Ensuring Data Integrity

Pharmaceutical Industry Association- PR 13th Annual Conference
June, 2015

Brian Duncan
Strategic Practice Lead
Quality Executive Partners, Inc.
Discussion Points

① Historical Perspective of Data Integrity Issues
② Basic Concepts & Expectations
③ Considerations for Ensuring Data Integrity
④ Foundation, Controls & Oversight
⑤ Common Pitfalls
⑥ Polling Data: Industry, Regulators & Consultants
Historical Perspective
Late 1980’s: Generic Drug Scandal

Widespread fraud, bribery

10 Companies:
  » Vitarine
  » Bolar
  » Copley
  » Par….

42 Individuals Involved

Motivation to Gain ANDA approvals quickly…

- Falsification of data
- Cover up of mfg investigations
- Fraudulently submitting brand name product in bio-equivalency studies

Debarment
Pre-approval inspections
FDA OCI
Application Integrity Policy

Bad Medicine: The Prescription Drug Industry in the Third World
By Milton Silverman, Milton Silverman, Mia Lydecker, and Philip R. Lee, Mia Lydecker, Philip Lee
Early 1990’s:
U.S. v. Barr Laboratories

FDA Inspection revealed issues:
» Lab Investigations
» Blend Uniformity
» Process/Cleaning Validation
» Data Integrity

Failure to acknowledge laboratory testing failures as a competitive advantage…
• Failing data omitted
• Misplaced records
• Results recorded on scrap paper
• Results reported as averages only

- OOS Guidance
- Stratified Sampling Draft Guidance
- FDA Injunction Process
2000’s: Part 11….& 211

Warning Letters focus on part 11:

» Pharmacia
» Solvay
» Sandoz

Leiner recalls all OTC products. Files Chapter 11....

Leiner recalls all OTC products. Files Chapter 11!

Able Labs the “darling of Wall Street” files Chapter 11!
Jail time for six!

Million USD

Earnings

Q1 ‘03  Q2 ‘03  Q3 ‘03  Q4 ‘03  Q1 ‘04  Q2 ‘04  Q3 ‘04  Q4 ‘04  Q1 ‘05

0  5  10  15  20  25  30  35
2010’s: India & tbd (?)

Guidance for Delaying, Denying, Limiting or Refusing a Drug Inspection

Title 18

Making false or fraudulent statements, or concealing information to officials within the US Government
...And Today

- 15 Warning Letters issued in India, due to Data Integrity issues in past two years

<table>
<thead>
<tr>
<th>Warning Letter Issued To</th>
<th>Date Warning Letter Issued</th>
<th>In Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apotex Research Private Limited</td>
<td>01/30/2015</td>
<td>Here</td>
</tr>
<tr>
<td>Micro Labs Limited</td>
<td>01/09/2015</td>
<td>Here</td>
</tr>
<tr>
<td>Cadila Pharmaceuticals Limited</td>
<td>10/15/2014</td>
<td>Here</td>
</tr>
<tr>
<td>Marck Biosciences Ltd.</td>
<td>07/08/2014</td>
<td>Here</td>
</tr>
<tr>
<td>Apotex Pharmachem India Pvt Ltd.</td>
<td>06/17/2014</td>
<td>Here</td>
</tr>
<tr>
<td>Sun Pharmaceutical Industries</td>
<td>05/07/2014</td>
<td>Here</td>
</tr>
<tr>
<td>Canton Laboratories Private Limited</td>
<td>02/27/2014</td>
<td>Here</td>
</tr>
<tr>
<td>USV Limited</td>
<td>02/06/2014</td>
<td>Here</td>
</tr>
<tr>
<td>Wockhardt Limited</td>
<td>11/25/2013</td>
<td>Here</td>
</tr>
<tr>
<td>Agila Specialties Private Limited</td>
<td>09/09/2013</td>
<td>Here</td>
</tr>
<tr>
<td>Posh Chemicals Private Limited</td>
<td>08/02/2013</td>
<td>Here</td>
</tr>
<tr>
<td>Aarti Drugs Limited</td>
<td>07/30/2013</td>
<td>Here</td>
</tr>
<tr>
<td>Wockhardt Limited</td>
<td>07/18/2013</td>
<td>Here</td>
</tr>
<tr>
<td>Fresenius Kabi Oncology Ltd</td>
<td>07/01/2013</td>
<td>Here</td>
</tr>
<tr>
<td>RPG Life Sciences Limited</td>
<td>05/26/2013</td>
<td>Here</td>
</tr>
</tbody>
</table>

Source: Regulatory Affairs Professional Society, Feb 2015
But is it just India?

