



Micro-CT Digital Imaging Validation Challenges in a Regulated Environment

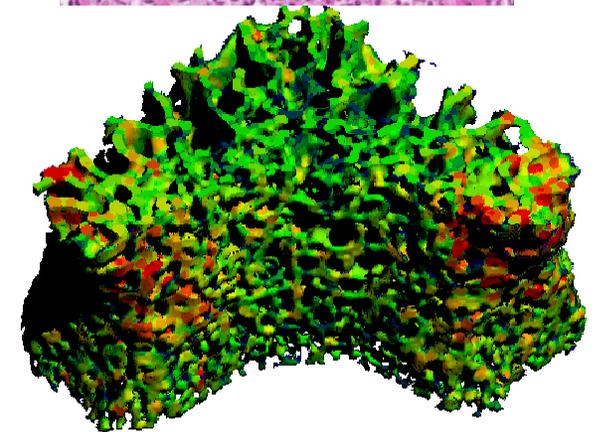
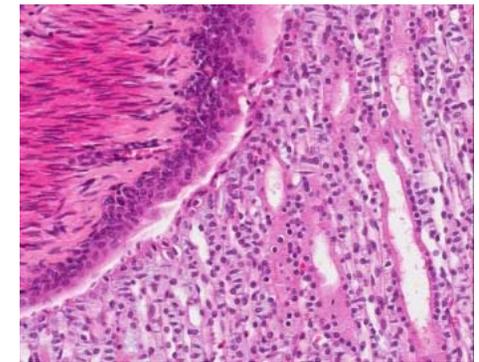
**Lelia Scott, Sr. Director Global Quality Systems
Fetal Imaging in Regulatory Developmental Toxicology Studies
21Apr2015 – Arlington, VA**

Agenda

- Digital Imaging Uses in Regulated Environments
- Advantages and Disadvantages
- Regulatory Requirements and Risks
- Mitigations
- Validation Challenges

Digital Imaging Uses

- Digital Pathology – Whole Slide Imaging
- Electron Microscopy
- CT Scanners
- Digital Photography
- Image scanning



Digital Imaging Uses

Today

- Illustrative
- Remote Consultation
- Quality Control



Future

- Remote Peer Review
- Image Analysis
- Interpretation and Conclusion
- Training

Advantages

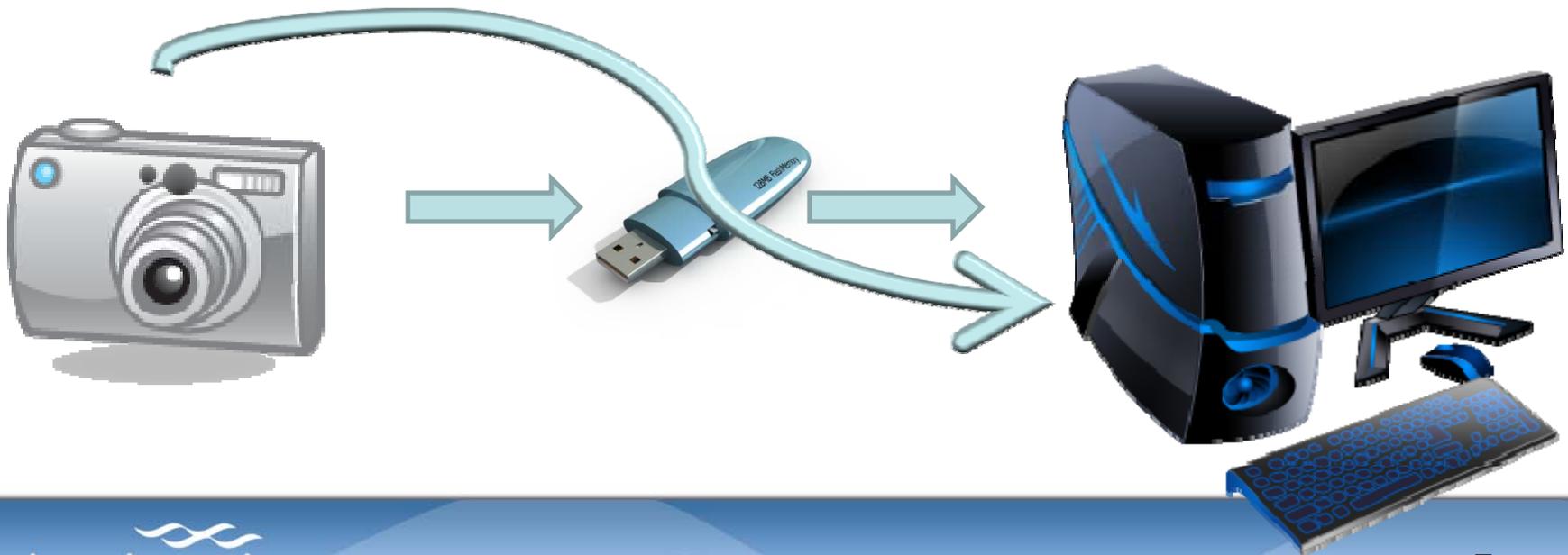
- Easily shared and copied
- Can be easily organized
- Image quality does not degrade over time
- Can be analyzed
 - Objective quantification, measurement, automatic and unbiased analysis
 - Reproducible from analyst to analyst
- Overall potential for reduced cost

