



# **GLP Compliance: Practical Applications in Digital Pathology**

Aperio Science Webinar Series  
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# Objectives

- Review the regulations that apply to instrumentation and digital pathology systems:
  - Domestic and international GLP regulations,
  - Domestic and international ERES requirements
- Present Aperio's strategy for compliance:
  - New GLP and ERES features in Aperio's digital pathology systems,
  - Validation of digital pathology systems

# Overview of potentially applicable GxP 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)

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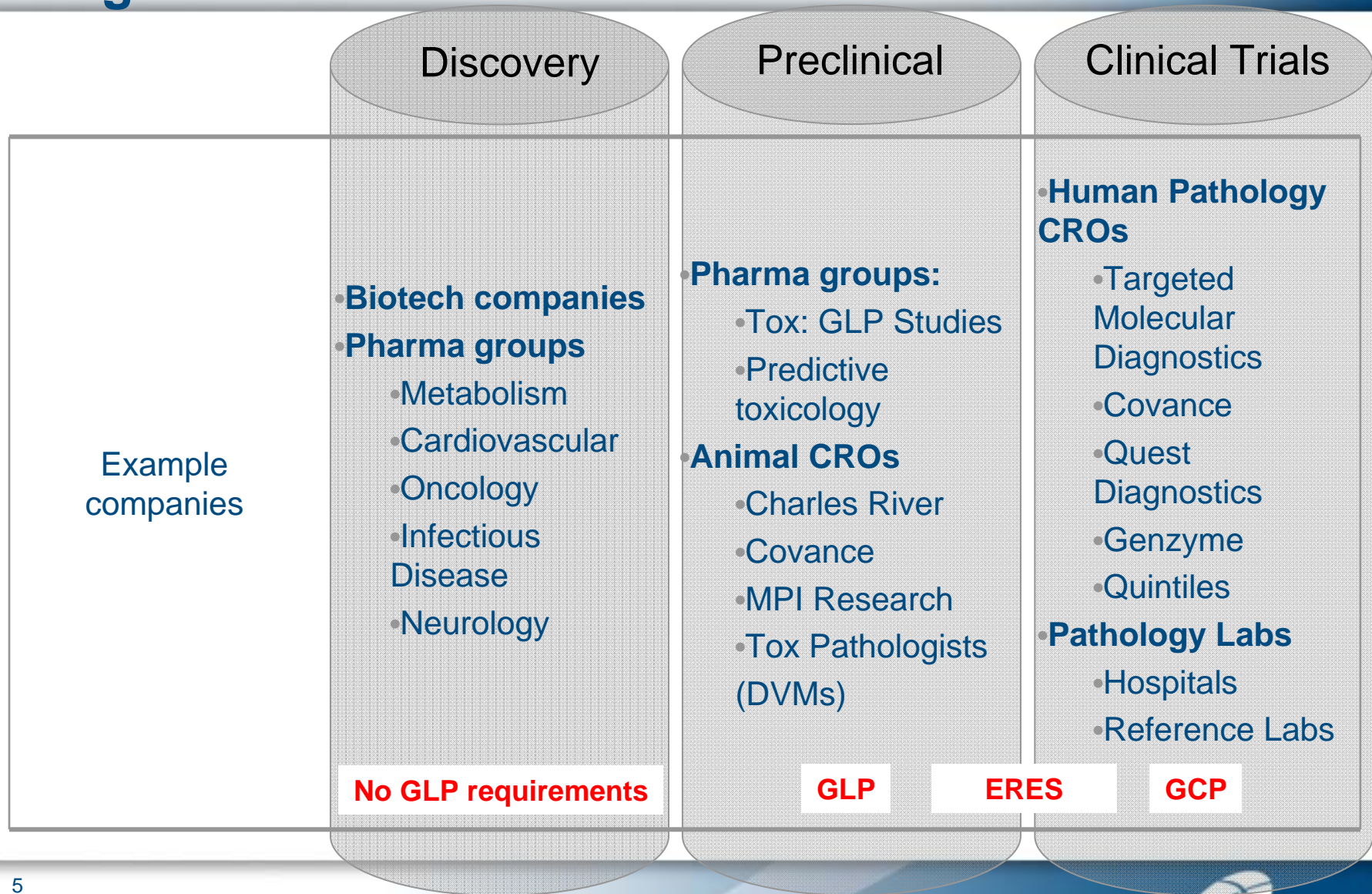


GLP (MHLW Ordinance No. 21)

GCP (Ordinances and Notifications)

ERES (PFSB Notification 0401022)

