

GLP Compliance in Digital Pathology

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Agenda

- General Considerations
 - General Laboratory Practices
 - 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

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)



OECD Principles of Good Laboratory Practice

Guidance Documents

ERES (Annex 11, "Computerised Systems")



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Overview of ERES and predicate GLP and GCP requirements

Stated or Implied Requirements from ERES regulations, GLP, and GCP	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		3 +>		
Instruments, software and systems must be validated		3 +>	3 +	>
System components must be inventoried		3 +>		>
Equipment must be adequately tested, calibrated, and standardized			3 +>	
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	3 +>	3 +>	>>	>
Audit trails must track who created/changed/deleted records	3 +>	>	>>	*
Authority checks must be in place	3 +>	3 +>	3 +>	
Device / terminal checks must be in place				
Additional controls must be placed on open systems				
Electronic signature manifestations indicate who / when / why	3 +>		3 +>	
Electronic signature irrevocably linked to record				
Electronic signature components and controls are enforced	3 +>	3 +>	>	
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]



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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.





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



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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



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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



On-site services for GLP validation, international multisite integration

etc



Image analysis for whole slide, automated, objective data



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

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Tissue Microarray Lab for biomarker discovery





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Qualification vs Validation

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

Capeto Carlos Sestars Year

 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

We have reviewed this proto system described herein.	col and prosp	pectively approve it for a	qualification (of the Spectrum
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Printed Name				
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- Protocols must be prospectively prepared
- Protocols must be approved before being executed



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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





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General guidelines regarding IQ, OQ, and PQ documentation

Step	Instructions	Expected Kesult	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 & characters in length.	Login completes	As specified Other (explain)	Pass Fail	•
	Click Save.				
30.	Click Log off	Spectrum displays Login Required screen	As specified Other (explain)	Pass Fail	
<u>Comm</u>	ents				
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	Ve have re Spectrum P	r Approval of Comple eviewed this protocol post flus system described herei	ted Protocol -execution, and conc n has been completed	our that operationa	al qualification of the
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- Results must be independently reviewed:
 - On a per-section basis
 - At conclusion of execution



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Data Repository/Viewer Validation





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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



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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) 255

Where and how much staining is there?

Classify <u>Pixels</u> Measure Pixel by Color (Stain)(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



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Validation: Comprehensive, Detailed, Documented