Disadvantages

- No security controls to prevent modification or falsification
- No audit trail
- Tools and applications not designed for regulated use
- Open source solutions do not allow for control, validation and change control by regulated users
- No mechanism for backup, archival and retrieval
- Complex validation for image analysis tools

Data Integrity

- 21 CFR Part 11.10 Controls for closed systems:
 - (a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.



Data Integrity

- *“if the data are transferred to a computer, modified in some way and then returned to an identical storage device to the one they were recorded on (eg to an identical looking CD which is passed off as the 'original'), it might matter. It would matter greatly if the item described as an 'original' were a photograph of a defendant apparently involved in a criminal activity.”¹ – www.parliament.uk*

Could this really happen?

- Debarment of Veterinarian for “manipulating computer images of cells to resemble two distinct images”¹ :
 - “1. Respondent knowingly and intentionally falsified a figure that was presented in manuscripts submitted to the Journal of Experimental Medicine and the Journal of Virology and in several PowerPoint presentations that purported to represent rectal mucosal leukocytes in some instances and lymph nodes in other instances.”²
 - “15. Respondent knowingly and intentionally falsified a number of figures and made false statements in the text of NIAID, NIH, grant application 1 R01 AI051954-01 submitted jointly with a colleague by relabeling figures based on research carried out with HIV-1 or HIV-2 and identifying the figures and text as research conducted with ovine lentivirus (OvLV).”²

Data Integrity

Questions:

- Can the image be altered?
- Can the modifications be detected?
- Is the data secure when transmitted



Data Integrity

Solutions:

- Store to read-only medium with no delete access
- Secure transmission
 - *Existing digital imagery authentication techniques are based on cryptographic principles and digital signatures. These schemes effectively protect the data from modification during transmission, but they offer no protection following transmission.”²*
- Checksums

Can you spot the difference?



f138eaa8175322ddeb2b35fc1e4b42f7



8419e53217b960c63047db9f5cac941b

Validation Challenges

- Scope
 - Define the intended use of the system (e.g. consultative, illustrative, image analysis)
 - Limit to specified functionality
- Define regulatory issues and mitigations
- Write good requirements
- Test for intended use
- Use and maintenance procedures
- Define limitations to the use of the system

Controlfilename: Radius R, Metaphysis, 30 µm

◆ Basic ◆ Advanced

General:
 Holder Type: Tube
 Mode:
 Evaluation: Default Evaluation Change...

