FDLI

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Drug and Device: Warning Letters and Data Integrity

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Interpretation of the FDA Data Integrity Draft Guidance & Preparing for Compliance

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Data Integrity

- cGMP sets the minimum requirements for data integrity

- Data integrity is critical to meeting cGMP

- FDA takes data integrity seriously

Consequences for Failure to Comply with Data Integrity Regulations

- Form 483s
- Warning Letters
- Import Alerts
- Recalls
- Complete Response Letters

FDA’s Draft Guidance

- Data Integrity and Compliance With cGMP, draft guidance for industry (April 2016)
- Q&A style guidance focused on frequently occurring problems with data integrity lapses and how they relate to cGMP in 21 C.F.R. § § 210, 211, and 212; clarifies the definition of key terms in FDA’s regulations.
- Is not a comprehensive list of data controls or a “how to” guidance.
- When final, it will represent FDA’s current thinking on data integrity and CGMP compliance.

What is Data Integrity?

- Data integrity – requirements for complete, consistent, and accurate data.

- Throughout cGMP

ALCOA
• **A**ttributable
• **L**egible
• **C**ontemporaneous
• **O**riginal or true copy
• **A**ccurate

Other Important Concepts

- Metadata
- Audit Trail
- Static vs. dynamic records
- Backup
- Systems

Paper and Electronic Records

- Same requirements for paper and electronic records:
  - § 211.68: back-up records complete, secure from alteration, erasure, or loss
  - § 212.110: data stored to prevent loss or deterioration
  - § § 211.110 and 211.160: activities be documented at the time of performance; scientifically sound laboratory controls
  - § 211.180: copies be true and accurate
  - § § 211.188, 211.194, and 212.60(g): complete information, complete data derived from all tests, complete record of all data, and complete records of all tests performed

Computer Systems

- cGMP-related computerized systems should be validated.
- Demonstrate the suitability of computer hardware and software to perform assigned tasks.
- Incidents related to computerized systems that could affect the quality the reliability of records or test results should be recorded and investigated.

Access to
cGMP Computer Systems

- Restrict the ability to alter specifications, process parameters, or manufacturing or testing methods by technical means where possible (for example, by limiting permissions to change settings or data).
- Assign the system administrator role, including any rights to alter files and settings, to personnel independent from those responsible for the record content.

When Does Electronic Data Become a cGMP Record?

- All Data generated to satisfy a cGMP requirement is a cGMP record.
- You must document, or save, data at the time of performance.
- If you record data on paper and then copy to the electronic record, you must retain the paper record.
- You may not do “test” runs that are not recorded.

Use of Samples During “System Suitability” or Test, Prep, or Equilibration Runs

- You may not conduct sampling and testing with the goal of achieving a specific result or to overcome an unacceptable result.

- You may not test into compliance.

How Often Should Audit Trails be Reviewed?

- You should review audit trails that capture changes to critical data with each record and before final approval of the record.

- You should regularly review audit trails related to: history of finished product test results, sample run sequences, sample identification, critical process parameters.

If You Find a Data Integrity Problem

- Handle through your internal compliance programs
- And should include:
  - Determining the Scope of the Issue
  - Discussions with Counsel
  - A plan for Remediation
- And likely will include:
  - Disclosure to Regulatory Authorities

Recent Warning Letter Citations Involving Data Integrity

- Failure to have sufficient controls to prevent unauthorized access and changes to data or omission of data
- Failure to investigate and resolve critical deviations
- Failure to record activities/data at time of performance
- Failure to ensure laboratory records include complete data from all tests
- Failure to establish/maintain procedures for quality audits
- Destruction of data
- Failure to identify data integrity issues

Required Responses to Warning Letters on Data Integrity Violations

- Comprehensive investigation and evaluation
- Risk assessment re reliability and completeness of quality information and effects on quality of drugs
- Management strategy
- Status report of above activities

Culture is the leading risk factor for compromising integrity and compliance*

Leadership may be lax in holding teams accountable to ethical & quality standards

- Lack of appropriate principles, systems, controls and oversight
- Fraud may be tolerated or encouraged

Financial success is often prioritized over product quality

- Unrealistic cost controls force inadequate investment in staffing, training and development, facilities, equipment, systems, controls, etc.

