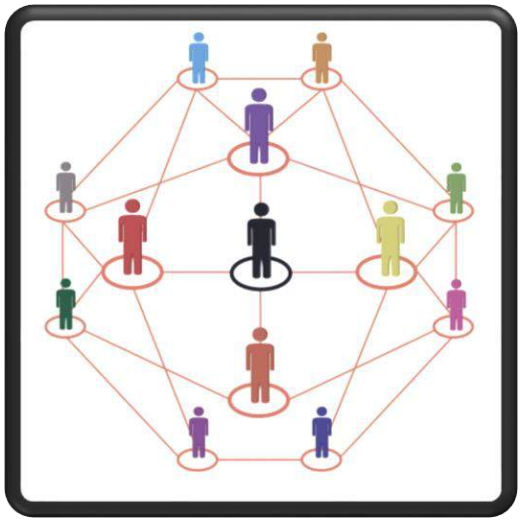

Data Integrity

Detecting & Mitigating Risk

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Topics

- The five areas where companies make mistakes with their data
- Key steps for success
  - Tips for securing/validating data
  - Avoiding data mistakes
- Tips for designing & implementing data integrity programs

What types of things can be, or lead to…

Data integrity issues?

The Barr Decision: Legal Precedent for Data Integrity

- Analysts must always follow a written procedure
- Data must always be recorded as part of the official record
- Laboratory error cannot be assumed
  - Lab errors are when an analyst makes mistakes in following the method, uses incorrect standards, or makes a miscalculation
  - Must be determined through a failure investigation to identify the cause of the OOS
- Analyst mistakes, such as calculation errors, must be specified & supported with evidence
- Documentation describing each step of the process & associated investigations must be preserved

The Barr Decision & Judge Wolin's comments are the basis of the FDA Guidance "Investigating Out-Of-Specification (OOS) Test Results For Pharmaceutical Production"

How Does This Happen?

Improper Practice

- A scientifically unsound or technically unjustified omission, manipulation, or alteration of procedures/data that lacks required quality control parameters

Fraud

- Deliberate falsification of quality assurance results, where failed or incomplete requirements are made to appear acceptable or completed during reporting

Definitions sourced & adapted from Oregon Technical Advisory Committee "Laboratory Ethics & Data Integrity "Train the Trainer" Presentation"

Why do improper practices occur?

Something that enables proper performance is missing

Operator/analyst reasons

- Lack of understanding of requirements & expectations
- Lack of proper operator training & qualification practices
- Lack of direction/detail in SOPs

Management reasons

- Lack of oversight of & involvement in daily operations
- Lack of communication of expectations
- Placing excessive/constant time pressures on personnel
- Lack of resources

Why does fraud occur?

To avoid something viewed as negative or punitive

Operator/analyst reasons

- To avoid additional work *(retesting, reprocessing, maintenance, etc.)*
- To cover up a mistake/failure/failing result
- To avoid missing hold times
- To avoid getting in trouble/having to report errors/deviations
- Because it's rewarded!

Management reasons

- To avoid looking bad to others *(particularly to upper management)*
- To avoid having to own up to a mistake/save face
- To avoid financial penalty or impact *(i.e. disposing of a batch of product impacts revenue, stock price, etc.)*
- To meet impossible targets, please clients/management

What are we talking about?

Data integrity: The extent to which all data are complete, consistent & accurate, throughout the data lifecycle

Data lifecycle: All phases in the life of the data *(including raw data)* from initial generation and recording through processing *(including analysis, transformation or migration)*, use, data retention, archive/retrieval and destruction.

Source: "MHRA GxP Data Integrity Definitions and Guidance for Industry" (draft version for consultation)

Where can data integrity issues occur?

- Analyst & operator preparedness
- Reviewers
- Management oversight

- Materials
- Equipment
- Processes & procedures
- Product control systems & access controls
- Contract labs, CMOs, CROs, CDMOs

- Capture
- Interpretation
- Review & approval
- Data acquisition & analysis systems

- Paper & electronic records
- Access controls
- Protection from loss

Inspection Observations: Data Integrity

Searching FDA warning letters for the phrase "***data integrity***" brought up 154 WLs dated 2012-2017, covering pharma, biotech, device, blood, GLP & GCP – both in the US and internationally

2012: 22
2013: 26
2014: 33
2015: 27
2016: 30
2017: 13 (Jan-Mar)