X-Ray Settings:
 Energy/Intensity: 68 kVp, 1470 µA, 100 W
 Filter:
 Calibration: 1: 68 kVp, BH: 200 mg HA/ccm, Scaling 8 Change...

Scout-View:
 ◆ enabled ◆ disabled
 Start Position (mm): 72.078
 End Position (mm): 146.233
 Angle (°): 90

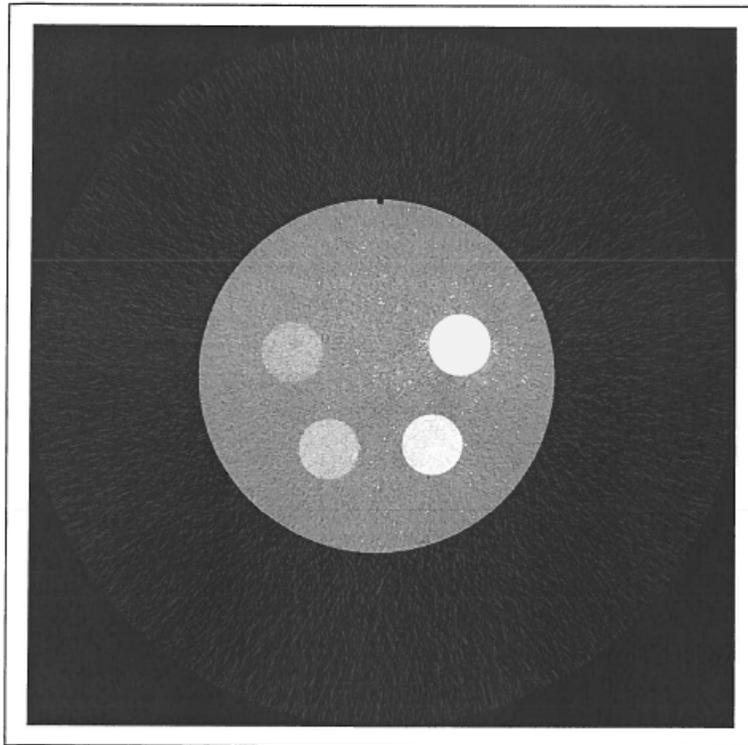
CT-Scan:
 Resolution: ◆ Standard ◆ Medium ◆ High ◆ Native ◆ Custom
 FOV/Diameter [mm]: ◆ 140.0
 Voxelsize (µm): 30.3 Default Size 2324x2324x372
 Number of Slices: 372 11.27 mm (1x372/372)
 Rel. Position of First Slice to Ref. Line (mm): 4.500
 Integration Time (ms): 225
 Average Data: 1

Number of Det-Lines: 390
 Number of Det-Lines: 390
 FOV/Scandiameter: 70.418
 SW-Binning: 1.000
 HW-Binning: ◆ 1x1 ◆ 2x2 ◆ 3x3
 Samples: 4608 Proj/180°: 900

Tot. No. of Slices: 372 Meas. Time: 5.5 min (342 mAs - CTDivol: 52.0 [mGy] - DLP: 58.6 [mGycm], Phantom ø100 mm)

Validation Challenges

- Comparing a digital image to the real thing?
 - Hue
 - Brightness
 - Magnification
- Testing image analysis tools
 - Measurement
 - Complex calculations and algorithms
 - Controls to compare density and geometry

