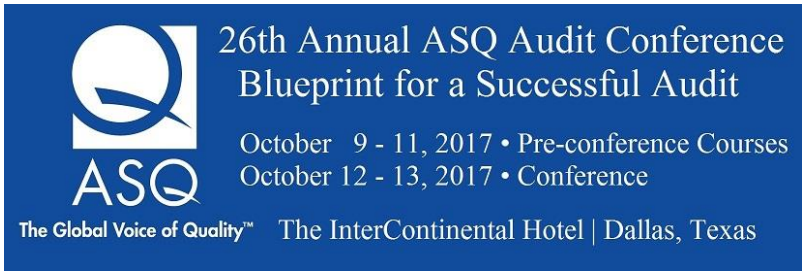

ASQ Audit Division
The Global Voice of Quality™

Preparing for Successful Data Integrity Audits

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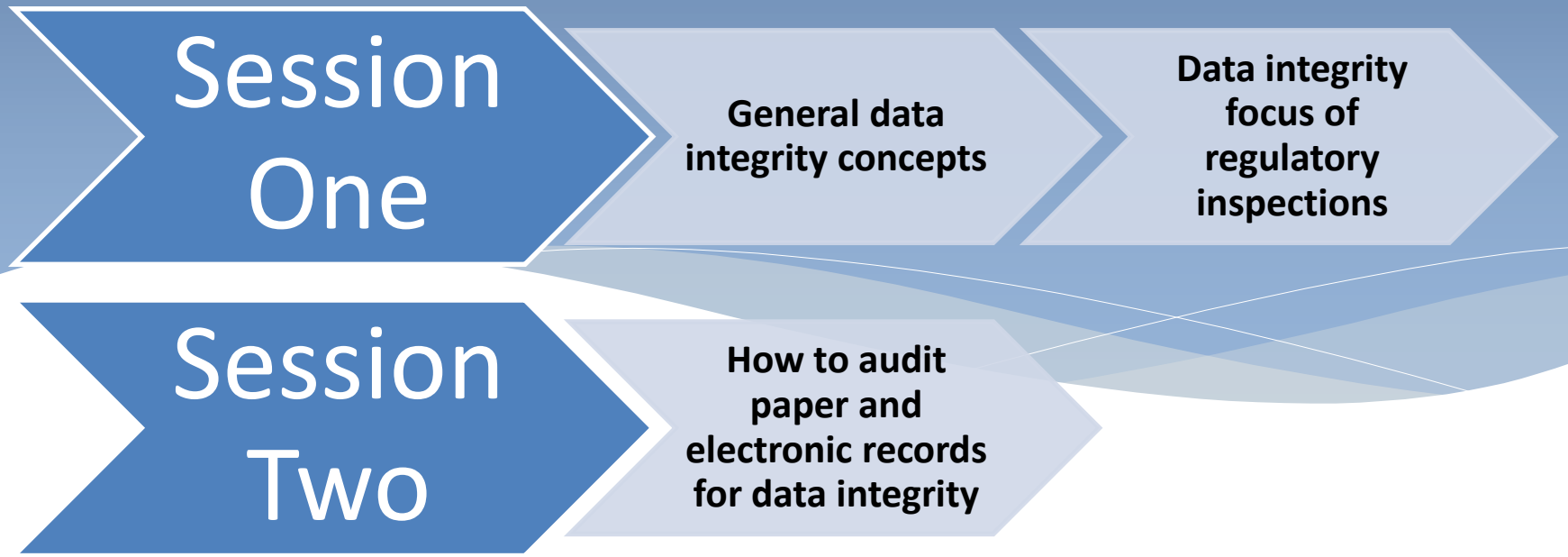
13 October 2017

Preparing for Successful Data Integrity Audits

- U.S. Food & Drug Administration and other regulatory agencies found major issues beginning in 2014

- Data Integrity has been a major concern for pharmaceutical and medical device companies since 2014

Preparing for Successful Data Integrity Audits



How to Audit Electronic and Paper Records for Data Integrity

October 12 - 13, 2017

How to Audit for Data Integrity

- Every quality audit is a data integrity audit.
  - Outside auditors have the lowest probability of finding Data Integrity Issues
  - Internal auditors have the highest probability of finding DI Issues

How to Audit for Data Integrity

Request auditee to provide at opening meeting:

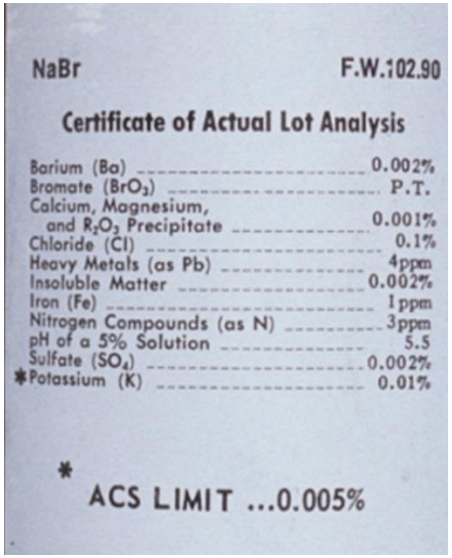
- List of all GMP computerized systems

Laboratory	• LIMS (Laboratory Information Management System) • Chromatography, including HPLC, GC • Standalone vs. networked systems
Manufacturing	• Manufacturing Requirements Planning • Building Automation Systems – monitor and alarm for environmental conditions • Automated production equipment
Enterprise/ Quality System	• Complaints, training, deviations, change control, document control
Data Storage	• Backups, archiving, retrieval of data after retirement

How to Audit for Data Integrity

Request auditee to provide at opening meeting:

- Procedures for laboratory data generation, review, and approval; Certificate of Analysis generation
- Certificate of Analysis (CofA) for specific released batch
  - Select a test that uses computerized systems
  - Trace from generation of data to CofA



NaBr F.W.102.90

Certificate of Actual Lot Analysis

Barium (Ba)	0.002%
Bromate (BrO_3)	P.T.
Calcium, Magnesium, and R_2O_3 Precipitate	0.001%
Chloride (Cl)	0.1%
Heavy Metals (as Pb)	4ppm
Insoluble Matter	0.002%
Iron (Fe)	1ppm
Nitrogen Compounds (as N)	3ppm
pH of a 5% Solution	5.5
Sulfate (SO_4)	0.002%
*Potassium (K)	0.01%

* ACS LIMIT ...0.005%

How to Audit for Data Integrity

Request auditee to provide at opening meeting:

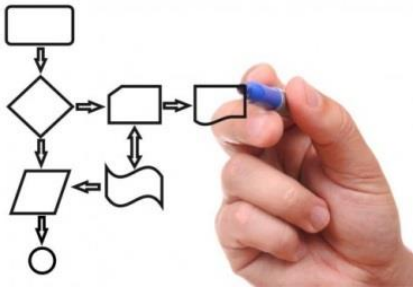
- Procedure for providing, changing, and removing user access to e-systems
- Procedure for investigating deviations
    - Does the procedure include how to address data integrity issues?

If you have concerns about putting instructions for how to handle DI issues into an SOP, know that all companies have some type of DI occurrence. It's part of human nature.

How to Audit for Data Integrity

<u>During opening meeting, select automated test from CofA</u>:

- For specific instrument:
  - SOPs for use of equipment, data archival, system administration, user access/security levels
  - Qualification of equipment showing how aspects of system use were qualified
  - Flowchart of data flow for computerized system, including data backup and archival
    - Who has access to modify or delete data from generation to archival?



How to Audit for Data Integrity

Data Governance/Data Management:

- Procedure/Program/Plan for Data Integrity
  - Computerized systems not fully compliant?
    - Gap analysis and remediation plan

- Employee training on DI principles and their responsibilities

How to Audit for Data Integrity

Data Governance/Data Management:

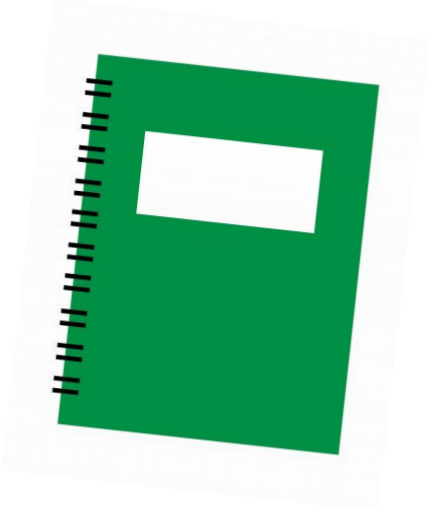
- Oversight of contractors and suppliers
  - Ensure contract laboratories and manufacturers have Data Integrity program and procedures
  - DI included in audits of contractors and suppliers
  - DI included in quality agreement with contractors and suppliers

- DI included in all Internal Audits

How to Audit for Data Integrity

During audit walkthrough, for selected system:

- Ask for system administrator, user, and second person reviewer to be present
- Ask for demonstration of system to generate, manipulate, and review data
- Review related paper logbooks
  - Equipment maintenance
  - Equipment use



How to Audit for Data Integrity

During audit walkthrough:

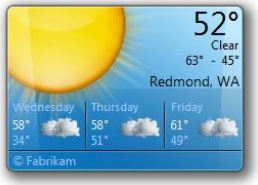
- Review configuration settings for computerized system
  - Password changes:
    - Required to change at first logon
    - Number of days before required to change
  - Users with specific access types
    - Generic system administrator username should not be enabled
    - Number of people with system administrator access (should be minimal)
    - Which people have system admin access (personnel with responsibility for data generated?)
  - Functions that specific access types (e.g., reviewer, analyst) can perform

How to Audit for Data Integrity

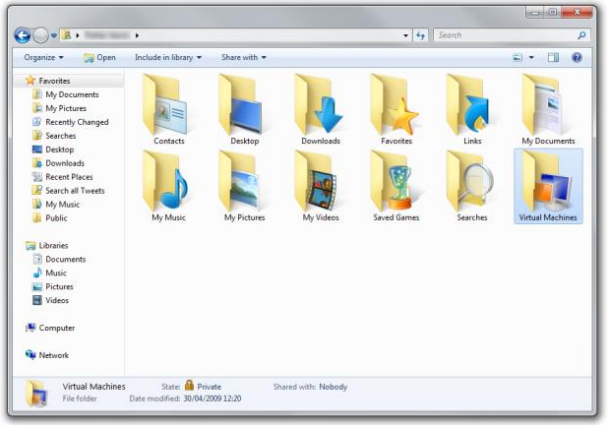
During audit walkthrough:

- Users with active accounts – current employees?
  - Training and access approval records
- Unique username/password (not shared)
  - Recorded password - under keyboard, behind monitor, in drawers
- Audit trail turned on; users cannot turn it off
- Contents of trash can
  - Data files that did not pass testing specifications

- User ability to change computer or server time/date



How to Audit for Data Integrity



<u>During audit walkthrough:</u>

- Data folders & files
  - Look at data chronologically
    - Aborted runs – reason documented in e-record or paper record
    - Sequential files with same or slightly modified name
  - Files hidden in folders separate from official test data
  - Dates and times on files
  - Tests performed match paper use logbooks for instrument

How to Audit for Data Integrity

During audit walkthrough:

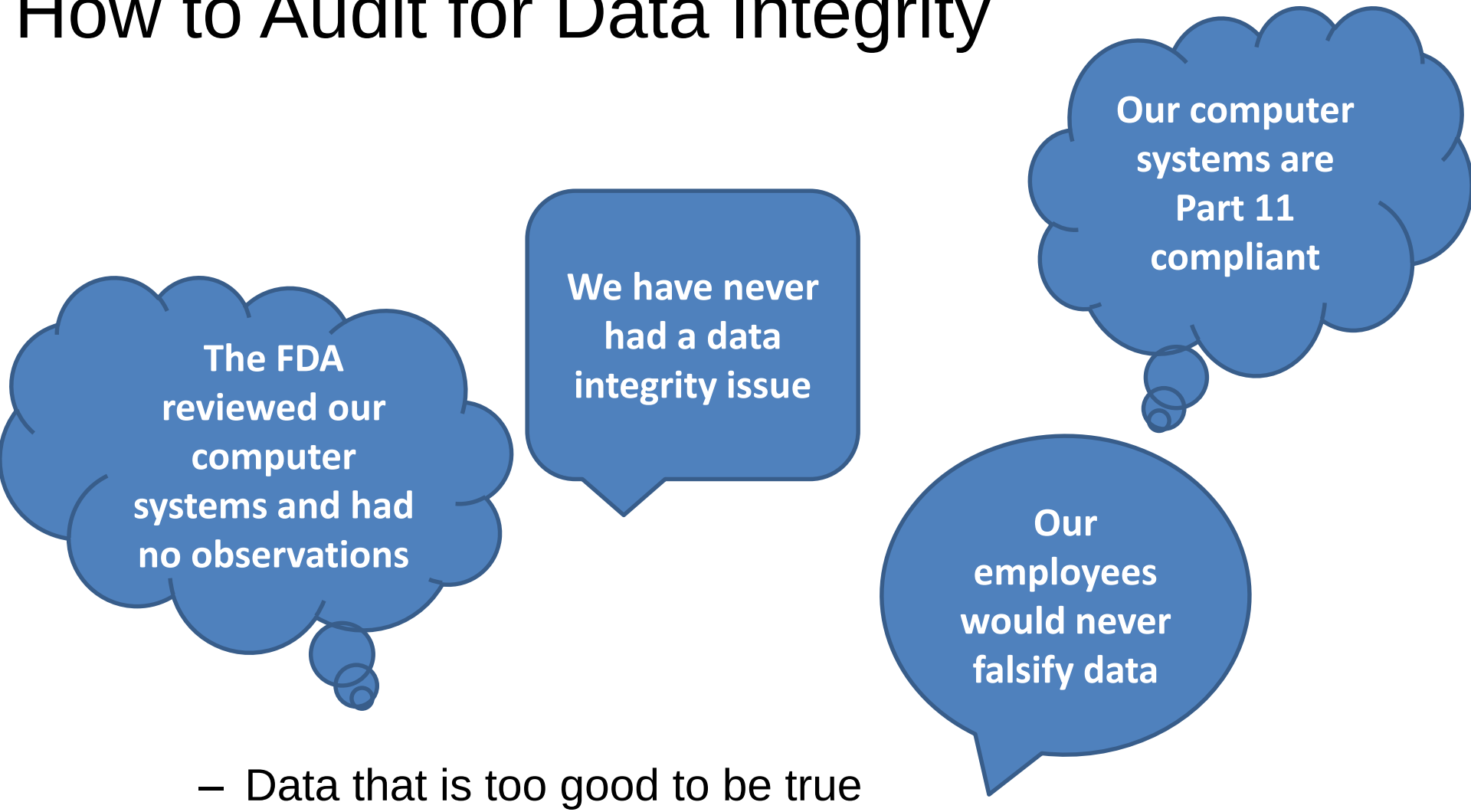
- Paper records:
  - Documents posted, on counters, in trash cans, in drawers
  - Personal notebooks in production and laboratory areas
    - Do they include GMP information?
  - Controlled issuance and reconciliation of laboratory forms
  - ALCOA plus principles