- It’s not just India/ Asia- Europe is in the mix as well

![Data Integrity WL's 2012 - 2014 by Country](chart.png)
2014 Top 483 Citations

Deficiencies in laboratory data systems continue to be a significant challenge for industry.

1. **DEFICIENT QC UNIT** - 211.22(d)
2. **INADEQUATE LABORATORY CONTROLS** - 211.160(b)*
3. FAILURE TO THROUGHLY INVESTIGATE FAILURES - 211.192
4. WRITTEN PROCEDURES NOT FOLLOWED - 211.100(b)
5. INADEQUATE PROCEDURES TO ASSURE QUALITY - 211.100(a)
6. PROCEDURES/PROCESS VALIDATION - 211.110(a)
7. INADEQUATE TESTING PRIOR TO RELEASE -211.165(a)
8. EQUIPMENT CLEANING AND MAINTENANCE -211.67(b)
9. EMPLOYEE TRAINING – 211.25
10. INCOMPLETE/INADEQUATE BA

*Also #2 in international inspections Up from #4 in 2013

Deficiencies in laboratory data systems continue to be a significant challenge for industry.
Enforcement Focus: Data Integrity

Warning Letters by Year
FDA Office of Manufacturing Quality

- 2013: 29% Letters Issued, 29% with DI Citations
- 2014: 63% Letters Issued, 63% with DI Citations
- 2015*: 100% Letters Issued, 100% with DI Citations

* 6 of 6 so far this year
Data Integrity Basics
DATA

- Raw Data
- Meta Data
- Unprocessed/Reprocessed
- “True Copies”
- Duplicate
The extent to which all data are complete, consistent and accurate throughout the data lifecycle
Expectations for Data

- Accurate & Legible
- Complete & Attributable
- Contemporaneous & Consistent
- Available & Enduring
- Trustworthy & Reliable
Data Integrity Breaches

- Intentional
- Unintentional
- Entry errors
- Deleting files
- Overwriting files
- Destroying records
- Misrepresenting data
- Falsification
- Fraud
Orphan Data

Data that is not reported or reviewed via the Quality System. This data is generated and resides in a computer system (and/or is deleted or overwritten) NEVER making it to any formal review or reporting.
“It’s not just the data that ends up in the final package….it’s equally or more importantly the data that may not!”

“….2,803 of 44,643 injection results were not processed or reported in the official data folder…”
-Apotex WL 1/30/15
Levels of Control

**Belt** = Operational controls such as:
- Audit trail
- Security allocations
- File naming conventions
- Data Review

**Suspenders** = Oversight such as:
Periodic Review of source database for orphan data
Considerations

❖ Man
❖ Method
❖ Machine
❖ Milieu
<table>
<thead>
<tr>
<th>Man</th>
<th>Method</th>
<th>Machine</th>
<th>Milieu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyst Operator</td>
<td>Procedures</td>
<td>Acquisition</td>
<td>Motivation</td>
</tr>
<tr>
<td>Supervisor</td>
<td>Instructions</td>
<td>Processing</td>
<td>Opportunity</td>
</tr>
<tr>
<td>Manager</td>
<td>Training</td>
<td>Storage</td>
<td>Rationalization</td>
</tr>
<tr>
<td>Executive</td>
<td>Records</td>
<td>Archival</td>
<td></td>
</tr>
</tbody>
</table>
Multiple:

- Factors
- Interfaces
- Influences
Foundation for Control & Oversight
Build and maintain a strong Foundation:

- Robust capable methods & processes
- Qualified high performing facilities & equipment
- Qualified, educated & skilled personnel
- Management expectation for code of conduct/values
- Interfaced systems which ensure compliance to registration i.e. Equivalence to clinical/bio-batch

...... a state of control
Implement **Controls** to ensure adequate data management:

- Validation
- Records of all raw data
- Security & audit trails
- Change Control
- Interfaces with key quality systems
- Required Data Integrity Training
Provide **Oversight** for Data Operations