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4		10	GEN	ERAL FUNCTIONALITY OF IMAGESCOPE SOFTWARE			Aperio Data System Operational Qualification, S	W Releas
2	SCORE		10.1	Slide Viewing		11	3.3 Poles: Data Table Field Permissions	
2				10.1.1 Opening Slides and Viewing Related Information		11.4 Dat	a Groupe	
4	REFERENCES			10.1.2 Methods for Viewing Images		11.4 Dat	a Groups	
5	DEFINITIONS AND ABBREVIATIONS			10.1.3 Image View Files (.SIS file)		11.6 Cor	nmunication Security	
6	INSTRUCTIONS FOR PROTOCOL EXECUT		40.0	10.1.4 Opening and Viewing Fluorescence Stained Images		11.0 001	6.1.SSI	
•	6.1 Customer Notification		10.2	Image Resolution		11.	6.2 Access to Spectrum over the Internet	
	6.2 Protocol Pre-Approval		10.3	Image Adjustment and Management	12	AUDIT TR		
	6.3 Good Documentation Practices			10.3.1 Generalized image Adjustment in imagescope		12.1 Cor	infiguration	
	6.4 Protocol Execution			10.3.2 Integrated Color Management (ICM)		12	1.1 General Audit Trail and Electronic Signature Configuration	
	6.5 Per-Section Review		10.4	Apportations		12.	1.2 Configuration of Audit Trail Reasons for Changes	
	6.6 Protocol Deviations		10.4	10.4.1 Drawing of Shapes and Apportation Audit Trail		12.	1.3 Configuration of Hierarchy Data for Audit Trail and Electronic Signature	е
	6.7 Customer Approval of Completed Pro			10.4.2 Accuracy of ImageScope Measurements			Testing	
7	IDENTIFICATION OF EXECUTORS AND RE			10.4.3 Appotation Lavers		12.2 Auc	lit Trail Operations and Electronic Signature Executions	
8	TEST MATERIALS AND PREPARATION FO		10.5	Linking		12.	2.1 Controls on Signing	
	8.1 Materials		10.6	Tracking		12.3	2.2 Audit Trail Operations: Capture of Reason for Change	
	8.2 Support Software		10.0	Spanshots		12.3	2.3 Components, Controls, And Functionality for Electronic Signature	
	8.3 Protocol Execution Notes		10.7	Extraction of Regions		12.	2.4 User Name Controls	
9	GENERAL FUNCTIONALITY OF SPECTRUN		10.0	10.8 1 Saving Extracted Regions		12.	2.5 Controls on Viewing and Generating Audit Trail Reports	
	9.1 System Configuration			10.8.2 Viewing Extracted Regions with ImageScope		12.	2.6 Generation of Audit Trail Reports	
	9.2 Spectrum Digital Slides, Specimens, a			10.8.3 Viewing Extracted Regions with External Viewing Sof		12.:	2.7 Accuracy of Audit Trail Reports	
	9.2.1 Digital Slides: Adding, Creatin		10.9	Image Rotation		12.3	2.8 Confirmation of Signer Identity	
	9.2.2 Creating, Deleting, and Modify		10.10) Smart Synchronization (SmartSync)		12.	2.9 Permanence of Signatures and Audit Trail	
	9.2.3 Creating, Deleting, and Modify	11	LOGI	ICAL SECURITY		12.:	2.10 Electronic Signature Functionality for LDAP-Authenticated Users	
	9.2.4 Creating, Deleting, and Modify		11.1	Account and Password Controls		12.3	2.11 Removal of Status Vocabulary	
	9.2.5 Additional Spectrum UI Verifica			11.1.1 Configuration of Account and Password Controls	13	WEBSCOF		
	9.3 Editing Spectrum Plus Data Tables an			11.1.2 Challenge of Account and Password Controls		13.1 Gei	neral webScope Functionality	
	9.3.1 Editing Data Tables			11.1.3 Logging or Reporting Invalid Login Notifications		13.2 We	DScope Annotations	
	9.3.2 Population of Data Fields for S			11.1.4 LDAP Account and Password Controls	14	ALGORITE	ins .	
	9.3.3 Searches: Initiating, Saving, a		11.2	Record Protection		14.1 Cor	ntiguration	
	9.3.4 Search Accuracy			11.2.1 Restrictions on Unauthorized Access to System and F		14.2 Dev	elopment of Macros from Algorithms, Functionality of Bright Field PPC Alg	orithm
	9.3.5 Return of Data Tables to Origin			11.2.2 Detection of Alteration to Image File		14.3 Fur	Inclining of Customer-Purchased Bright Field Algorithms	
FRM-02	74 Aperio Data System Operational Qualification		11.3	Roles		14.4 Flu	ch Analysis in Spectrum Plus	
rkev: A These Doo	Aperio DCO# 2011- uments are the property of Aperio Technologies, Inc. and shall not be reprot			11.3.1 Assignment and Creation of Roles		14.0 Dau	iit Trail and Removal of Custom Macros from Database	
without th	e expresseu written consent of Aperio reconologies, Inc.			11.3.2 Roles: Command Permissions	15			
		E EDM 000		Assesse Data System Operational Ovalification, SIM Palason 44	10			



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Role-Based Security

 Administration control Role based permissions Logon required •Read/write Password protected •Data entry •Editing •Status changes User Details Data group testuser122 •Study •Sharing •etc

Logio

Retype Password:	•••••	
Password:	•••••	(at least 5 characters)
Full Name:	testuser123	
Login:	testuser123	

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



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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



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Audit Trails

🕏 Aperio ImageScope v10.0.16.1771 - [Barcode: Slide ID: 53 File: C:\Images\Copy (6) of ... 🚽 🗖 🗙 🖆 🖆 🕸 🚏 🗶 🌒 🗳 😳 🗠 🖷 🛄 🔻 🛄 🖗 🕵 🔍 📓 📝 👯 🖉 % 🥐 🗔 🌢 🕼 📖 🗆 🔿 🖌 🔲 📲 🔟 🕶 😨 1X ≤ X ¥ X E C:\Images\Copy (6) of For dit Trail Tests su 20K Annotations - Detailed View Summary 🖽 🗄 Layers 👩 🗛 🗙 📈 Layer Attributes - 🗉 🔳 Layer Regions 🛛 🖶 🖂 📰 🗰 Region Length (um) Area (um2) Text ayer 49 Algorithm Positive Pixel Count Nwp = Number of Weak Positive Positive Pixel Count ou 1 401.4 208 Date 2008/09/22 04:02:06 PM StartTime EndTime 04:02:07 PM Status n. StatusDescription Algorithm Positive Pixel Count 2004-08-11 8 1 0 0 Version Nwp = Number of 208 Weak Positive Np = Number of 1033 Positive Nsp = Number of Strong Positive Iwp = Total Intensity 38646. of Weak Positive lp = Total Intensity of 155119. Positive Isp = Total Intensity of 99 Strong Positive lavg = (lwp+lp+lsp)/(Nwp+Nt 156.09 <