# Who has to be compliant with which regulations?



# Overview of ERES and predicate GLP and GCP requirements

<b>Stated or Implied Requirements from ERES regulations, GLP, and GCP</b>  <b>Requirement</b>	<b>USA 21 CFR Part 11</b> "Electronic Records; Electronic Signatures"	<b>EU Annex 11</b> "Computerized Systems"	<b>Japan PFSB Notification,</b> "Use of Electromagnetic Records and Electronic Signatures..."	<b>Predicate GLP and GCP</b> 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		✓	✓	✓

# Aperio's Approach Toward Compliance: Digital slide as raw data, 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

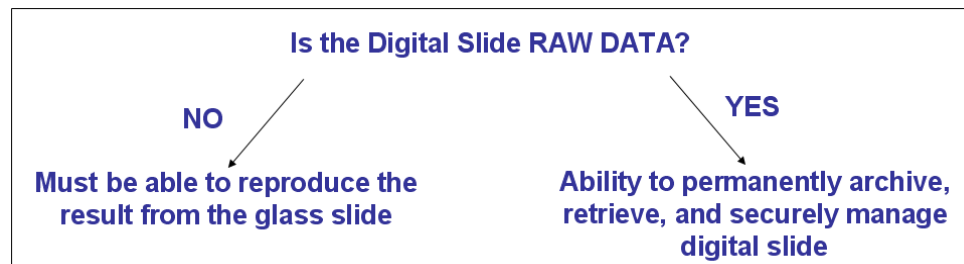
*"The review concludes that all the necessary technology for telepathology is available and there is strong published evidence for a diagnostic accuracy comparable with glass slide diagnosis..."*

Aperio's FDA clearances

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

# Aperio's Approach Toward Compliance: Digital slide as raw data, or glass slide?

- Substantial debate still remains in the industry regarding the definition of raw data as it pertains to slide images



- Aperio's approach can satisfy your needs regardless of which approach you take

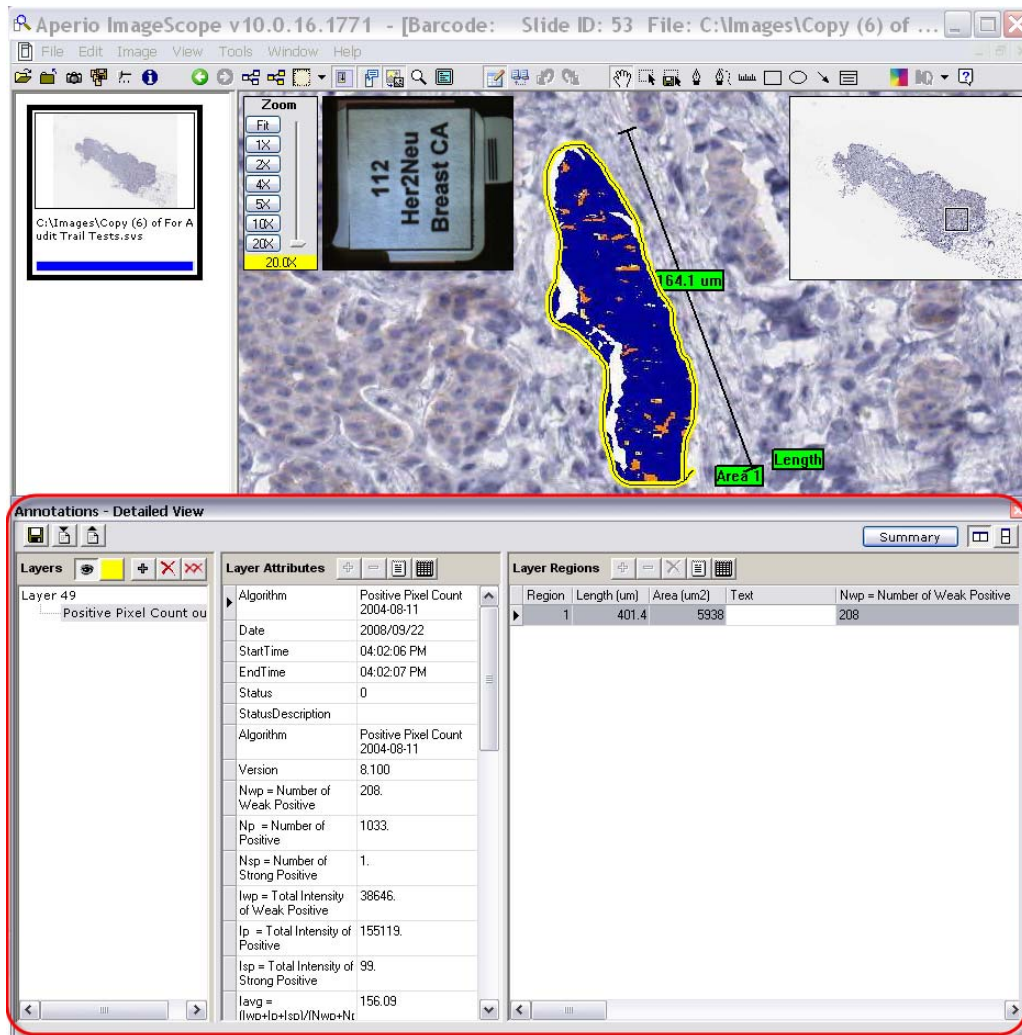
(Further detail in *Toxicologic Pathology* 2007, 450-455, D. Tuomari et al, "Society of Toxicologic Pathology Position Paper on Pathology Image Data: Compliance with 21 CFR Parts 58 and 11")

