Data Integrity:
Is Complacency Putting You At Risk

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Data Integrity Definitions

- Definition used by FDA for internal training:

  "Data are of high quality if they are fit for their intended uses in operations, decision-making and planning . . . as data volume increases, the question of internal consistency within data becomes paramount…."

- **ALCOA** acronym used by FDA to define expectations:

  Attributable
  Legible
  Contemporaneous
  Original
  Accurate

Data Integrity Violations Come in Many Forms

- Geographical areas ranging from domestic to international
- Firms ranging from small to large, new to well established
- Involvement ranging from an individual employee to a conspiracy
- Frequency of occurrence ranging from isolated to pervasive
- Observed in data generated premarket and postmarket
- Data types ranging from medical data to production data, paper based records and electronic records
- Acts of commission as well as omission
- Cases involve all types of regulated products
- Identified via regulatory inspections ,Whistleblowers, internal findings, other…

Importance of Data Integrity

- Continues to be a priority
  - FDA Investigators receive specialized training to detect data integrity, data manipulation, and fraud
- Regulators must be able to rely upon the accuracy and completeness of data / information generated to meet applicable regulatory requirements
- Assurances of product safety, identity, strength, purity, and quality are dependent on the validity of data and information obtained
- Data integrity violations
  - Erode public confidence
  - Impugn product quality and patient safety
  - Have a devastating impact on implicated organizations

Importance of Data Integrity

- Depending on the facts of the situation, objectionable FDA Inspection findings may result in the following:
  - Recall
  - Warning or Untitled Letter
  - Import Alert
  - Application Withdrawal
  - Application Integrity Policy Invocation
  - Injunction
  - Seizure
  - Criminal Prosecution
  - Civil Money Penalty
  - Debarment from participating in certain FDA-regulated activities

These are not alternative remedies

Data Integrity Lifecycle Framework

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FDA Investigator Instructions

"If a firm is keeping electronic records, determine if they are in compliance with 21 CFR Part 11. At a minimum, ensure that:

(1)the firm has prepared a plan for achieving full compliance with part 11 requirements and is making progress toward completing that plan in a timely manner

(2)accurate and complete electronic and human readable copies of electronic records, suitable for review, are made available

(3)employees are held accountable and responsible for actions.

If initial findings indicate the firm's **electronic records may not be trustworthy and reliable**, or when electronic recordkeeping systems inhibit meaningful FDA inspection, a more detailed evaluation may be warranted."

- FDA Enforcement Compliance Policy Manual, Attachment A
http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133927.htm

Data Integrity at Creation

Example Questions to Ask

- Have personnel been trained on good documentation and good data integrity practices?
- How does the firm ensure that analysts enter ALL test data, not just the passing test results?
- For transcribed data, what verification processes are in place?
- When data is scanned, how does the firm ensure the evidentiary admissibility of the scan (e.g., “certified or true copy”)?
- Has the system been validated and under change control?
- Did validation just consist of IQ\OQ? Did it include data field boundary testing? Report print-out verifications?

Data Integrity During Active Usage

Example Questions to Ask

- Did the firm verify computerized calculations *prior* to usage on the data?
- Does the firm claim to use "paper records only" but then actively use e-records to release batches, make safety and efficacy decisions, etc.?
- How does the firm ensure that previously recorded SUSAR data cannot be altered when reviewed?
- At what point do lab supervisors compare lab notebook entries to HPLC or GC audit trails? How do they document this review?

