Connecting People, Science and Regulation

Data Integrity: Quality Culture & Code of Conduct

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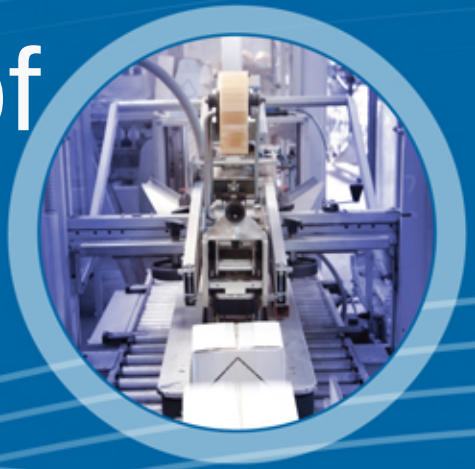

Quality Culture & Code of Conduct

It is a privilege to work in an industry that makes a difference in the lives of patients. Every employee has an obligation (duty) to engage in behaviors and practices such that all stakeholders can trust that their decisions are based on data and information that are accurate, truthful, and complete.

Data Integrity Continuum

System Error

Individual Mistake

Individual Malfeasance

Institutional Malfeasance

GMP regulations do not require determining intent while accessing Data Integrity, however companies should determine intent. Even with deliberate falsification of records, companies must understand the dynamics that drove and allowed the individual to do this if companies are to truly fix the issue and prevent its reoccurrence.

Without an understanding of the true root causes for human misbehavior, companies may be forced to take widespread actions that may not be indicated, especially when factored with the preventive data integrity measures already in-place.

Unintended Error | Deliberate Falsification

Data Integrity & Fraud: The Misconduct Scale

GMP Violations		
Ignorance	Sloppiness	Malfeasance
Misconduct of uninformed kind	Misconduct of lazy kind	Misconduct of sleazy kind
Act is unintentional; Non-Compliance is unintentional	Act may or may not be intentional; Non-compliance is unintentional	Act is intentional; Non-compliance is intentional
Discarding source documents after accurate transcription; Deleting e-files after printing	Inaction, inattention to detail, inadequate staff, lack of supervision	Data manipulation, data falsification, mis-representation, with holding critical information
Misconduct does not include honest error or honest difference of opinion.		

Adapted From: Misconduct in Research- Innocent Ignorance or Malicious Malfeasance; Stan W Woollen, Biomonitoring Program, FDA

Data Integrity: Causes & Mitigation

Malfeasance	**Quality Culture & Code of Conduct** • Ethical Behavior • Speak-up Culture • Tone at the Top • Enforcement & Discipline
Sloppiness	**Management Controls** • Quality Systems • Auditing & Monitoring • Accountability & Supervision • Resource Allocation

Ignorance	**Knowledge, Training, & Awareness**
	• Policies, Standards, & Procedures
	• GMP Training
	  • Electronic Data Management
	  • Training of Auditors

What is Culture ?

- The collective pattern of beliefs, values and expectations.
- Observable Actions and Behaviors
- Unwritten rules – “the way we do things around here”
- **Culture and leadership are interdependent.** Senior leaders say, do and reward behaviors that create culture and allow for or derail successful implementation of change.

Motives or Risk Factors for Fraud

Misconduct cases are predominantly driven by Individual self Interest

- Were under career pressure
- Knew, or thought they knew what the answer would turn out to be if they went to all the trouble of doing the work properly, and
- Were working in a field where individual experiments/tests are not expected to be precisely reproducible.

Ref: David Goodstein, Caltech; Conduct and Misconduct in Science
<http://www.physics.ohio-state.edu/~wilkins/onepage/conduct.html>
[Tuesday, 28-Jan-2014 17:30:15 EST]
Edited by: wilkins@mps.ohio-state.edu on Monday, 15-Jan-2001 14:29:13 EST

- Were under financial pressure/ greed

Code of Conduct To Assure Data Integrity

- PDA is developing a code of conduct to be voluntarily adopted by
  - Manufacturers of finished drug products for clinical trials and commercial distribution
  - Companies that conduct clinical trials in support of new drug applications
  - Laboratories that develop methods or formulations intended to support new drug applications
  - Suppliers of excipients and active pharmaceutical Ingredients (APIs)
  - Contract manufacturing organizations (CMOs)
  - Contract research organizations (CROs),
  - Contract testing laboratories
  - Contractors, consultants, suppliers and vendors that provide services and data that support the production and control of drug and biological products

Elements of a Code of Conduct for Data Integrity in the Pharmaceutical Industry (DRAFT)

(Website Address)

Key Concepts in Data Integrity Code of Conduct

- Management with executive responsibility must establish quality standards, requirements and procedures, and is obligated to maintain and monitor the performance of the quality systems that ensure availability of safe and effective drugs.

- Every employee at each company is responsible for his/her own behavior and practices to ensure that the bond of trust between the company and its stakeholders, namely the patients and regulators, is not broken due to data integrity issues.

- The principles outlined below may be incorporated into a stand alone Code of Conduct that is specific to Data Integrity for GXP operations. Alternatively, the identified elements may be incorporated into broader Code of Conduct that encompasses all aspects of business values and ethics, or may be integrated with existing policies that address Ethics and Compliance or Quality Agreements with supply chain partners.

Key Concepts in Data Integrity Code of Conduct

- The Company will establish mechanisms for employees to notify Company officials about any instance of known or suspected misconduct or wrongdoing , or their concerns about potential data integrity issues, including option to report issues anonymously if they so choose and if local laws permit.