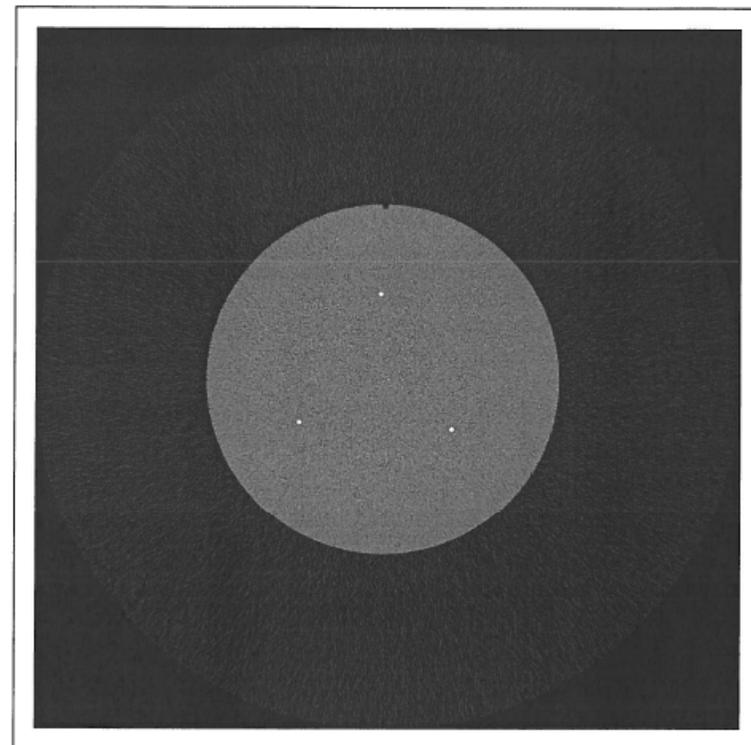


Cylinder Densities [mg HA/ccm]		Alu Rod Volume [mm ³]	
Mean1 ± SD	-6.2981 ± 43.5726	Rod Volume	-
Mean2 ± SD	99.8502 ± 45.3001		
Mean3 ± SD	203.1192 ± 46.2599		
Mean4 ± SD	404.2826 ± 49.9070		
Mean5 ± SD	793.5568 ± 57.0092		
No of Measured Slices	84	Rod Threshold	-

Mean	Mean Value of Region in mg HA/ccm	Rod Vol.	Volume of Segmented Aluminium Rod
SD	Std.Dev. of Values in Region in mg HA/ccm		
Slope	1572.453	Printed:	
Intercept	-385.399		

3D Density and Geometry Phantom Evaluation

μ CT



Cylinder Densities [mg HA/ccm]		Alu Rod Volume [mm ³]	
Mean1 ± SD	- ±-	Rod Volume	14.4909
Mean2 ± SD	- ±-		
Mean3 ± SD	- ±-		
Mean4 ± SD	- ±-		
Mean5 ± SD	- ±-		
No of Measured Slices	150	Rod Threshold	155

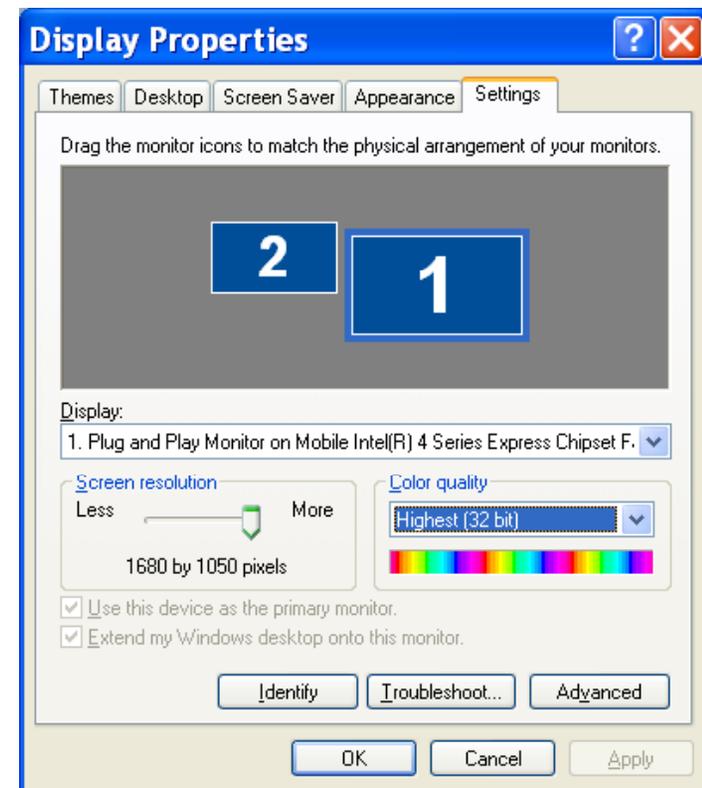
Mean	Mean Value of Region in mg HA/ccm	Rod Vol.	Volume of Segmented Aluminium Rod
SD	Std.Dev. of Values in Region in mg HA/ccm		
Slope	1572.453	Printed:	
Intercept	-385.399		

