Data Integrity
Denial Ain’t Just a River in Egypt: Panel Discussion

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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
FDA Enforcement Action

- FDA will take action against companies that commit data fraud or provide false information to the agency

- “Companies must provide truthful and accurate information in their marketing applications…The American public expects and deserves no less.”

Janet Woodcock, M.D., Director, CDER
February 25, 2009 FDA News Release
Importance of Data Integrity

• Continues to be an FDA priority
  – 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
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
- Acts of commission as well as omission
- Cases involve all types of regulated products
- Identified via regulatory inspections, whistleblowers, internal findings, other…
• Using FDA’s findings as a standard, has your firm evaluated internal data integrity systems to determine if similar underlying cGMP/QSR deficiencies exist and whether data manipulation may have occurred?
• Is your company’s prevailing mindset that data integrity problems only happen to “other people”?

Is your firm in denial?
Panel Discussion Topics

• The types of data integrity violations identified during recent FDA Inspections
• The regulatory, civil, and criminal penalties associated with data integrity violations
• FDA expectations for review of electronic data and information
• How to conduct internal and external audits from a data integrity perspective
• Actions to take if data integrity concerns are identified within your company or at a contractor
Data Integrity Considerations

John Avellanet
Managing Director & Principal, Cerulean Associates LLC
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
ICH Data Integrity

“…Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly....”

- 2008 FDA GCP Training for Investigators, Drs. David Lepay & Jean Toth-Allen, OGCP
- 2011 FDA presentation on PAIs of Biologics, Anastasia G. Lolas, CDER
- quote from ICH E6 § 5.1 Quality Assurance and Quality Control
Example Considerations

• 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 copy”)?
• Has the system been validated and under change control?
Example Considerations

- 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?
PDF corruption of 6 day old batch record discovered when QC double-checked the PDF prior to releasing the last of the batch

As of September 2014, firm remains **unable to print or re-save the file** despite direct help from Adobe
Example Considerations

- Does the firm retain raw lab data/digital clinical source 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?
Database corruption from SQL-based clinical EDC at CRO after trial lock

As of October 2012, only the descriptors (i.e., “text” “number”, etc.) of data that should have been there could be recovered
Example Considerations

- 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?
“Documents and e-data spend more than 80% of their lifespan in an archived (e.g., stored) state.”

- ARMA International
Graphical product insert from 2005 with detailed risk information on it.

As of December 2012, this is **all that the company could recover** from its approved electronic proof.
**Data Integrity Lifecycle Controls**

- **Data Creation**
- **Processing Manipulation**
- **Semi-Active Storage (or transmittal)**
- **Long-Term Archival**

What are your specific cGXP data integrity controls (ALCOA+)?

Ex: what are your chain-of-custody data controls across vendors, sites, etc.?

What are your policies, SOPs, training, audit and cultural controls?

Ex: how do you manage inevitable pressure to “optimize” the data to better the bottom line?
Translation:

Good data integrity requires

cross-functional framework

risk-based philosophy

pragmatic mentality
What Controls Do You Have So…

FDA can rely upon your data?

Physicians can rely upon your data?

Patients can rely upon your data?

Investors can rely upon your data?
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Clinical Data Integrity Violations – A GCP Perspective

Beverly Lorell, MD, FACC
Senior Medical & Policy Advisor, King & Spalding LLP
Scientific Data Integrity: A Hot Issue

- Many scandals with intense media attention
  - Pharmaceutical and medical device clinical studies, as well as cutting edge basic science

- Globalization of clinical trials and complexity

- Eroding public confidence

- Far-reaching repercussions
  - Delay in regulatory review and approval, retractions of public data, impact on clinical guidelines/standards

As examples,
"Rise of the Retractions"

- Investigator misconduct accounts for ~50% of retractions.
Clinical Data Integrity: Recent Scrutiny

**Chinese Trial Misconduct Delayed Bristol-Myers Medicine**

By Drew Armstrong | 2013-07-09T00:12:03Z

Drugmakers have increasingly been turning to China for large clinical trials because they’re cheaper and there’s a bigger population of subjects to draw on.

Now U.S. regulators have stepped in, questioning sloppy data and irregularities from the world's most populous country.