Autocratic leaders not interested in two-way communications or team engagement

- Staff work to “please the boss” vs. doing the right thing

**Source: David Gebler, Suffolk University*

Culture is the leading risk factor for compromising integrity and compliance*

Organizations may not be focused on innovation and continuous improvement

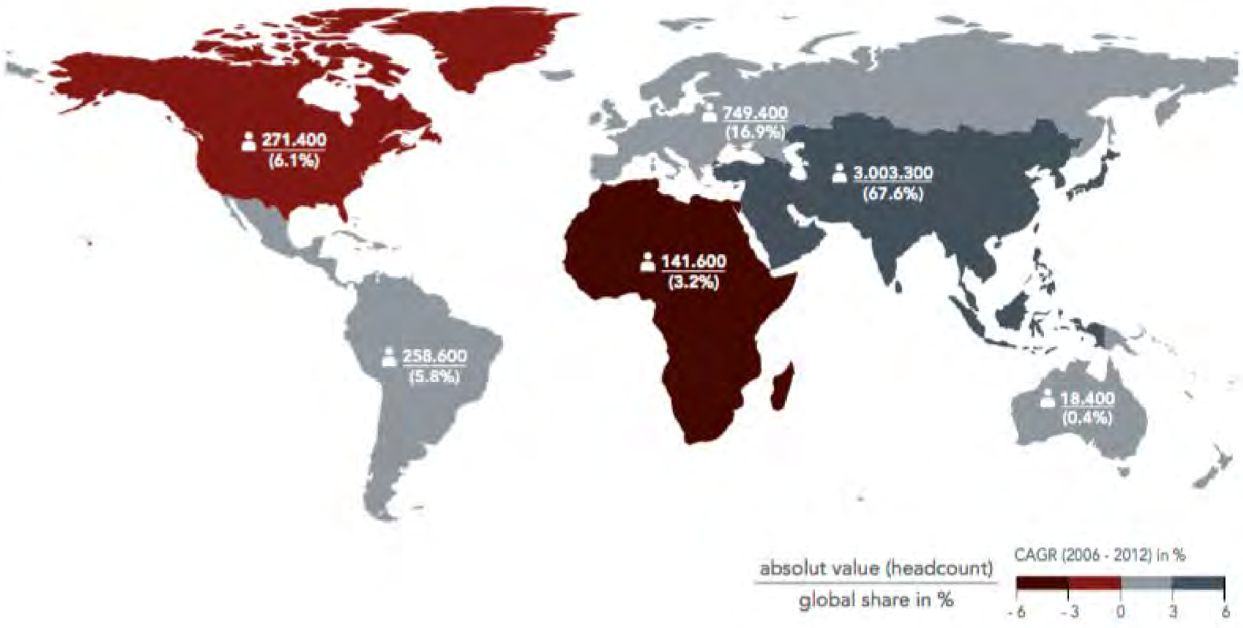
Large multinationals or departmental silos may limit communications & teamwork

Complacency, culture of fear, poor morale (e.g. post acquisition, layoffs)

Shallow focus on compliance vs. deeper understanding of product quality

Generics growth & globalization add layers of risk

*Global Pharmaceutical Employment**



- Production/employment is continuing to shift to emerging nations
- The patent cliff has resulted in volume flowing from few to many manufacturers (consistent to variable)
  - › Generics account for 88% of U.S. retail prescriptions (GPhA 2/16)
  - › ~ 80% of APIs and ~40% of finished drugs are imported
- Organizations may lack the financial strength or expertise to design & implement Quality Systems effectively
- Regulatory oversight while improving (e.g. FDASIA/GDUFA/OPQ) remains suboptimal