# New ScanScope and Spectrum Plus Features: 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

# New ScanScope and Spectrum Plus Features: 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

# New ScanScope and Spectrum Plus Features: Audit Trails



UserName: erikstaley  
 Date/Time: 2008-09-22 16:24  
 Filters: Tables == Slide: 53  
 Audit Start Date: 2008-06-22 16:16:07  
 Audit Stop Date: 2008-09-22 16:16:07  
 Audited User: erikstaley  
 Operations: Inserts, Updates, Deletes

## Audit Trail Report

Legend: █ Insertions  
█ Updates  
█ Deletions

16:15:50

### Inserted AnnotationAttribute: 703

DateTime	User	AnnotationId	AttributeName	AttributeValue
2008-09-22 16:15:50	erikstaley	51	Status	0

### Inserted AnnotationAttribute: 704

DateTime	User	AnnotationId	AttributeName	AttributeValue
2008-09-22 16:15:50	erikstaley	51	StatusDescription	

### Inserted AnnotationAttribute: 705

DateTime	User	AnnotationId	AttributeName	AttributeValue
2008-09-22 16:15:50	erikstaley	51	Algorithm	Positive Pixel Count 2004-08-11

### Inserted AnnotationAttribute: 706

DateTime	User	AnnotationId	AttributeName	AttributeValue
2008-09-22 16:15:50	erikstaley	51	Version	8.100

### Inserted AnnotationAttribute: 707

DateTime	User	AnnotationId	AttributeName	AttributeValue
2008-09-22 16:15:50	erikstaley	51	Nwp = Number of Weak Positive	208.

### Inserted AnnotationAttribute: 708

# New ScanScope and Spectrum Plus Features: Role-Based Security

Spectrum™ aperio

User: **Spectrum Administrator, Role: SysAdmin** [Cases](#) [Specimens](#) [Digital Slides](#) [TMA Blocks](#) [Analysis](#) [Administrative](#) [Help](#) [Font Size](#) [Log off](#)

**Roles**

[Role Definitions](#) / [Command Permissions](#) / [Data Table Field Permissions](#)

**Data Table Field Permissions**

Fields	ES_Test_Role	Guest	SysAdmin	Default
[-] Cases				
Case ID	Read Only	Read Only	Read Only	Read Only
Patient ID	Full Control	Read Only	Full Control	Full Control
Name	Full Control	Read Only	Full Control	Full Control
DOB	Full Control	Read Only	Full Control	Full Control
Gender	Full Control	Read Only	Full Control	Full Control
Ethnicity	Full Control	Read Only	Full Control	Full Control
Hospital	Full Control	Read Only	Full Control	Full Control
Physician Name	Full Control	Read Only	Full Control	Full Control
Physician Phone	Full Control	Read Only	Full Control	Full Control
Clinical History	Full Control	Read Only	Full Control	Full Control
Final Diagnosis	No Access	Read Only	Full Control	Full Control
Summary	Read Only	Read Only	Full Control	Full Control
Comment	Read Only	Read Only	Full Control	Full Control
Date Reported	Read Only	Read Only	Full Control	Full Control
Status	Full Control	Read Only	Full Control	Full Control
Data Group	Full Control	Read Only	Full Control	Full Control
Customer Name	Full Control	Read Only	Full Control	Full Control
[-] Projects				
[-] Courses				
[-] Lessons				
[-] Genie Projects				
[-] Training Sets				

# Validation of GLP Laboratory Systems and Digital Pathology Equipment

This section discusses:

- Reasons for validation of GLP systems,
- Consequences of not validating GLP systems,
- Goals of Aperio's IQ/OQ/PQ service,
- Benefits of using vendor-supplied validation services,
- Potential shortcomings of vendor-supplied validation services,
- Challenges, and addressing them through Aperio's modular approach,
- Examples of validation protocol sections, and a case study for Aperio's method of validating linear and area measurements in ImageScope,
- How the IQ/OQ/PQs are summarized and presented

# Why validate your GLP laboratory equipment?

- Per US GLPs (21 CFR § 58.61, 58.63(a)):
  - “Equipment used in the generation, measurement, or assessment of data... shall be of appropriate design and adequate capacity...”
  - “Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized”
- Per US ERES Regulations (21 CFR § 11.10(a)):
  - “...procedures and controls shall include the following: Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records”

# 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 ...”

# Goals of the IQ/OQ/PQ service

- Provide a customer-facing IQ/OQ/PQ package to accompany v10 release
- Why?
  - As noted, FDA and international regulatory agencies require validation of such systems in many company's implementations,
  - Ease customers' burden with compliance,
  - Complements new regulatory-oriented functionality that comes with v10 release
  - Many other system/software manufacturers provide this type of service (though no other digital pathology vendor offers it)

# 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 and v/v of the hardware and software,
  - Vendor's existing work saves time and cost of developing these on your own

# Vendor-Supplied Validation Packages: Addressing shortcomings

Common Problem	Aperio's Solution
Vendor protocols are inadequate: Significant in-house remediation is required by customer to validate system	Comprehensive and modular IQ, OQ, and PQ set designed to cover all critical functionality
Vendor's field staff use poor documentation practices when executing protocols	Aperio staff trained on documentation practices Aperio has a dedicated GLP professional Protocols contain documentation practices reminder and instructions to default to customer's preferred documentation practices if requested
Vendor's protocols are in an unusual format, or are presented electronically	Aperio's protocols are developed using a standard formatting and layout

# Definitions: IQ, OQ, and PQ

	Definition	Examples
<b>IQ</b>	<p><b>INSTALLATION QUALIFICATION:</b>  <i>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.</i></p>	<ul style="list-style-type: none"> <li>• Correct equipment has been received in an undamaged condition,</li> <li>• All connections among instruments, computers, servers, and network are connected correctly,</li> <li>• Computers have correct CPU and memory,</li> <li>• Correct OS and software titles installed</li> </ul>
<b>OQ</b>	<p><b>OPERATIONAL QUALIFICATION:</b>  <i>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.</i></p>	<ul style="list-style-type: none"> <li>• General system operations function correctly,</li> <li>• Audit trails capture correct information,</li> <li>• Electronic signatures are rendered correctly,</li> <li>• Security roles grant or restrict the correct permissions,</li> <li>• Users without credentials cannot log into system</li> </ul>
<b>PQ</b>	<p><b>PERFORMANCE QUALIFICATION:</b>  <i>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.</i></p>	<ul style="list-style-type: none"> <li>• Customer can go through typical laboratory workflow,</li> <li>• Customer's worst-case load scenario doesn't overwhelm server(s).</li> </ul>

# 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
<i>Printed Name</i>		____/____/____
<i>Title</i>		
<i>Printed Name</i>		____/____/____
<i>Title</i>		

### DSR Identification

<i>Aperio's System Model Number</i>	<i>Aperio's System ID</i>	<i>Recorded by: (Initials/Date)</i>

### Customer Information

<i>Customer Name</i>	<i>Address of Installation Site</i>
<i>Customer Contact Person</i>	

### 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
<i>Printed Name</i>		____/____/____
<i>Title</i>		
<i>Printed Name</i>		____/____/____
<i>Title</i>		

FRM-0096	Aperio Spectrum Plus Operational Qualification Protocol	
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- 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




## 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:

	<b>INCORRECT: Data is written over.</b> List and sum the amperage of all other items drawing electrical current from this circuit	Sum recorded at right	6.5 AMPS
	<b>INCORRECT: Data is obscured.</b> List and sum the amperage of all other items drawing electrical current from this circuit	Sum recorded at right	<del>5.5</del> AMPS 6.0
	<b>Correct documentation practices</b> List and sum the amperage of all other items drawing electrical current from this circuit	Sum recorded at right	<del>5.5</del> AMPS 6.0 EGS 01/02/08 Added incorrectly