**Bristol-Myers Squibb Co. (BMY) and Pfizer Inc. (PFE)'s** blood thinner Eliquis, approved in December, was stalled for nine months because of misconduct, errors and an alleged cover-up attempt at a Chinese trial site overseen by Bristol-Myers, according to documents posted by the U.S. Food and Drug Administration. The delay came after the company told the FDA that patients got the wrong medicine, records were secretly changed and "serious adverse events" went unreported, the documents show.

**Evotec announces update on DiaPep277®**

**The complex challenge of undoing erroneous research**

Graham D. Cole® and Darrel P. Francis

International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, 59-79 Fulham Road, London SW10 9LY, UK

Hamburg, Germany - 08 September 2014: Evotec AG (Frankfurt Stock Exchange, Prime Standard DE 000 566480 9, WKN 566480) was informed that US company Hyperion Therapeutics, Inc. ("Hyperion") has terminated the development of DiaPep277® for newly diagnosed Type 1 diabetes.

In a press release published by Hyperion on 08 September 2014 at market opening in the US, the states that it has uncovered evidence that certain employees of Andromeda Biotech, Ltd. ("Andromeda"), which Hyperion acquired in June 2014, engaged in serious misconduct, involved with the trial data of DiaPep277®. Hyperion announced that it will complete the DIA-AID 2 Phase 3 trial, but will terminate further development in DiaPep277®.
Clinical Data Integrity: Recent Scrutiny

Novartis Unit Charged By Japan Over Research Data

The clinical research scandal in Japan has now formally ensnared Novartis (NOVN.XT +0.43%). Prosecutors have brought charges against the drug maker’s local unit, and re-arrested a former employee for allegedly altering data in a study involving the Diovan blood pressure drug in order to make the medicine appear better than rival treatments, The Wall Street Journal writes.

Former Novartis Employee Arrested in Japan
Prosecutors Allege He Illegally Altered Research Data

By KANA INAGAKI
June 11, 2014 2:48 a.m. ET

TOKYO—Japanese prosecutors on Wednesday arrested a former Novartis AG employee on suspicion of falsifying research data, deepening a scandal over the Swiss drug giant’s practices in its second-largest market.
Will YODA End Debate Over rhBMP-2?

Independent review finds BMP no better than graft for lumbar spinal fusion

Terry Stanton

The word is in from the Yale Open Data Access (YODA) project: recombinant human bone morphogenetic protein (rhBMP-2), the product marketed as Infuse® by Medtronic, Inc., offers no appreciable benefit over autograft in spinal fusion surgery. The judgment is the result of an unprecedented move by the manufacturer, which turned over all patient data to the YODA project for review.

YODA’s findings

Their reports, published in the June 18, 2013, issue of Annals of Internal Medicine, state that rhBMP-2 “provided little or no benefit compared with bone graft and may be associated with more harms, possibly including cancer.” Furthermore, the YODA groups found that the study authors underreported complications for both on-label and off-label indications and that they “selected analyses and results that favored rhBMP-2 over ICBG.”
FDA Bioresearch Monitoring
Objectives

• To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials

• To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications, and

• To assess compliance with FDA’s regulations governing the conduct of clinical trials
Most common Sponsor deficiencies

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

Most common Investigator deficiencies

- Failure to follow investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for investigational product
- Failure to comply with IRB requirements
- Inadequate human subjects protection (failure to report AEs and obtain informed consent)
Recent Trends - Warning Letters


• Failure to maintain records and accurately report serious adverse events

3. Failure to maintain required records under § 812.140(b)(4) and make the reports required under § 812.150(b)(1) through (3) and (5) through (10) [21 CFR 812.2(b)(1),(v)].

As sponsor of an investigation you are responsible for maintaining specific records that are accurate, complete, and current, and preparing and submitting specific reports that are complete, accurate, and timely. You failed to adhere to the above-stated regulation. Examples of your failure to adhere to these requirements include, but are not limited to, the following:

- Records concerning many adverse device effects were not available for FDA inspection, nor were the unanticipated adverse device effects submitted to FDA as specified by this regulation. Specifically, you failed to report several serious adverse events including:
  - breast cancer (6 months after MME),
  - a death related to an undiagnosed cancer (4 months after MME),
  - a death of unknown etiology (possible TIA 30 days after MME), and
  - a subject who withdrew from the study and was also newly diagnosed with cancer.