**Source: WiFOR Research Report, February 2015.*

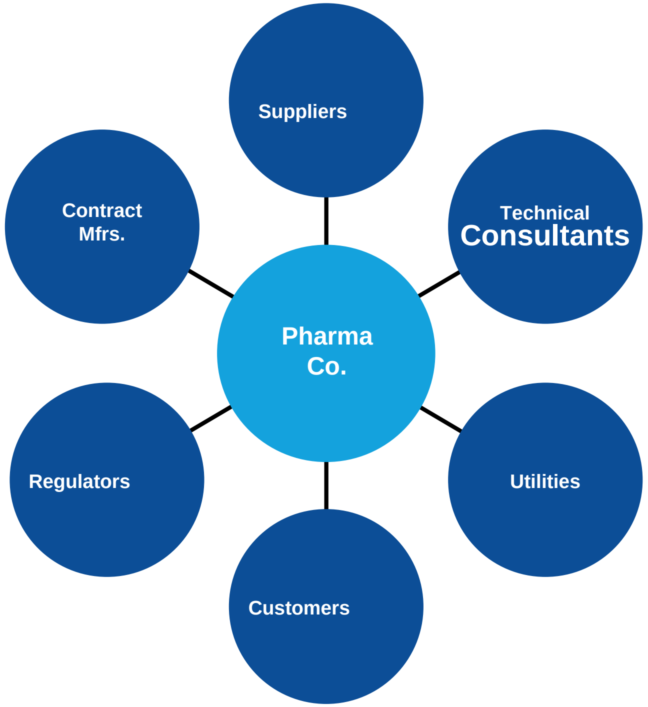
Other root causes of data integrity problems

Internal Quality System deficiencies and from suppliers & outsourcing partners

- *Weak ecosystem, systems, processes, equipment, and products that increase the risk of data integrity problems (amplified by the heightened focus on metrics by FDA/industry)*

Poor procedures, training gaps and/or lack of awareness of rules or requirements

- *Selective data collection/retention, backdating, retesting, failure to document/investigate problem findings, fraud*
- *Ignorance: not being aware of regulatory requirements and/or poor training*
- *Practices of inspecting quality into product (vs. quality at source)*
- *Shared passwords, lack of integrated systems, conflict of interest in various roles*



Human & system errors

- *Mistakes: e.g. transposing data such as 4.78 vs. 4.87*
- *Synchronization: errors that occur when data is transmitted from one computer to another*
- *Changes in technology, where one item is replaced when it becomes obsolete or no longer supported, making old records unreadable or inaccessible*

Other root causes of data integrity problems

Personal integrity problems

- *Willful falsification or fraud*
- *Fear of retaliation, job loss*
- *Poorly designed incentives*
- *Cognitive dissonance*
- *Normalcy bias*
- *Level of control and connectedness*
- *Perceived low risk of being caught*
- *Laziness, willingness to take short-cuts*
- *Selection of passing results and exclusion of those that are failing*
- *Unauthorized changes to data made post acquisition*
- *Backdating test results to meet the required commitments*
- *Creating acceptable test results without performing the test*
- *Using test results from previous batches to substitute testing for another batch*

Photo Source: Forbes.com

Five leading solutions for remediating & preventing data integrity problems

- Investigating and remediating data integrity issues through CAPA and other Quality Systems
- Creating a culture of quality
- Developing visible, engaged leadership that is committed to continuous improvement
- Recruitment and retention strategies that support sound GMP & GDP practices
- Practical balanced performance management

Being Proactive

- Impossible to predict which individual sites will have data integrity issues
- Not always at geographically remote sites or those with high production volume
- Not just in India or China – occurring in the U.S. and Europe
- Need to be proactive with all facilities – a data integrity issue at one facility often leads regulators to question whether a broader problem exists
- Evaluate issues that arise at one site to ensure they are not occurring at other sites

Being Proactive:
Taking Steps to Identify Issues

- Effective internal audit program puts the company in best position to self-identify data integrity issues
  - *Incorporate data integrity reviews into the audit program*
  - *Include data integrity component in the internal audit SOP*
  - *Train auditors to detect data integrity issues*
- Consider occasional third-party involvement
- Take seriously reports of data issues – initiate prompt investigations

Thank you!

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