- Company will establish and follow procedures for conducting an independent, fair, balanced and documented review, and if warranted, an in-depth documented investigation of any alleged instance of falsification, fabrication, or other misconduct involving data integrity issues.

Disclaimer

The following Case Studies are fictionalized versions based on real life scenarios . Any resemblance to persons living or dead, or companies still operating, closed or merged is purely coincidental.

Case Study 1

Too Embarrassed to Act

Loop Holes in HPLC Data Acquisition System- Security Resulting in Dry Labbing

Learning Goal:

- Interview Tactics Used
- Importance of Swift Actions
- Importance of Communication Strategy

Case Background

- A QC Chemist running an HPLC assay for potency noticed the peak height of one of the batches was atypically low indicating a potency of about 75%.
- The chemist re-injected the same sample prep, and again got low results (about 75% potency).
- The chemist followed OOS investigation procedure, checked results for other tests completed for the batch (Dissolution Test completed by another chemist). The batch had met dissolution thereby contradicting the potency result. The chemist repeated the potency test in triplicate and got 75% potency again.
- Dissolution test was repeated and failed.
- OOS Investigation could not find a laboratory cause, manufacturing investigation uncovered 1 of 4 API canisters weighed was not added

Case Background (contd).

- Change of focus of OOS investigation from 75% potency to acceptable dissolution test. Chemist 2 claimed dissolution sample switched inadvertently.
- One Supervisor suspected fraud, contacted management, and HR. Management discussed the issue in staff meeting. Agreed this was serious yet Non-conformance investigation languished for 3 months, chemist counseled to be more careful in labeling samples, Non-Conformance investigation closed.
- Anonymous individual reported concern through hotline.
- Special investigators visited site within 24 hours and confirmed incident, NDA Field Alert issued resulting in 5 investigators from FDA within 2 hours of reporting incident.
- Since Firm had voluntarily disclosed issue and started Independent Investigation FDA agreed to give the firm a chance to complete the independent investigation and report findings. Two FDA Investigators stayed at plant and started GMP Inspections of areas other than lab.

Case Investigation & Communication Strategy

- **Establish Dissolution Test was performed by reviewing instrument logs, facility and laboratory badge access, and data acquisition system login**
- Find the chromatogram and Injection with 75% peak height
  - Audit trail
  - Nightly Server back-up
- Interview each chemist individually
  - Confront with available evidence and statement made by co-workers. Maintain anonymity of information obtained.
  - Interview investigation targets as well as individuals who were not targets but could provide evidence and/or insight
  - Interview management
- Provide updates to Regulators and Company Executive Management

Investigation Findings

- A temporary Chemist found a way to rename data files using Windows OS function
- Data acquisition system audit trail could not track changes made using Windows commands
- Five other temporary chemists, two regular chemists, and one supervisor were aware of the loop hole.
- Temporary chemist was considered a ‘Star’ for being productive and efficient,
- Over 500 batches potentially affected
- Site QA Management was not decisive immediately after 75% potent batch was discovered this sent wrong message to the chemist involved.
  - Temporary chemists believed practice was condoned.
- Site Management did not escalate the matter
- Too many system super users

Company Actions Depicting Culture

- Disciplinary Actions To Set Tone
  - Terminations: Chemists, Supervisor, and Laboratory Director
  - Voluntary Separation: Site Compliance Director & Site Quality Director
  - Resignation: Quality Vice President
- Commitment to Regulators
  - Lesson learned training to all laboratory personnel globally
  - Share lessons learned with regulators
  - Share information on Lab System Security and audit trail at an Industry Meeting
- Commitment to Fix System
  - Audit trail on servers and work with system vendor to fix problem

Are the actions taken adequate to establish a good Quality Culture?

Case Study 2

No Win Position

Raw data on scrap pieces of paper and written on hand

Learning Goal:

- Getting to root cause

Case Background

- Company auditor found scrap of paper in waste basket with numbers scribbled.
- Interviews with laboratory personnel and laboratory supervisor established numbers were pH data.
- Similar incident was noted in an audit 2 years earlier. Chemist was terminated.
- Supervisor informed auditor of zero tolerance policy and chemist will be terminated

Investigation Findings

- The repeat incidents occurred in one specific lab and involved the same product.
- Incident occurred despite training of lab personnel on good documentation practices
- Product being tested was not buffered, and the PH meter would not stabilize easily.
- Results in spec or OOS would depend on moment data recorded
- Formulation scientists were aware of problem but blamed QC chemist

Company Actions Depicting Culture

- Was termination of the two chemists appropriate?
- Did lab management get to true root cause?
- What do the actions say about Quality Culture

Case Study 3

Covering for the team

Signing for another employee

Learning Goal:

- Understanding your operations
- Importance of a speak-up culture
- Getting to root cause

Case Background

- QA batch record reviewer noticed initials of employees working in aseptic filling room did not match initials of operators on record.
- All employees were trained on documentation practices and SOP specifically prohibited employees initialing documents as another employee.
- SOP for interventions during filling required each operator to enter activity performed.
- In case of line jam, one operator standing by the control panel would stop the line, and another operator standing by the line would remove jammed vials using aseptic technique.
- Per procedure, each operator was required to document their activity

Investigation Findings

- QA investigation revealed the initials did not match because a operator had entered a co-workers initials besides task performed using the co-workers nick name

- During investigation interview, operator acknowledged he signed for his co-worker and rationalized that it was too burdensome for his co-worker to leave his work station and make entries in the batch record.
- Operator also rationalized that if he did not document, most probably his co-worker would not document his actions.

Company Actions Depicting Culture

- Is termination of the operator appropriate action?
- What additional actions should the company take?
- What do the actions say about the company culture ?

Thank You!