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 <b>New Password</b> and <b>Retype New Password</b> fields, enter a new password that contains at least one non-alphanumeric character and is at least 8 characters in length.  Click <b>Save</b> .	Login completes	<input type="checkbox"/> As specified <input type="checkbox"/> Other (explain)	Pass   Fail
30.	Click <b>Log off</b>	Spectrum displays <b>Login Required</b> screen	<input type="checkbox"/> As specified <input type="checkbox"/> Other (explain)	Pass   Fail

**Comments**

Section results recorded by: \_\_\_\_\_ Date: \_\_\_\_\_  
 Section results reviewed by: \_\_\_\_\_ Date: \_\_\_\_\_

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

**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
<i>Printed Name</i>		____/____/____
<i>Title</i>		
<i>Printed Name</i>		____/____/____
<i>Title</i>		

# 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., HIPAA)

# Addressing challenges: Aperio's Modular Approach

## Installation Qualifications:

ScanScope and Control PC IQ	One IQ per ScanScope
Spectrum Plus / DSR IQ	One per overall installation

## Operational Qualifications:

ScanScope and Control PC OQ	One OQ per ScanScope
Spectrum Plus OQ	One per overall installation (covers ImageScope and related software functionality as well)

## Performance Qualifications:

Generalized Workflow PQ	Option for customers with a standard installation
Custom Workflow PQ	Aperio provides framework for customer to develop own PQ (or Aperio can develop it)
System Load Test PQ	For multiple ScanScope implementations

# Example protocol content: ScanScope and Control PC IQ

Aperio ScanScope and Control PC Installation Qualification Protocol

**8 Installation Qualification**

8.1 ScanScope and Control PC: Receipt, Inventory, and Inspection

<b>Purpose</b>	This section documents that all ScanScope and Control PC equipment have been received by the customer and that all components are in good condition.			
<b>Prerequisites and Comments</b>	<ol style="list-style-type: none"> <li>1. Unpack the ScanScope equipment per MAN-0014.</li> <li>2. Include a copy of the customer's PO and/or PR in Attachment 2.</li> <li>3. Examine the ScanScope externally and internally to determine if it has been received in good condition.</li> <li>4. Examine the light source, Control PC, monitor, and accessories to determine if they have been received in good condition.</li> <li>5. Compare the received items to the customer's PO and/or PR.</li> </ol>			

Component	Item Name or Part #	Serial #	Received in good condition?	Matches customer's order?
ScanScope	<input type="checkbox"/> CS <input type="checkbox"/> CS-O <input type="checkbox"/> CS-Oil Scanner <input type="checkbox"/> XT		Yes   No	Yes   No
Light Source			Yes   No	Yes   No   N/A
Control PC with mouse and keyboard			Yes   No	Yes   No   N/A
Control PC monitor			Yes   No	Yes   No   N/A
20x Objective			Yes   No	Yes   No   N/A
Spare light bulb			Yes   No	Yes   No   N/A
Autoloader and Slide Tray (XT only)		<i>from autoloader:</i>	Yes   No   N/A	Yes   No   N/A
Autoloader Slide Racks, 8x (XT only)			Yes   No   N/A	Yes   No   N/A

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- Equipment inventory (everything received in good condition?)
- Site prepared?
- ScanScope set up with correct components in place?
- Control PC set up and all connections in place?
- All software installed and configured correctly?

# Example protocol content: Spectrum Plus / DSR IQ

- 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)

<b>Purpose</b>	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			
<b>Prerequisites and Comments</b>	<ol style="list-style-type: none"> <li>1. Unpack the MSA(s).</li> <li>2. Examine the MSA(s) and drives to determine if they have been received in good condition.</li> <li>3. Slide out power supplies to determine part numbers and serial numbers.</li> <li>4. Compare the received items to the customer's PO and/or PR in Attachment 2.</li> </ol>			

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

Section results recorded by: \_\_\_\_\_ Date: \_\_\_\_\_

Section results reviewed by: \_\_\_\_\_ Date: \_\_\_\_\_

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# Example protocol content: ScanScope and Control PC OQ

Aperio ScanScope and Control PC Operational Qualification Protocol

## 9.4 Component Functionality

This section verifies that components involved with ScanScope operations function within tolerance and in an expected manner.

