To Identify some Effective Strategies for Managing Data Integrity by:

• **Ensuring that all Employees Perform Duties & Obligations** In a Manner that Fulfils Requirements of all Stakeholders

• **Providing Adequate Resources** (Financial, Personnel & Systems) for:
  
  • Establishing & Maintaining Effective Systems, Processes and Controls to **Prevent** Data Integrity Lapses From Occurring, and To **Detect** and **Correct** Violations If Lapses are Detected
  
  • Verifying that Systems, Processes and Controls for Data Integrity Perform as Intended & Conform to Applicable Requirements
Perspectives on Data Integrity

Regulatory Priorities Have Refocused on Data Integrity

Reminders about Key Concepts

Five Strategies to Prevent Data Integrity Lapses

Five Strategies to Detect Data Integrity Lapses
Perspectives Provided today are Based on Nearly 50 Years Experience as an:

- **Auditor** - Detecting Data Integrity Lapses, and

- **Consultant** - Helping Companies to Prevent & Remediate Data Integrity Lapses

Perspectives are Based on Having:

- Witnessed Data Integrity Lapses in Many Companies Worldwide, and

- Seen What Works Well to Prevent and Detect Data Integrity Issues, For Example: ...continued
Introduction - Perspectives on Data Integrity

For Example: (Continued)

- **Employee Conduct** (Examples)
  - Signing Entries for Activities they did not Perform
  - Backdating Records
  - Discarding Raw Data & Destroying Original Records
  - Entering Data after the Fact (Entries Out of Sequence)
  - Disregarding OOS test Results, Hiding original OOS Analytical Records
  - Altering entries in Production & Control Records (logbooks, batch records, analytical records, etc.)
  - Entries for "Tomorrows Batch" pre-entered today

... continued
For Example: (Continued)

Management Conduct (Examples)

- Creating Duplicate Batch Production and Control Records
- Repeating Unsuccessful Drug Development Project, then hiding original records
- Manager Signing Batch Record Entries for 10 Other Employees
- Reviewers finding Missing Entries & Instructing employees (via post-it-note) to alter the records
- Management Hiding records and materials from auditor to prevent detection of GMP deviations
- Lying to Auditor
- Supervisor created logbooks 2 years after the fact (after request to audit logbooks)
Someone Once Said "Life is a Series of Choices"

Perspectives on the Progression of Choices for Data Integrity....

- Data Integrity Begins & Ends with a Series of Good Choices
- The Best Choice is Always an Ethical Decision
- Ethics Means Different Strokes for Different Folks
- Employees are One Stroke (Click, Action or Decision) Away from a Data Integrity Lapse, Reminder...
  - “Good People Choose to Do Bad Things for Good Reasons”
  - "Bad People Choose Do Bad Things for Bad Reasons"
- Some Really Bad Choices were made by Every Debarred Felon ... continued
Choices (Continued)

• When Well Intentioned People Make Mistakes, Ethics Determines the Actions that Follow
• "Stuff Happens" ... So Document It
• You Can Never go Wrong Documenting the Rationale for Your Decisions
• Employee Error is Never the Root Cause, it's a Symptom
• Mistakes Build Character, Especially if you Can Avoid the Mistakes of Others

• If it Feels Wrong, Don't Do It

• Lying to the FDA is a Crime - Is it Worth it?

• If You Believe the Regulation is Unnecessary, then You Better be Careful!

Reminder
Proactive Data Integrity Always Trumps Remediation
Data Integrity is a Priority of Regulatory Agencies Worldwide
Data Integrity Matters to Regulators Because...

- Regulators Have a Duty to Uphold the Laws & Regulations they Enforce
- Data Integrity is Fundamental to All Matters for All Agencies who are Always alert for:
  - **Inadvertent** Omissions or **Unintentional** Mistakes
  - **Willful Misconduct** (Intent to Deceive or Mislead) is a Criminal Act, such as intentionally:
    - Making False Entries on GxP Records
    - Submitting False Information in an Application
    - Providing False Information Verbally (Lying) or Obstructing a Government Agent (Withholding Material Information)
Regulators Must Make Decisions Based on:

- Records Prepared by Each Company
- Expectation is that all Data & Information reflect what actually happened, i.e. Records are:
  - **Accurate**
  - **Truthful**
  - **Complete**

Assurances of Product Identity, Strength, Purity & Safety

- Are Dependent on Valid (Unbiased) Data Being Documented and/or Summited Regulatory Applications
Data Integrity Violations are Certainly Not New to the Regulators

- Regulators have found Falsification & Fraud for As Long as there been Laws & Regulations for Pharmaceuticals

- Data Integrity Breaches Have a Long and Storied History, and are the "Roots" for Many Pharmaceutical Laws & Regulations

Renewed Focus by Regulators

- Data Integrity Has Always been a Priority of Regulators, but Recent Trends Reflect an Adverse Compliance Level

- Abatement of Data Integrity Breaches is an Elusive FDA Goal Despite FDA's Attempts to Discover & Rectify Violations (Punish the Violators) ...continued
Renewed Focus by Regulators (Continued)

• Recent Worldwide Regulatory Inspections Have Detected Serious Data Integrity Lapses in Many Pharmaceutical Companies Worldwide

• Recent Press Reports reveal a Notable Incidence of Regulatory Sanctions that Reflect a Renewed Priority Focus by Many Regulatory Agencies (FDA, EU, WHO, etc.).

• Nearly every week Headlines in the Press Reveal Additional Companies having Serious Data Integrity Issues: For Example: ...continued
Recent Headlines are Replete with Egregious Data Integrity Incidents Relating to Pharmaceuticals

For Example:

"Another Indian firm under fire for shoddy clinical trials work"

- "Another Indian clinical research organisation, XXX, is in trouble over defective trials work, according to a warning issued by the World Health Organization."