Common Issues/Inspection Observations

Personnel Qualification

- Inadequate training
- No demonstration of competency
- Using improper techniques
- Inexperienced reviewers/managers (lacking background to enable detection of issues)
- Managers focused on throughput versus accuracy/integrity
- Differences between site & CMO/contract lab personnel
- Unqualified/inexperienced personnel performing tasks
- Not enough qualified personnel
- Active fraud/falsification

Common Issues/Inspection Observations

Task Preparation & Execution

- Unapproved suppliers/CMOs/contract labs used
- Systems/Equipment *(including data acquisition/recording systems)*
  - Not calibrated/validated – accuracy/reliability issues
  - Lack appropriate access controls *(ability to override system controls, overwrite/alter/delete information/process controls, etc.)*
- Materials
  - Unlabeled samples/materials/processing equipment
  - Unapproved/unverified materials used
- Procedures
  - Not thorough enough, leading to variability in performance
  - Missing requirements for data recording/collection
  - Missing data capture/quality control/oversight steps

Common Issues/Inspection Observations

Data Collection (Capture/Interpretation/Review)

- Mishandling of OOS/deviations – failing to record, report, investigate, or covering up OOS *(including discarding/not documenting failing results)*
- Documenting work that wasn't done *(including employees not present when work documented as performed)*
- Manipulation of data *(integration parameters, etc.)* without explanation
- Inadequate investigations, including failure to identify root cause/CAPAs
- Use of unvalidated analytical methods
- Inaccuracies between data systems & specification documents

Common Issues/Inspection Observations

Data Collection (Capture/Interpretation/Review)

- Handling issues
  - Personnel overloaded and cutting corners
  - Documenting changes to approved records without re-approval/verification
- Failure to follow procedure, including:
  - Mislabeling/not labeling samples/materials/processing equipment
  - Not completing/pre-completing documentation
  - Running "trial" samples

Common Issues/Inspection Observations

Data Maintenance & Archiving

- Access control issues
  - Password/access sharing
  - Ability to edit/delete methods/data
- Lack of backups/protection of records from loss
  - Failure to retain raw data/complete data as generated
  - Incomplete files/records of data acquired/generated
  - No backups, or backups that write over earlier data
  - Altering/writing over failing data
- Hybrid systems – processes for management & maintenance of both paper/electronic records
- Issuance/control of batch records, worksheets & notebooks
- No/disabled audit trails

FDA Expectation: Data Integrity Remediation

In response to this letter, provide the following:

- A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting - including:
  - A detailed investigation protocol & methodology, with a summary of all laboratories, operations & systems covered by the assessment & justification for any exclusions
  - Interviews *(conducted by a qualified third party)* of current & former employees to identify the nature, scope, and root cause of data inaccuracies
  - An assessment of the extent of data integrity deficiencies at your facility, describing all operations in which you discovered data integrity lapses
  - A comprehensive retrospective evaluation of the nature of the manufacturing and laboratory data integrity deficiencies *(evaluated by a qualified third party)*
- B. A current risk assessment of the potential effects of the failures on the drug quality, including analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity & risks posed by ongoing operations.

FDA Expectation: Data Integrity Remediation, con't

- C. A management strategy with details of your global CAPA plan, including:
  - A detailed plan describing how you will ensure the reliability & completeness of all data generated
  - A comprehensive description of the root causes of your data integrity lapses, including evidence that the current action plan is commensurate with the findings of the investigation & risk assessment, and indicating whether individuals responsible for data integrity lapses remain able to influence data
  - Interim measures describing actions being taken to protect patients & ensure drug quality *(such as notifying customers, recalling product, additional testing, adding lots to stability programs, drug application actions & enhanced complaint monitoring)*
  - Long-term remediation efforts & enhancements to procedures, processes, methods, controls, systems, management oversight & human resources *(e.g., training, staffing improvements)* designed to ensure data integrity
  - A status report for any of these activities already underway or completed

Impact of Data Integrity Issues

Case Studies

Able Labs (2005)

Improper/fraudulent practices performed by analysts/supervisors:

- Records lacked complete data (in-process, finished product, stability samples)
  - Cutting & pasting chromatograms, computer records
  - Resampling & substituting vials in tests
  - Changing sample weights & processing methods to achieve passing results
  - Not documenting results for specific products/batches
  - Unreported OOS results found in electronic data files
  - Original processing methods not recorded
- Routine resampling/reinjecting/reprocessing when OOS obtained
- Failure to follow established laboratory control procedures