### 9.4.1 Macro Camera Alignment, Rotation, and Image Quality

<b>Purpose</b>	This section verifies that: 1. The macro camera is aligned properly 2. The macro camera is rotated to the right plane 3. The macro camera is well focused and provides good image quality
<b>Prerequisites and Comments</b>	This test requires an Aperio Calibration Slide (ACS) (FIX-0017-CAL). Ensure that the identity of this slide has been logged in Section 7 as a Test Material before proceeding.  For CS: Load slide into Position 1 of the tray. For XT: Place slide in the manual loading tray.  Note that some tests are specific to CS or XT ScanScopes, and that some test instructions differ between CS and XT. Check the N/A box in the Actual Result field and circle N/A in the Disposition field for instructions that do not apply to the ScanScope under OQ.  The Console software must be started to run this test  Perform the following tests at 20x magnification

Step	Instructions	Expected Result	Actual Result	Disposition, Initials/Date
1.	<b>CS Only:</b> Right-click on <b>Position 1</b> and select <b>Replace Slide</b>	Any present slide image disappears and background is depicted in gray	<input type="checkbox"/> As specified <input type="checkbox"/> Other (explain)  <input type="checkbox"/> N/A	Pass   Fail   N/A
2.	<b>CS Only:</b> Right-click on <b>Position 1</b> and select <b>Set Current Slide</b>	Arrow ( ▶ ) appears next to Position 1	<input type="checkbox"/> As specified <input type="checkbox"/> Other (explain)  <input type="checkbox"/> N/A	Pass   Fail   N/A
3.	Click the <b>Manual Load</b> button and then click <b>Manual Scan</b>	A slide image appears in the upper pane	<input type="checkbox"/> As specified <input type="checkbox"/> Other (explain)	Pass   Fail
4.	In the <b>Scan Area</b> tab, click <b>Find Tissue</b>	Tissue finder operation completes	<input type="checkbox"/> As specified <input type="checkbox"/> Other (explain)	Pass   Fail
5.	Adjust the green Scan Area so that it encompasses the box and cross hair located in the center of the slide (refer to <b>Figure 9.4A</b> for an example)	Box and cross hair are within Scan Area	<input type="checkbox"/> As specified <input type="checkbox"/> Other (explain)	Pass   Fail

- ScanScope operations function as expected
- Control PC security in place

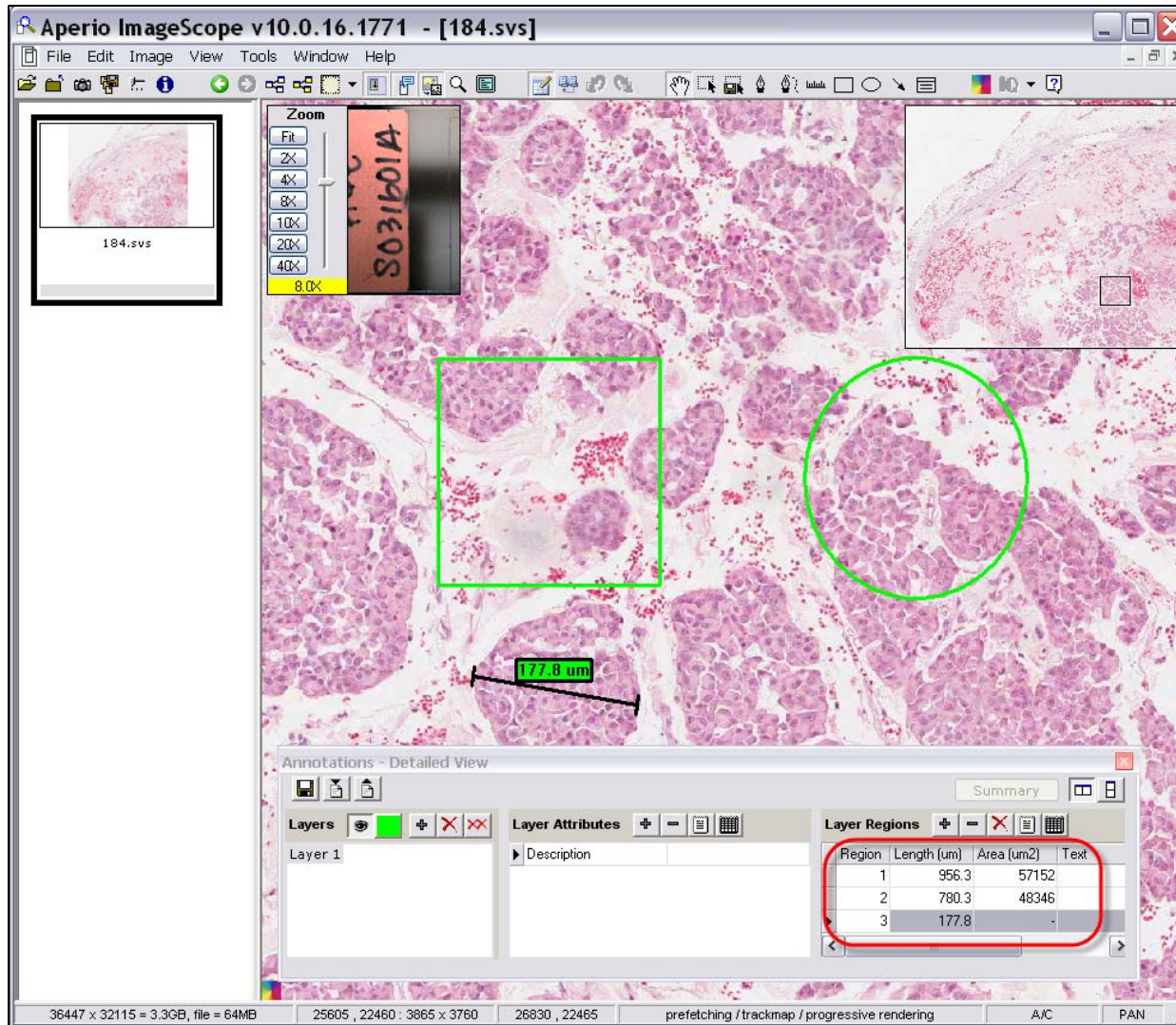
# Protocol content: Spectrum Plus / DSR OQ