ALCOA-plus

How to Audit for Data Integrity

- Management Responsibility
  - Work environment:
    - Staff encouraged to communicate failures and mistakes, including data reliability issues
  - Corrective and preventive actions taken
  - Ensure adequate information flow between staff at all levels
  - Actively discourage management practices that might inhibit the active and complete reporting of such issues
    - Hierarchical constraints
    - Blame cultures

How to Audit for Data Integrity



- Data that is too good to be true
- Paper records from computerized systems are mistakenly considered original (raw) data although they do not include metadata

How to Audit for Data Integrity

- Auditors need to determine:
  - Is occurrence of a data integrity issue isolated or a pattern for an individual, operational unit, or an entire organization?
  - Is occurrence a bad practice or intentional manipulation?

What is the risk to the product quality?

Additional Sources of Information

- **MHRA GMP Inspection Deficiency Data Trend 2016**
  https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/609030/MHRA_GMP_Inspection_Deficiency_Data_Trend_2016.pdf
- **Current Expectations and Guidance, including Data Integrity and Compliance With CGMP**, Sarah Barkow, PhD, Team Lead, CDER/OC/OMQ Guidance & Policy, ISPE DI Workshop, June 5, 2016
  https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm518522.pdf
- **Compliance Trends**, Paula R. Katz, J.D., Dir., Mfg. Quality Guidance & Policy Staff, Office of Mfg. Quality, Office of Compliance, CDER, India Pharmaceutical Forum, Mumbai, India, Feb. 24, 2017
  https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM549445.pdf

Additional Sources of Information

- **Regulatory Perspective: Data Integrity Guidance,** PDA Data Integrity Workshop, Paula R. Katz, J.D., Dir., Mfg. Quality Guidance and Policy Staff, CDER/Compliance, Sep. 14, 2016
  https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM539554.pdf

- **Takahashi: Look Out for These Data Integrity Issues**, Pink Sheet & Gold Sheet, by Bowman Cox (subscription required), Mar. 28, 2014

- **FDA GMP Warning Letters Review: API Supplier Warnings Surge on Data Integrity Concerns**, Pink Sheet, by Bowman Cox (subscription required), Apr. 26, 2017

Additional Sources of Information

- **FDA GMP Warning Letters Review: Foreign Drug Product Firms Hit Hard on GMP Basics**, Pink Sheet, by Bowman Cox (subscription required), Apr. 27, 2017

- **Data Integrity: Surveying the Current Regulatory Landscape**, Pharmaceutical Online, Barbara W. Unger, Aug. 4, 2016

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Questions?