- Routine operational controls
- Data Integrity vigilance
- “For Cause” audits
- Quality Metrics
- Management Controls - **metrics**
Leadership Actions define objectives, expectations, and culture towards Data Integrity .....everyday!
Data Systems Integration

Integrate Computer Systems to reduce opportunity

HPLC  CDS  LIMS  ERP
Potential for Conflicts

Guard against conflicts of interest which can include friendship

*Everything is fine*
“This is not your mamma’s GMP audit!”
Potential:
Unintended Consequences

Watch for and guard against unintended consequences!
Too much confidence in computerized systems to solve all of life’s problems!!!
Survey Says!
The audience was asked to rate their firm(s)’ level of compliance to a basic set of DI related questions or statements, with the following options:

<table>
<thead>
<tr>
<th>Response Options</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Indicates agreement that the required controls are consistently in place and followed</td>
</tr>
<tr>
<td>Kind of</td>
<td>Respondent feels fairly comfortable that adequate controls are in place for the most part and followed with few exceptions</td>
</tr>
<tr>
<td>Not Really</td>
<td>The firm may have some elements in place, but not fully or the respondent has some doubts about the robustness of the controls in place and whether they are fully followed</td>
</tr>
<tr>
<td>No</td>
<td>Has little confidence the appropriate controls are in place and/or followed</td>
</tr>
<tr>
<td>Don’t know</td>
<td>Not enough information to respond or give a general opinion on</td>
</tr>
</tbody>
</table>

For the purposes of this exercise, we chose to rate the responses to each question based on the combined percentage of (Yes + Kind of) responses, broken down by demographic group. Since each question was polled independently, not all respondents answered every question presented. For some groups, that meant there was not enough data for a meaningful representation.
The Audience

Demographic of Respondents:
39th Annual International GMP Conference, Athens, GA

Group Self-Identified As

- Quality Assurance: 106
- Manufacturing: 23
- Consultant: 17
- Regulator: 12
- Quality Control: 12
- Executive Management: 11
- Regulatory Affairs: 9
- Research & Development: 7
- Other: 6
The Top 3

**TOP 3: Question #10**

Appropriate controls are defined by the OOS procedure to control repeat testing, re-testing, re-sampling, re-processing of data, and archiving of all data.

![Graph showing highest and lowest rated questions]

*Highest rated question, with strong overall response*

Note: FDA generally abstained from answering this question (3 of 12 voted - not enough data to rank)
Data controls exist around hard copy paper documents to preclude destruction and manipulation. These controls include the issuance & reconciliation of controlled master documents.

Consistently high response, 2nd highest rated question overall
The Top 3

**TOP 3: Question #6**

*All computerized systems have password and audit trail capability and these controls are activated.*

- **QA**: Generally confident, but QA, Consultants and Regulators less so…

For each demographic group:
- **Highest rated question**
- **Lowest rated question**
The Bottom 4

BOTTOM 4: Question #5

A full inventory of all computerized systems is maintained, including stand alone PCs attached to instruments. This includes an inventory of multi-use spreadsheets.

Confidence consistently weaker across most groups

Regulators Note: this was the lowest scoring question, of the questions FDA chose to answer.
The Bottom 4

Bottom 4: Question #11

Executive Management has oversight of all data integrity breaches and maintains appropriate communication/escalation pathways for reporting of concerns

Less agreement in responses, w/ QA, QC and Consultants less confident

Note: questions #11 & #5 tied for lowest QA responses
The Bottom 4

**BOTTOM 4: Question #9**

*Appropriate controls and oversight by the QCU (Quality Assurance) exist over contract operations (mfr & labs) to ensure the integrity of all data.*

This question had the widest range of responses across the demographic groups.

For each demographic group:
- **Highest rated question**
- **Lowest rated question**
Laboratory methods and procedures contain recommended integration parameters. Any (limited) manual integration &/or reprocessing is overseen and approved by laboratory management.

Lowest scoring question of the overall set

Note: FDA generally abstained from answering this question (3 of 12 voted- not enough data to rank)
Important to Note

Remember:

Data integrity issues can just as easily happen when good people are trying to do the right thing OR are trying to do what they think you as management want them to do.

Those actions may be uninformed or misguided, or simply due to a lack of proper controls, oversight …

AND EDUCATION!
Thank You!

bduncan@qualityexecutivepartners.com

www.qualityexecutivepartners.com

Follow QxP on LinkedIn!