- General functionality of Spectrum Plus and the DSR
  - Creating, deleting, and modifying database objects,
  - Audit trail functionality,
  - 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.
- Logical security
  - Account and password controls,
  - Record protection and detection of alteration to image raw data,
  - Data groups and role permissions.
- Electronic signature

# Protocol content: Spectrum Plus / DSR OQ

- Algorithms
- WebScope application
  - General functionality
  - Annotations in WebScope and audit trail
- Data export
- Digital slide conferencing
- Reporting
- Image file and database backup and restore

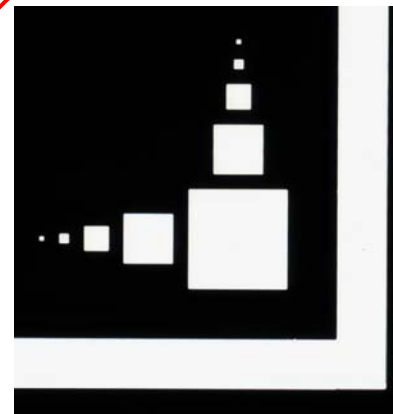
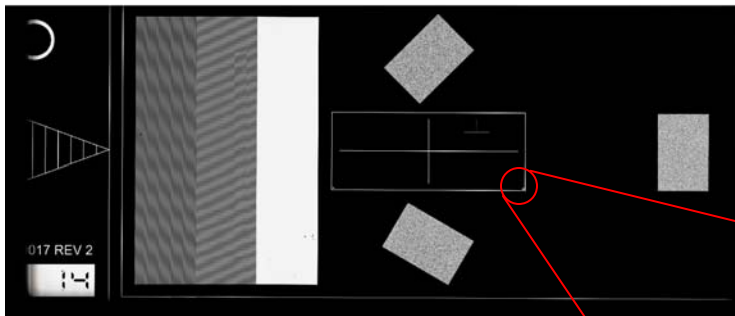
# Case Study: Spectrum Plus / DSR OQ Qualification of Linear and Area Measurement



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 Qualification of Linear and Area Measurement

Aperio Spectrum Plus Operational Qualification Protocol

**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:	
	Circumference		Width x 3.1416 =	From Step 13:	
	Area		(Width/2) <sup>2</sup> 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) <sup>2</sup> =	From Step 17:	

Comments

# Presentation of IQ, OQ, PQ Results



## SECTIONS AND CONTENTS OF THE SCANSCOPE AND SPECTRUM PLUS VALIDATION BINDER

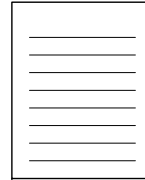


### TITLE PAGE AND INDEX

Contains:

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

Typical Size: 1 or 2 pages

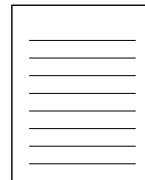


### VALIDATION FINAL REPORT

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

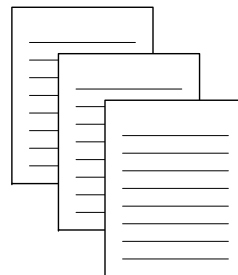


### VALIDATION PROTOCOLS: IQ, OQ, PQ

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

# Acknowledgements

Thank you to the following Aperio team members for their assistance with this webinar:

- Dr. Steven Potts
- Mr. Tiff Kramer
- Dr. Kate Lillard-Wetherell, Aperio
- Ms. Nicole Siska

# 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 Signatures 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

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# Q & A

- Why don't microscopes have to be validated for GLP use?