3D Density and Geometry Phantom Evaluation

μ CT

Validation Challenges

- Remote image view settings
 - Security
 - Screen settings
 - Viewing tools (version?)
 - Web conferencing tools
 - Network speed (bandwidth)
 - Modification of file type
 - Compression



Audit Trail

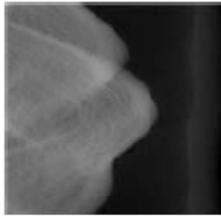
The system audit trail records must contain the following information:

- identity of operator entering the transaction
 - date and local time of the transaction
 - old (previous) entry
 - new entry
 - action taken (i.e., create, modify, delete)
 - reason for the change
-
- What if the record never changes?

Backup and Archival

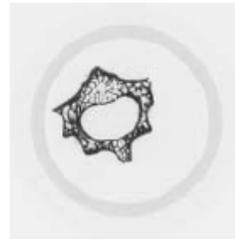
- What is the electronic record?
 - Digital image
 - Database records (meta data)
 - Overlaid images
 - Processing data and reports
 - Audit trail
- Do you have the ability to archive on a per study basis?

scan



.RSQ
RAW sequence data

uct_reconstruction



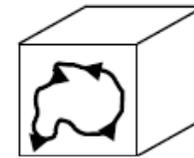
.ISQ
IMAGE sequence data
(gray scale, 2 byte, signed integers)

contouring



.GOBJ
graphical object
(green line)

3D evaluation



.AIM
white box
(gray scale, 'any image')

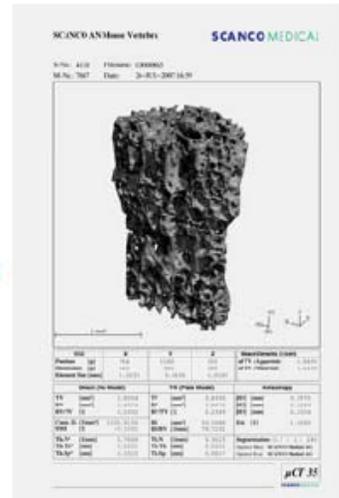
thresholding (Gauss)



_SEG.AIM
segmented object
(binary file, black/white)

calculating histomorphometry (evaluation scripts)