• Violative promotion of investigational device

2. Failure to comply with FDA regulations that prohibit promotion of an investigational device until after FDA has approved the device for commercial distribution and representation that an investigational device is safe or effective for the purposes for which it is being investigated [21 CFR 812.2(b)(1),(vii)].

A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not promote or represent that an investigational device is safe or effective for the purposes for which it is being investigated. You have failed to adhere to this regulation. Examples of this include, but are not limited to, the following:

On your website, http://www.amri-intl.com, (and the brochure included on your website), the investigational device is being represented as safe and effective. The website states:
Recent Trends - Warning Letters

“Advanced Interventional Pain Center” – Mar. 14, 2014

• FDA determination that device is Significant Risk (SR) – enrolling patients before submitting IDE to FDA

  1. Failure to submit an IDE application to the FDA and obtain approval of the IDE prior to allowing subjects to participate in the investigation [21 CFR 812.20(a)(1), 21 CFR 812.42, and 21 CFR 812.110(a)].

On April 18, 2013, FDA notified you as the sponsor that the (b)(4) device is a significant risk (SR) device, as defined in 21 CFR 812.3(m). Therefore, an IDE application approved by FDA is required before subjects are enrolled and an investigation can begin.

• Failure to maintain accurate and complete records, including source documents and financial disclosure under Part 54

  3. Failure to maintain accurate, complete, and current records related to the investigation [21 CFR 812.140(a)(2), 21 CFR 812.140(b)(3), and 21 CFR 812.140(d)].

• Failure to report deviations from investigational plan

  4. Failure to conduct the investigation according to the investigational plan and failure to report deviations from the investigational plan [21 CFR 812.110(b)].
Many Portals for Scientific Integrity Allegations

- FDA advisory committee meetings
  - Clinical Event Committee – event adjudication;
  - Data Monitoring Board – sponsor interactions
  - Geographic region data disparities

- Clinical investigators and medical journals
  - Medical journals (e.g., BMJ, NEJM, Lancet, NEJM)
  - Direct interaction with media and/or members of Congress

- Media and other watchdogs
  - Forbes, WSJ, NYT
  - ProPublica, Retraction Watch, and more!
FDA Initiatives

• Falsification of data/omission of material facts
  – “Reporting Information Regarding Falsification of Data” - Final Rule pending

• Globalization of clinical trials
  – “Human Subject Protection; Acceptance of Data from Clinical Studies for Medical Devices” - Final Rule pending

• Sharing of GCP inspectional data
  – “FDA-EMA GCP Initiative” and other programs

• Risk-based monitoring
  – “Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring” - New guidance
Challenges for Sponsors

“Sponsors are responsible for selecting qualified investigators... and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation.” 21 C.F.R. 812.40

- During an ongoing clinical investigation, when and how should internal GCP audits be conducted?

- When do issues of potential data integrity rise to level of “significant new information about an investigation?”

- When and how should voluntary disclosures be made to FDA Office of Compliance?
Data Integrity Violations – A GMP Perspective

David Elder
Vice President – Management, Parexel International
Data Integrity

• Issues with data integrity have been the downfall of several companies. There are few things in business (or in life) that are more important than integrity. When any one issue is found, ALL other actions, answers, documents, records, and people become questionable.

• A few examples of recent findings....
• “Your firm frequently performs “unofficial testing” of samples, disregards the results, and reports results from additional tests. For example, during stability testing, your firm tested a batch sample six times and subsequently deleted this data”

• “Similar unacceptable data handling practices were observed in your laboratory’s conduct of gas chromatography (GC) analyses. The FDA investigators reviewed what appear to be data from “unofficial” injections … Therefore, it appears that out-of-specification data … was considered to be “unofficial,” while passing data were reported as the "official" results for the batch”
WL, November 2013, Wockhardt

• “our investigators identified your practice of performing “trial” sample analysis for high performance liquid chromatography (HPLC) analyses at your Chikalthana and Waluj facilities prior to acquiring the “official” analytical data for release and stability testing”
WL, Smruthi Organics Ltd, March 2014

• Our investigators identified calibration and media preparation records that were not authentic in that the persons that signed each record as having performed the activity were not at work on the day the work was accomplished.