*Validation is implied in the GLPs for some equipment. A requirement for validation appears only in 21 CFR Part 11, and that is only for some systems that generate electronic records (refer to [Slide 14](#)). A standard microscope, per the GLPs, must be of suitable design and well maintained, but validation isn't required to prove that. If true measurements using an ocular scale, for example, are derived, then calibration of that component would be required.*

- What is the average time to complete the IQ/OQ/PQ package? Typically, how long does the entire validated installation take for two ScanScopes?

*IQ of the ScanScope instrumentation and IQ of DSR hardware and software takes approximately half a day each (subtotal = 1 day). OQ of the ScanScope takes about one day, and OQ of the DSR takes two to three days (subtotal = 2 or 3 days). PQ, allow one day. The total time to complete IQ/OQ/PQ is about 5-6 days. Add 1.5 to 2 days for each additional ScanScope in the system. A two ScanScope system including DSR would therefore take approximately 8 to 10 days.*

- Considering the various regulatory agencies around the world involved with GLP studies, to your knowledge, are they in agreement that your validation program is acceptable for their requirements?

**How does CFR21 Part 11 correlate with the Japan EREST guideline? Can we assume that they are equivalent?**

*Regulatory agencies don't certify validation programs. However, as Aperio's program covers all ERES and predicate GLP/GCP regulations for the US, EU, and Japan, Aperio is confident that the validation program is suitable for worldwide use. Refer to the table on [slide 6](#), which shows correlation between 21 CFR Part 11 and the Japanese guideline.*

- Can microarray data be validated with this system?

*Since tissue microarray (TMA) is used typically in discovery research, it is not included in the validation protocols. It could be undertaken as a custom validation project.*

## Q & A (continued)

- Will the slide and related files have to be stored with the study file as raw data? How would you store the digital slide with the study file? I understand the file size is quite large.

*A reference to the digital slide file and the methods of retrieval would suffice for compliance. This is common practice in other cases of high-volume raw data, (for example, HPLC-Mass Spec).*

- Do you help with internal documentation required by my company specifically?

*Part of every validation project is a preliminary review of the protocols by the customer. This is the time for the customer to stipulate any special requirements for satisfying their needs. We want to make sure the work we do meets or exceeds the client's own established regulatory and documentation standards.*

- Can the image annotations optionally not be recorded for pathology peer review?

*When auditing is turned on, all annotation activity (drawing, mark-up changes and deletions) will be recorded. Permissions can be set to limit the ability of a viewer to delete annotations, and annotations can be toggled visible/non-visible, but all parties opening a digital slide will be able to see them or toggle their visibility.*

- Does your GLP testing requirement take into consideration, any or all integration with an outside Pathology or Laboratory information system and the interaction between the two systems, to include meta data, patient information transfer between systems?

*The base, prewritten protocols were developed for only the immediate input and output interfaces of the system such as query result files or barcode decoding. Our DSR OQ also validates exporting of data from the Spectrum Plus database by way of the common CSV format. Any non-standard data flow protocols would need to be added as a custom section in the PQ. We will do custom validation for 3rd party devices and/or data stores as an additional service.*

## Q & A (continued)

- *What about providing a validation for therapeutic markers, using Aperio's software, ie ER, PR, HER2Neu?*  
*Yes, that would fall under custom validation work.*
- *Is access to the raw data audit-trailed (i.e., the "cyber-equivalent" of asking a colleague for an informal opinion)?*  
*The viewing of data is not audited, only changes to database tables and records. An audit viewing feature is slated for release 11.0 of Spectrum Plus.*
- *Will software be re-validated with each release?*  
*Yes, in part. The amount of revalidation depends upon the extent of changes in the new release. A revalidation would verify installation of the new release and would validate all new functionality as well as revalidate any legacy functionality that is affected. This approach ensures that your digital pathology system is maintained in a validated state while minimizing activity and paperwork to do so.*
- *Does Valicom offer other validation services for other systems and protocols?*  
*Yes. Valicom provides compliance and validation services to the life science and medical device industries, and specializes in computer system validation and laboratory instrument validation. Please visit the Valicom website at [www.valicom.com](http://www.valicom.com) for more information. Full contact information can be found on [slide 36](#).*