch Monitoring: Good Laboratory Practice (Nonclinical Laboratories)*
  - FDA, *Guidance for Industry, Computerized Systems Used in Clinical Investigations*
  - FDA, *Validation Documentation Inspection Guide*
  - FDA *Guidance for Industry, Part 11, Electronic Records; Electronic Signatures – Scope and Application*
  - FDA *Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations*
  - USP <1058>, *Analytical Instrument Qualification*
- EMEA regulations and guidances:
  - *OECD Principles of Good Laboratory Practice*, 1997
  - *The Application of the Principles of GLP to Computerised Systems,* 1995
  - Annex 11, "Computerised Systems," 4/8/2008 draft, in *The Rules Governing Medicinal Products in the European Union*, Volume 4
- Japan MHLW regulations and guidances:
  - Ordinance No. 21, *Good Laboratory Practices* 3/26/97
  - PFSB Notification No. 0401022, "Use of Electromagnetic Records and Electronic Singatures for Approval of, or License for Drugs"
- Position papers:
  - *Toxicologic Pathology* 2007, 450-455, D. Tuomari et al, "Society of Toxicologic Pathology Position Paper on Pathology Image Data: Compliance with 21 CFR Parts 58 and 11

Questions