• Our investigators identified the practice of performing trial injections for HPLC analyses prior to running the release and stability tests that are then reported. There was no justification for the practice of the trial preparations and injections.
Data Integrity

FDA-483, Ranbaxy-Toansa, January 2014

- Paraphrased observations (leading to extension of Consent Decree and IA to this additional manufacturing site)
  - Overwriting raw data files that had failing results
  - Test/Sample injections with failing results
  - Reported results differed from raw data
  - Backdating of records; pre-filled records
  - Samples/Records found in drawer in laboratory labeled “blank paper”
Data Integrity

December 16, 2013

- The MHRA is setting an expectation that pharmaceutical manufacturers, importers and contract laboratories, as part of their self-inspection programme must review the effectiveness of their governance systems to ensure data integrity and traceability.
  - This aspect will be covered during inspections from the start of 2014, when reviewing the adequacy of self inspection programmes in accordance with Chapter 9 of EU GMP.
  - It is also expected that in addition to having their own governance systems, companies outsourcing activities should verify the adequacy of comparable systems at the contract acceptor.
  - The MHRA invites companies that identify data integrity issues to contact: GMPIInspectorate@mhra.gsi.gov.uk

Food for Thought: Does the self-inspection/internal audit and supplier management function of a company include trained individuals capable of detecting data integrity issues if they exist?
Data Integrity Is Not Isolated To Lab Operations (Real Examples Noted)

• Applications filed with Regulatory Agencies:
  – Records in FDA Applications Contained Different Signatures for the Same Person
  – CMC Section in NDA Submitted to FDA Was Different from Copy on File at the Company. Company Unable to Verify Which Version Was Correct
  – CMC Section Contained Validation Data Reported to Be from Production Autoclave, But FDA Inspection Revealed Production Autoclave Had Not Yet Been Installed on Dates Recorded
  – Certain testing data submitted with application could not be verified from review of laboratory notebooks or electronic raw data
Data Integrity Is Not Isolated To Lab Operations (Real Examples Noted)

- Quality System Documentation:
  - Observed employee fraudulently signing weighing record for activity he did not perform
  - Supervisor created logbooks after the fact for two years (after FDA requested to review)
  - Cleaning employee was suspected of lying, so 5 FDA investigators returned to the plant during the next cleaning to simultaneously watch actual practices in five different areas. FDA confirmed employee had lied
  - Employee discarded project file (raw data, chromatograms, analytical worksheets) to hide records from detection by auditor (& company management) Entire completed original batch records for several lots were found in supervisors possession, duplicate records had been created for the document retention files
  - Entries for “tomorrow’s” batch had already been filled out
  - Desk drawer at analyst workbench contained multiple OOS worksheets that had not been reported to QA
  - Log book contained dated entries that were out of sequence
  - In-process batch record with blanks for significant steps, post-it-note created by supervisor instructing employee to fill in the blanks
Data Integrity Is Not Isolated To Lab Operations

WL, July 2014, Zhejiang Jiuzhou Pharmaceutical

- Failure to document manufacturing operations at the time they are performed.
  - When reviewing the entries in your… logbook for the days immediately prior to the inspection, our investigator found missing entries. Your operators stated that lines were left blank to later add information about cleaning events that may have occurred during a previous shift. During the inspection, our investigator found other similar instances of missing data or belated data entry in your manufacturing records. These practices are not consistent with CGMP.

  - In addition, during the inspection, one of your quality unit employees presented the investigator with a batch record containing his signature, stating that he had performed the review of this batch record. The employee later admitted that he had falsified this CGMP record and stated that he in fact had not performed the review, despite having signed the batch record as the QA reviewer and having released the batch. This data falsification and the record-keeping deficiencies described above raise doubt regarding the validity of your firm’s records.
Acknowledgement/References

- Presentation, FDLI Pharmaceutical GMP training program, July 2014, D. Elder
- Presentation/Training, R. Tetzlaff, PhD
- FDA Training Course, Drug Inspection Training, Data Integrity Section