Able Labs (2005)

Other related failures:

- Inadequate GMP training for chemists
- Lack of training of chemists
- Lack of oversight by management
- Failure to investigate OOS results
- Failure to investigate the lack of documentation explaining reinjection/retesting OOS samples
- QCU did not review electronic data, audit trails in the data acquisition system

Able Labs (2005)

Impact

- Testing irregularities allowed release of drug products failing in-process, finished product & stability specifications
- Caused the firm to submit erroneous data in annual reports
- All products recalled in one of the largest drug recalls EVER
- Company filed for bankruptcy, subsequently folded
- All 500 employees lost their jobs as a result

Outcome

- Criminal charges (5 yrs prison & $250k fine) & debarments (5 yrs)
- R&D Manager; Head of QC; Analytical Control Supervisor; Lab Manager; Assistant Lab Manager; Lab Supervisor
  - 4 found guilty & debarred (1 turned state's evidence)
- Under questioning, Head of QC acknowledged receiving direction from former CEO to oversee a "secret project" to falsify & manipulate test data & quality assurance records. ***Anyone participating received a bonus.***

"Consumers were put at risk, a company that employed 500 people was destroyed, and shareholders were left with nothing in the end. This is the legacy of the fraud perpetrated at Able Labs by these defendants."

"Those who willfully falsify and manipulate the various tests required during the manufacturing process put the public health at risk, and do so at their own peril."

FDA & DoJ Perspective

Source: US DoJ Press Release, March 8, 2007. "Four Managers of Now-Defunct N.J. Generic Drug Maker Admit Fraud"

Other recent examples: Ranbaxy Labs

Issues

- Falsified data on both approved & R&D products, product applications (1600+ instances found)
- Altered storage conditions & age of samples
- Falsified stability data
- Documented testing that occurred when individuals were not physically present

Impact

$500 million fine plus…

- Import Alerts – 2008 + (Products not allowed into US)
- Criminal charges filed – 2008
- Application Integrity – 2009+ (Rejection of pending/future product applications)
- Consent Decree – 2012, expanded in 2013
- Pled guilty to 7 felonies – 2013
- Company sold to Sun Pharma, all products to be rebranded in US – 2014

Other recent examples: Cetero Research

- 1900+ instances of employees manipulating & falsifying data from 2005-2010
- Falsified dates & times
- Manipulated equilibrations & samples to meet acceptance criteria
- Lack of documentation of activities
- Impact:
  - 122 drug studies compromised for Pfizer, Merck, and others; ~100 different medications affected
  - Some sponsors told to redo drug submissions, perform data integrity audits to be able to market products approved with Cetero's data - 2012
  - Bankrupted company, sold & reorganized as "PRACS Institute" – 2012
  - PRACS filed for bankruptcy, shut down, all workers laid off – 2013

Tips to Assure Data Integrity

How to identify & mitigate data integrity risks

Securing data: Do procedures & practices meet expectations?

- Assess your procedures against the following (at a minimum):
  - 21 CFR 11 – Electronic Records & Signatures
  - 21 CFR 211.68 – Automatic, Mechanical & Electronic Equipment
  - 21 CFR 211 Subpart J – Records & Reports
  - Data integrity guidance from FDA, MHRA, PIC/s, EMA & WHO
  - OOS Investigation Guidances from FDA & MHRA
  - ICH Q10 Guideline, Pharmaceutical Quality Systems
- Do procedures define what people actually do? And are they being used?
- Do your procedures, practices & systems encourage compliance?
- Do your metrics/RCA identify and track procedure issues?

Securing data: Equipment & system validation/controls

- Accuracy & control:
  - Ensure alignment with GAMP 5, GAMP Good Practice Guides
  - Validate all equipment, lab methods, computer processes & data calculation/transfer mechanisms
  - Ensure accuracy of calculations & transfers
  - Test OS updates prior to installing
  - Limit access to downloads/competing browsers for web-based applications
- Security:
  - Define/test security levels & roles
  - Crosscheck accounts, permissions & credentials (i.e. access forms)
  - Set controls around passwords (expiration, # of attempts, etc.)
  - Beware of hosted/cloud-based system risks