Data Integrity While Semi-Active

Example Questions to Ask

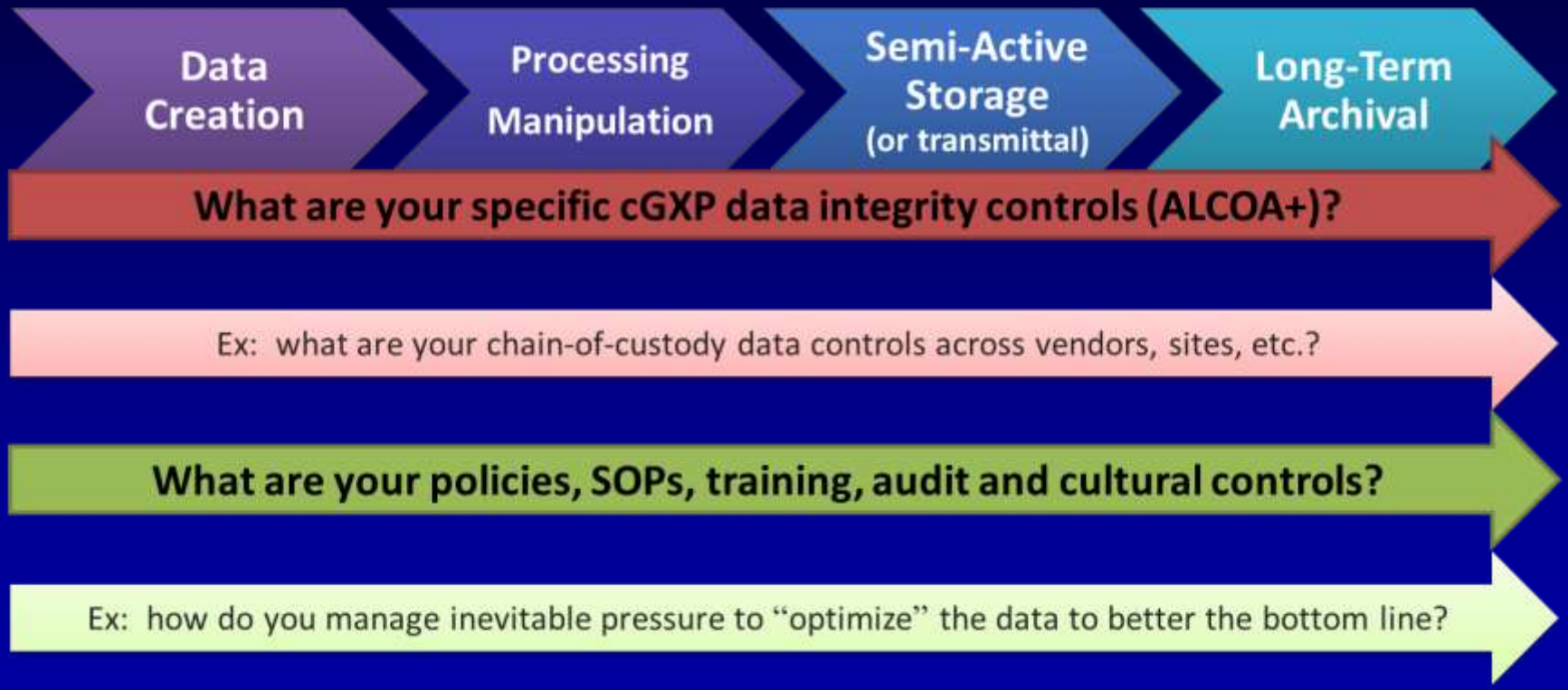
- Does the firm retain raw lab data/digital clinical source data, manufacturing raw data along with context (e.g., metadata)?
- What were the process checks undertaken prior, during, and after clinical trial database lock? Transmittal to the sponsor?
- Does the firm have traceability on its complaint records to ensure that none of the data is left out of any later analysis (such as for an APR or QSMR) or when transmitted?