evaluation sheet



final results

trabecular evaluation

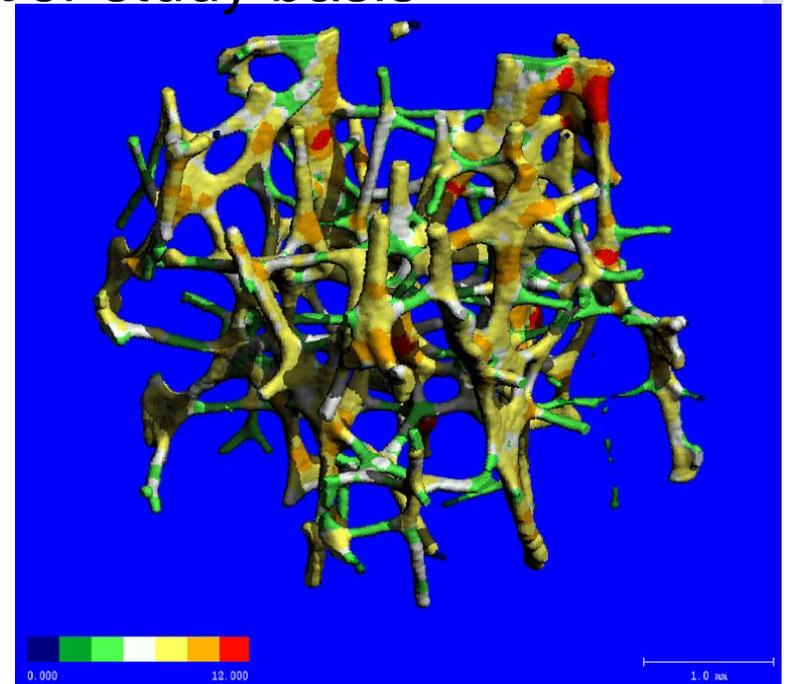
_TH.AIM
_SP.AIM
_TH.TXT
_SP.TXT

midshaft analysis

_MOI.TXT

Backup and Archival

- Special challenges:
 - Storage space and retention period
 - System design for archival on a per study basis
 - Centralized systems



Vendor Assessment

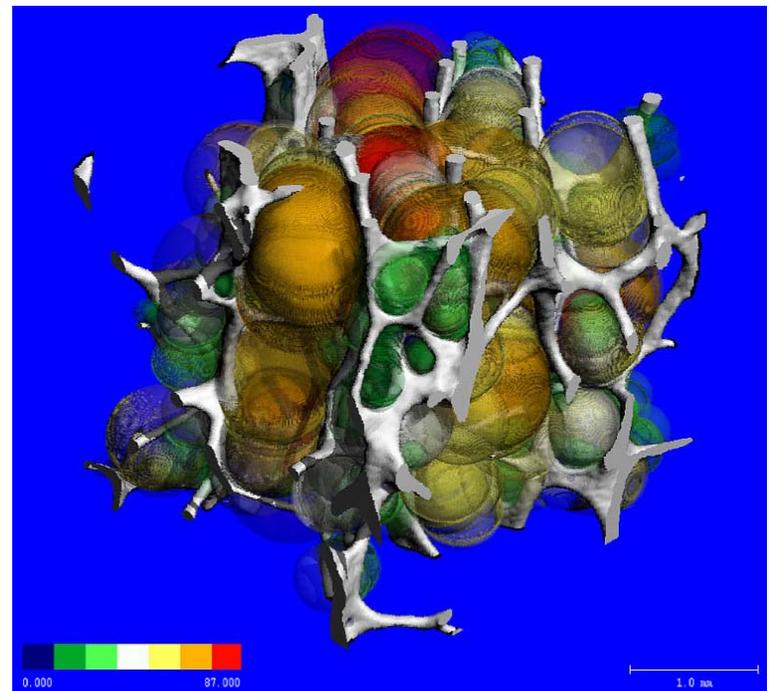
- Quality management program
- Documentation to support development and testing to a system development life cycle
- Procedures
- Testing
- Software versioning control
- Bug reporting and problem resolution

Vendor Assessment

- System designed for use in a regulated environment – How does the system address the following?
 - Data integrity and Security
 - Audit trail requirements
 - Backup, archival and retrieval on a per study basis
 - Electronic signature
 - Centralized database structure and date/time stamp

Digital Imaging Summary

- Many potential uses and advantages
- Points to consider:
 - Image security / data integrity
 - Audit trail
 - Backup and archival
 - Centralized server
 - Testing challenges
 - Controlled viewing



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- Janet Burgenson, Charles River Pathology Associates

References

1. Select Committee on Science and Technology (1998). So what is special about Digital Images? Fifth Report. <http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/064v/st0503.htm>
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