Securing data: Quality Agreements

- Ensure quality agreements are in place with suppliers, contract labs & CMOs
  - Capture communication processes for issues/problems/changes
  - Define oversight & responsibilities/authorities for reviews/changes
- Audit data integrity controls & practices for any company from which you're accepting data/work – you're accountable for it!
  - Assess your quality agreements against the FDA guidance & Eudralex V4, Chapter 7 "Outsourced Activities"
  - 3 of the 5 "illustrative cases" in the FDA's Quality Agreement guidance relate directly to data integrity

Securing data: Maintenance & archiving practices

- Control practices
  - Issue, track & reconcile batch records, worksheets, lab notebooks
  - Centralize!
  - Beware of duplication *(i.e. departmental copies of records, multiple copies of databases/spreadsheets, etc.)*
- Archiving practices
  - Define a records retention policy – and practice it
  - Ensure ability to retrieve in a timely fashion!
  - Verify backups exist, are not overwriting data & are maintained per procedural/GMP requirements
  - Store in a secure location – fireproof, limited access – offsite?
  - Records may be kept as "true copies" – but ensure thoroughness if scanning in originals for archiving

Securing data: Perform regular data integrity audits

- Identify possible issues/questionable practices – **before** they become problems
- Audit data & records – look for anything questionable
- Audit labs/areas where data is generated – look for anything questionable *(in recycle bins/trash, in drawers in the lab, around equipment, etc.)*
- Can your entire process, including reviews & decisions, be recreated from your records?
- Perform regular, on-floor quality checks, during operations & testing
  - Verify that people are doing what they're supposed to – and what they are documenting
- Check personnel qualification to perform
  - How do you qualify your people to perform operations?
  - Do you have evidence they're able to perform correctly?

Avoiding data mistakes: Be proactive!

- Remove opportunities for data integrity problems
  - Implement automated processes, i.e.:
    - Manufacturing execution systems/electronic batch records
    - Process Analytical Technology (PAT) for real-time monitoring/information gathering
    - Programmable logic controllers (PLCs)
    - Laboratory information management systems (LIMS)/lab control & communication software
  - Error-proof tasks/processes where possible
- Identify areas of risk *(risk assessment/management tools, trend recent/past deviations, etc.)* – address those areas first
  - Look to ICH Q9 & 10, FDA Process Validation Guidance for ideas/direction

Resource appropriately – or be realistic about expectations

Avoiding data mistakes: Focus on people!

Training for operators/analysts/managers should include…

Content

- GMP/Part 11 requirements & expectations
- Company code of conduct, ethics & fraud policies (ZERO tolerance)
- Validation & change control
- Good documentation practices
- Deviations
- Barr Decision & FDA OOS Guidance (as appropriate)
- Task training, including an assessment of competence

Messages

- Data quality/integrity is a top priority
- Document everything & keep all documentation
- Communicate problems immediately
- Take the time to do tasks right, each time & do not document a task that wasn't completed (includes reviews)
- Follow the SOP as written, or revise the SOP – no shortcuts/unauthorized changes
- Expect failures on occasion
- Be honest about mistakes – people have error rates!

Avoiding data mistakes: Focus on people!

Managers must lead by example & assess/develop their people!

- Provide quality policy, related goals, support for quality, ensure communication & appropriate resources to meet quality goals
- Review performance of the quality system, monitor product/process quality
- Continually improve the quality system
- Establish the appropriate culture of quality, problem solving & continuous improvement
- See ICH Q10 & FDA Guidance "Quality Systems Approach to Pharmaceutical GMPs" for specific details of expectations

Management must actively & repeatedly communicate the importance of quality!

How would you answer the DoJ's questions on people?

Source: Transcript of Department of Justice speech at 2013 CBI Pharmaceutical Congress

- Do we have the right people? Do they have the right training/expertise to recognize problems that can arise?
- Do people have the right incentives to see, report and fix problems?
- Are people satisfied and engaged?
- Are people and policies working in harmony? Do policies reflect how real people work and what they are capable of?
- Do you personally have visibility into what your people are actually doing?

Avoiding knowledge of problems in your organization will not shield you from liability.

Summary

- Data integrity issues can end careers and destroy companies
- Most data integrity issues are avoidable with appropriate oversight & controls
- Many data integrity issues have to do with people's execution of practices or decisions – including calibration and validation program design & execution
- Set & educate people on your expectations & regulatory requirements for the tasks they perform – then hold them to those expectations

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  - "To CBT or Not to CBT…It Shouldn't Be a Question"
  - "The 5 Basic Tenets of Data Integrity – And How Failures Occur"
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Thank you!

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