Data Integrity of Archives

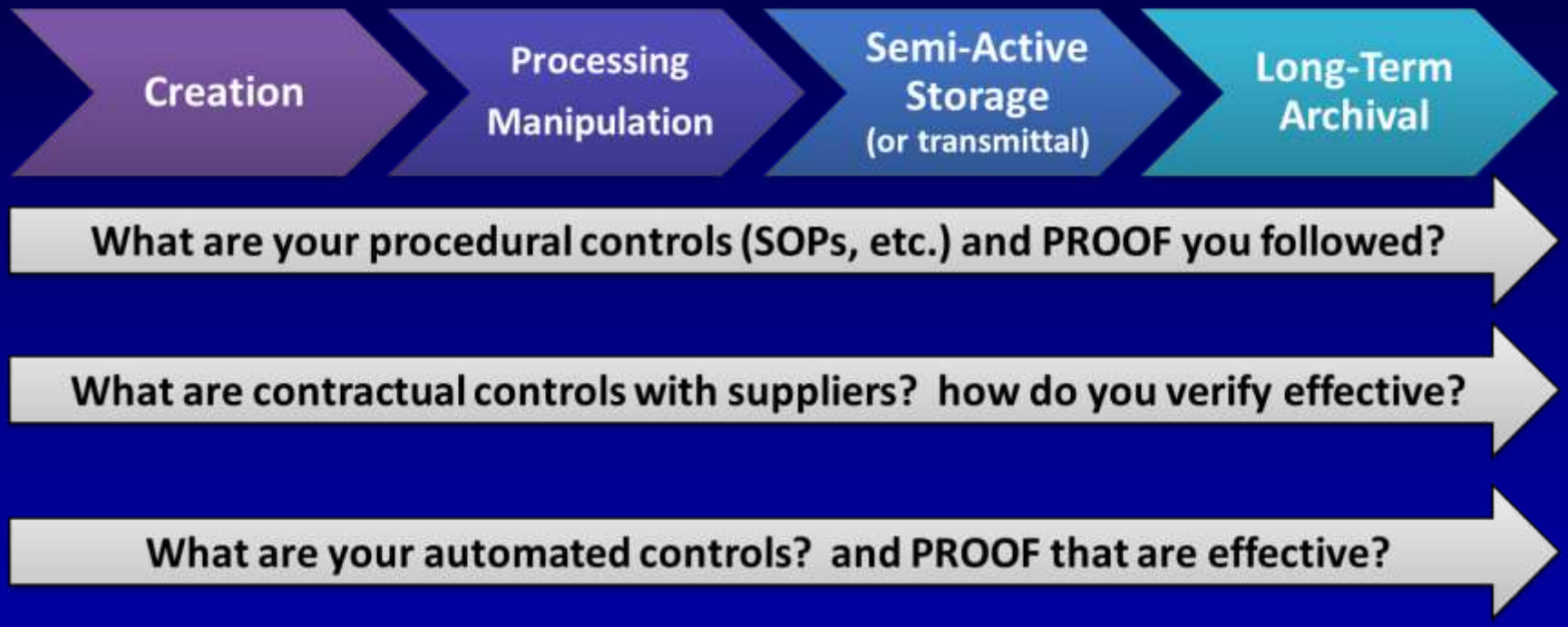
Example Questions to Ask

- If the firm uses a storage vendor, is the vendor qualified?
- How often does the firm sample its long-term archives to ensure continuing storage suitability and prevent data deterioration?
- What controls does the firm have on retained record destruction to prevent inadvertent loss of required data?
- Does the firm have a digital media migration strategy?

Data Integrity Lifecycle Controls



Data Integrity Lifecycle Controls



Data Integrity
A GCP Clinical Trial Perspective

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Data Integrity Violations

BIMO Inspections Classified FY 2014

Center[1]	CI	IRB	Spon/Mon/CRO[2]
CBER	109	8	3
CDER[3]	472	91[4]	83
CDRH	203	52	51

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection – failure to report AEs and informed consent issues

- Inadequate monitoring
- Failure to bring investigators into compliance
- Inadequate accountability for the investigational product
- Failure to obtain FDA and/or IRB approval prior to study initiation

Data Integrity Violations

What types of violations may lead to delay in approval or a complete response letter?

- Sponsor/CRO: Data entry quality control
- Sponsor/CRO: Database changes after initial database lock and study unblinding
- Investigators: Systemic deficiencies *Persistence of critical errors across study sites raises "questions about the reliability of data at other, non-inspected sites" and "sponsor oversight".*
  - Enrollment of subjects who violate eligibility criteria
  - Inaccurate administration of the test product
  - Omission of procedures critical to interpret study endpoint
    - Ann Meeker-O'Connell and Leslie K. Ball http://www.fdli.org/resources/resources-order-box-detail-view/current-trends-in-fda-inspections-assessing-clinical-trial-quality-an-analysis-of-cder-s-experience

Self-Identification

How to prevent and identify potential clinical data integrity issues

- *Real* diligence in selecting and engaging
  - Clinical investigators and sites
  - Site monitors
  - Clinical research organizations
  - Internal or external parties responsible for database management
- *Real risk-based site and data monitoring* (not less monitoring)
- Audits – early during trial
  - Who and what data will be audited, who sees results, who is accountable for decision-making?
  - Who is responsible for remediation (including GCP "CAPA")
- Quality by Design