- 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



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Audit Trails

🥖 Spectrum - Audit Trail - Windows Intern	et Explorer			_ 8 ×
🕞 🕞 🗢 🔺 http://localhost/AuditList.php	?TableName=Project&AuditInserts&AuditUpdates&A	uditDeletes&AuditStartDate=2011-06-29 00:00:00&AuditStopDate=2011-06-29 23:59:59&Ids[]=4	🗾 🗟 🐓 🗙 🎦 snagit	P-
File Edit View Favorites Tools Help				
🚖 Favorites 🛛 👍 🔁 Suggested Sites 👻 💋] Free Hotmail 🤌 Web Slice Gallery 🝷			
😬 🗸 🛦 Spectrum - Audit Trail 🗙 🌾	TechSmith Spagit, Screen		h 🕶 🗟 👻 🖻 👘 Page 🕶	Safety 🕶 Tools 🕶 🔞 🕶
Spectrum Search	Advanced Search		User: Curtis, Role: Study_Patholo	_{gist} Øaperio
Projects Specimens Digital Sliv	des TMA Blocks Analysis Secon	1Slide Administrative Help Log off		
UserName: Curtis		Audit Trail	Legend:	Insertions
Date/Time: 2011-06-29 13:59 Filters: Tables == Project: 4		Generate PDF Report		Deletions
Audit Start Date: 2011-06-29 00:00:00		Export To CSV File		Accesses
Audit Stop Date: 2011-06-29 23:59:59				
Operations: Inserts, Updates, Del	letes			
Updated Project: 4				
DateTime	User	Status		
2009-03-06 14:08:05	hmeyer	In progress		
2011-06-29 12:07:59	User	Status Completed		
2011-00-2012:01:00	dummistrator	Completed		
Updated Project: 4				
DateTime	User	Status		
2011-06-29 12:07:59	administrator	Completed		
Date lime	User	Status In programs		
2011-00-2012.10.41	uunmistrator	in progress		
Undated Project 4 Authorized by Cu	urtis Reason for Change: Changed Status			
DateTime	User	Status		
2011-06-29 12:13:41	administrator	In progress		
DateTime	User	Status		
2011-00-29 12:29:44	Curus	Competed		
Updated Digital Slide: 128 Reason fo	or Change: New Results - repeat for kidney s	tudy		
DateTime	User	Comment		
DateTime	User	Comment		
2011-00-23 13.30.49	Cuius	UUUU I COLILO		
		Spectrum Plus + TMA Version 11.0.0.725 © Copyright 2006-2010 Aperio Technologies, Inc. All Rights Reserv	red.	Þ
				<u> </u>
ene	Removable Dick (Er)		Local intranet	
📒 Start 🗍 🚝 Spectrum - Audit Trai	Kentovable Disk (E:)		« 🖷 🗞 🖉 🖓 😽	🔊 武 💋 🏸 T:2A bw



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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 Mu	Itiple Storage	Array (MSA)
----------	----------------	-------------

1. Unpack t	n and that they match the Customer's order
Prerequisites and Comments 2. Examine condition. 3. Slide out 4. Compare	ie MSA(s). the MSA(s) and drives to determine if they have been received in good power supplies to determine part numbers and serial numbers. the received items to the customer's PO and/or PR in Attachment 2.

Component	ltem 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

Section results reviewed by:

Date

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Aperio Spectrum Plus / DSR Installation Qualification Protoc Rev: 2 Aperio Technologies These Documents are the property of Aperio Technologies, Inc. and shall not without the expressed written consent of Aperio Technologies, Inc. used for manufacture or sale



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



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



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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

T able for Recordi I. ImageScope w Regions table.	ng Results for <i>i</i> <i>i</i> ll report perime	Accuracy of Images	Scope Measurements e in the Length (um) colu	ımn of the Annotat	ions Layer
2. Calculation for	Percent Differer	nce is: <u>(100 *</u>	<u> Value from Cal. Cert</u> Value from (<u>- Value from Imag</u> Cal. Cert.	eScope)
Object	Dimension	As Indicated on Cal. Cert.	As Calculated from Cal. Cert	As Measured in ImageScope	Percent Difference
Large Rectangle	Width			From Step 11:	
(Nominally 15 mm wide x 6 mm high)	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:	



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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
 - General Laboratory Practices
 - 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



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- Craig Fenstermaker
- Mark Wrenn
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- 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: <u>http://www.fda.gov/foi/warning.htm</u>
- 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



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Questions





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