Potential Remediation Strategies

Suggested remediation strategies, i.e., corrective actions

- Accountable, timely, and definitive remediation plan: what must be corrected, by whom, when, and timeline for repeat monitoring (and audit, if applicable)
- Prioritize remediation by risk
  - Immediate risk to human subject safety & welfare, breach of eligibility, failure to administer test product per protocol, failure to conduct evaluations critical to major efficacy & safety endpoints (including under-reporting of adverse events)
  - Data falsification
- For site deficiencies, directly communication with the clinical investigator – not just study coordinator – is critical
- As sponsor, ensure the prompt "securing of compliance" of investigator with investigational plan or termination.

FDA Initiatives

FY2015 BIMO "**Specialization Action Plan**"

- **Working group**, including CDER, CBER, CDRH among other centers, Office of GCP, Office of Regulatory Affairs (ORA), Office of Regulatory Operations and Policy (OGROP)
- **Task**: Evaluate and recommend development plan for a cross-center specialized BIMO program with dedicated investigators

> The working group believes, first and foremost, a specialized BIMO program with dedicated BIMO investigators will result in higher quality BIMO inspections. Increased specialization and dedication of investigators in the BIMO program will result in investigators gaining more in-depth knowledge of BIMO regulations, policies and industry practices related to BIMO, and therefore, will allow them to refine the unique skills needed to conduct these inspections. Specialization and dedication will also provide for an enhanced professional development program for ORA investigators, including a robust curriculum of specialized training and practical experience for ORA investigators interested in specializing in BIMO or ascending to management positions within the program.

Data Integrity
A GMP Perspective

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Data Integrity Violations

Data integrity issues in GMP span the entire spectrum of documents created to capture the performance of GMP-governed tasks and related operations, including, but not limited to:

- Deliberate wrongful conduct
  - Records falsification such as recording passing results in place of failing results; recording data after the fact when it was not recorded contemporaneously; back dating documents; forgery of signatures or initials; deliberately discarding raw data; making unauthorized changes in computerized data or meta data, and other similar acts
  - Motivators: "Achieve Gain or Avoid Pain" almost always involved at some level
- Conduct related to lack of training or incompetence such as:
  - Use of scrap paper to record data, discarding source data, failing to note deviations that occur; other similar instances
- "Innocent" conduct that results in inaccurate data recording or loss of data, such as
  - Wrong dates or times entered on documents unintentionally
  - Mistakenly entering data from one product or batch on a record for another product or batch
  - Misplacing or mis-filing records

Self-Identification

Effective measures that can be taken to minimize these issues or detect them when they occur include:

- Establishing clear policies about the importance of data integrity
- Establishing severe consequences for deliberate wrongful conduct, up to and including termination
- Providing “safe” means for employees to report data integrity problems without fear of retaliation
- Providing education and training in good documentation practice to all employees
- Training operations managers, QA personnel, OJT trainers and internal auditors to effectively audit data integrity and include it in routine audit planning

Potential Remediation Strategies

When **deliberate** data integrity problems are known or suspected:

- Obtain competent investigative assistance from third party, e.g.:
  - Consultant with investigative experience
  - Attorney
- Establish the scope of the problem
- Bracket dates when suspect acts occurred
- Determine product(s) effected
- Develop internal investigation plan
- Identify / isolate suspect documents
- Locate raw data
- Compare raw data to summaries
- Tabulate data and sort by each variable
- Identify / resolve inconsistencies

Potential Remediation Strategies

- Consider possible motivation – "Achieve Gain or Avoid Pain" – where might this be operative?
- Examine organizational structure
- Examine responsibilities and duties of each employee
  - Identify employee(s) suspected of being involved
  - Consider managers, directors, senior personnel
  - Conduct interviews
- Determine scope of involvement of each employee

Potential Remediation Strategies

- Examine all work of suspect employees
- Determine root cause of problem, e.g.:
  - Poorly defined responsibilities
  - Training gap
  - Incompetence
  - Deliberate wrongful acts
  - Financial gain
  - Other causes
- Take personnel action where necessary and justified by facts

FDA Initiatives

- Data integrity has always been a major concern for FDA
- Historic examples:
  - G.D. Searle animal safety testing investigation, early 1970s, and Industrial Biotest investigation, same period, led to the promulgation of the GLP regulations (21 CFR Part 58)
  - Generic drug scandal, late 1980s, later expanded from the generic sector to innovator companies. Led to the passage of the Generic Drug Enforcement Act, gave FDA debarment authority, led to the nationwide adoption of the preapproval inspection program as it currently exists
  - Many other similar examples
- Current FDA reemphasis on data integrity related largely to globalization of the industry and new issues created by advances in automation in the lab and drug production, creating new vulnerabilities

FDA Initiatives

- Many recent Warning Letters cite serious data integrity issues, for example:
  - Marck Biosciences, Kheda, India
  - Wockhardt Limited, Aurangabad, India
  - Yunnan Hande Bio-Tech. Co. Ltd., Kunming, Yunnan Province, China
  - Several others; search on ”integrity” in the FDA web site domain for Warning Letters for examples
- FDA doing directed training for Investigators in detection of data integrity issues, emphasis on computer systems, but data integrity is not exclusively a computer system issue
- FDA officials have publicly stated* they are reexamining internal policies on when Warning Letters can issue to permit issuance in certain situations where Untitled letters currently are sent

(*Source: Statements made by CDER Compliance staff at *GMP by the Sea* and *PDA-FDA Joint Regulatory* conferences, 2015)

Hypothetical GCP Scenario

Interactive Discussion

GCP Scenario

During a monitoring visit to a clinical site for a double-blinded RCT, the study monitor observes that:

- Two subjects, who each have a protocol "Exclusion," were enrolled and have already been administered the 1st cycle of test drug or placebo
- For a different subject, the site Principal Investigator signed and dated a CRF form for a protocol-mandated visit; however, he was out-of-town that day

What Would You Do?

The site is a “big enroller” and the P.I. is a key opinion leader. You want to get things back on track. Which of the following tactics would you initiate at this site?

a) Review the site IRB requirements for notification.

b) Insert “protocol violation waivers” in the study file for the subjects with exclusion criteria, and continue both in the trial

c) Break the blind for the 2 subjects to ensure they’re only getting placebo

d) Ask the study coordinator to “keep an eye on” the investigator

e) Remove the CRF for the subject’s visit on PI’s vacation day and enter a new CRF to categorize the event as a “missed visit”

f) Schedule an urgent meeting with the site P.I.

What Would You Do Next?

Following an urgent one-on-one visit with the P.I., follow-up monitoring six weeks later shows probable “cloned” entries for 3 subjects for vital sign entries that are mandatory to be done 30 minutes after each cycle of test drug administration. Also, one serious adverse event was not reported to Sponsor per protocol or to IRB per its requirements. Which would you now consider?

a) Reprimand and/or replacement of the study coordinator
b) Provision additional training to the site
c) Termination of the investigator
d) Notification to DSMB
e) Initiation of a targeted audit of other sites

Hypothetical GMP Scenario

Interactive Discussion

GMP Scenario

During a regulatory inspection, it was observed that:

"Quality oversight was lacking resulting in significant GMP deficiencies. Management was not aware of the QC laboratory practice of sometimes conducting trial test runs prior to an official run – all of which used real product. This resulted in OOS data results not being recorded and OOS investigations not being conducted/reported."

How Was this Identified?

Regulatory health agency inspectors compared:

- laboratory notebook recordings by analysts
- HPLC audit trail start/stop times and dates
- laboratory sample receiving tracking and disposal records
- overall procedures (SOPs and work instructions) for conducting the tests, preparing samples, etc.

What Would You Do?

Which TWO of the following tactics would you take to try to help fix – and prevent in the future – this issue?

a) Retrain all laboratory analysts to record all equipment usage, not just successful runs

b) Implement a new procedure whereby the lab supervisor conducts a periodic spot-check of lab notebooks vis-à-vis system audit trails

c) Update internal quality audit procedures to conduct periodic spot-checks of lab notebooks vis-à-vis audit trails

d) Retrain lab analysts to only use industry standard solutions for trial test runs