  (Reuters: LONDON/MUMBAI, July 7, 2015)

"EU bans 700 generic drugs for manipulation of trials by XXX"

- "The European Union has banned the marketing of around 700 generic medicines for alleged manipulation of clinical trials conducted by pharmaceutical research company XXX"

MHRA Expects Self Audits of Governance Systems for Data Integrity (Including Outsourced Activities)

MHRA Intends to Verify during inspections beginning in 2014

MHRA Invited Self Disclosure to GMPInspectorate@mhra.gsi.gov.uk

MHRA Highlighted its Intention to Focus Inspections on Data Integrity Beginning in 2014

**Reason** - "...Bad Practice and .. intentional fraud have been observed across all geographical locations and sectors of the industry..."

MHRA Provides Insight into its Expectations for Data Governance & Provides Definitions for Key Terms

MHRA GMP Data Integrity Definitions and Guidance for Industry March 2015

Introduction:
Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality. This document provides MHRA guidance on GMP data integrity expectations for the pharmaceutical industry. This guidance is intended to complement existing EU GMP relating to active substances and dosage forms, and should be read in conjunction with national medicines legislation and the GMP standards published in Eudralex volume 4.

The data governance system should be integral to the pharmaceutical quality system described in EU GMP chapter 1. The effort and resource assigned to data governance should be commensurate with the risk to product quality, and should also be balanced with other quality assurance resource demands. As such, manufacturers and analytical laboratories are not expected to implement a forensic approach to data checking on a routine basis, but instead design and operate a system which provides an acceptable state of control based on the data integrity risk, and which is fully documented with supporting rationale.

Data integrity requirements apply equally to manual (paper) and electronic data. Manufacturers and analytical laboratories should be aware that reverting from automated/computerised manual/paper based systems will not in itself remove the need for data integrity controls. This may also constitute a failure to comply with Article 23 of Directive 2001/83/EC, which requires an authorisation holder to take account of scientific and technical progress and enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Throughout this guidance, associated definitions are shown as hyperlinks.

Establishing data criticality and inherent integrity risk:
In addition to an overarching data governance system, which should include relevant policies and staff training in the importance of data integrity, consideration should be given to the organisational (e.g. procedures) and technical (e.g. computer system access) controls applied to different areas of the quality system. The degree of effort and resource applied to the organisational and technical control of data lifecycle elements should be commensurate with its criticality in terms of impact to product quality attributes.

FDA Enforcement Priorities for Data Integrity Violations Have Been Affected by a number of External Influences
• **There is Really Nothing Much New with the:**
  - Types of Violations being found
  - Laws that define Prohibited Acts
  - FDA Investigative Techniques (Except Focus on Data Integrity)

• **Why Has FDA Revised its Enforcement Priorities for Data Integrity?**
  - Former FDA Commissioner Put Violators on Notice that Enforcement would be a Priority (Vigilant)
  - Many FDA Employees More than Willing to Advance Enforcement Sanctions
  - Recently FDA has been Collaborating with DOJ, OIG & Other Agencies to Investigate Violations involving Criminal Acts
  - DOJ Seems More Willing (than in the Past) to Support Criminal Charges For Issues Related to GMPs & Manufacturing
<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Sanctions/Recoveries</th>
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<tbody>
<tr>
<td><strong>2014</strong></td>
<td>$4.9 B Recovered</td>
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<tr>
<td></td>
<td>4,017 Persons/Companies Excluded</td>
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<tr>
<td></td>
<td>971 Criminal Actions</td>
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<td></td>
<td>533 Civil Actions</td>
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<tr>
<td><strong>2013</strong></td>
<td>$5.8 B Recovered</td>
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<td>3,214 Persons/Companies Excluded</td>
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<td></td>
<td>960 Criminal Actions</td>
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<td>472 Civil Actions</td>
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<td><strong>2012</strong></td>
<td>$6.9 B Recovered</td>
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<td>3,131 Person/Companies Excluded</td>
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<tr>
<td></td>
<td>181 Criminal Convictions</td>
</tr>
<tr>
<td></td>
<td>367 Civil Actions</td>
</tr>
</tbody>
</table>

External Factors That Influence FDA Enforcement

- **Congressional Oversight**
  - Impact of Committee on Oversight and Government Reform*
    - Scrutiny of FDA Policies and Practices*
    - Congressional Testimony By FDA Tends to Stimulate Enforcement**
    - FDA is likely to Focus on companies with history of non-compliance (*i.e.*, shift of FDA inspection resources to high risk areas)

FDA Promised to Prosecute More Senior Executives

• Jan 29 2010, GAO-10-221*

“Food and Drug Administration, Improved Monitoring and Development of Performance Measures Needed to Strengthen Oversight of Criminal and Misconduct Investigations"

FDA Commissioner’s Reaction

• “…increase the appropriate use of misdemeanor prosecutions… to hold responsible corporate officials accountable.”

• See Mar 4, 2010 Letter to Senator Grassley)**

• Impact on Industry

• Senior Executives Should be Mindful that FDA is likely to continue its increase in Prosecutions under the doctrine of strict liability for Data Integrity Violations

** http://grassley.senate.gov/about/upload/FDA-3-4-10-Hamburg-letter-to-Grassley-re-GAO-report-on-OCI.pdf
External Factors That Influence FDA Enforcement

- **GAO Audits of FDA**
  - **Sep 14, 2011, GAO-11-936T,** FDA Faces Challenges Overseeing the Foreign Drug Manufacturing Supply Chain
  - **Sep 30 2010, GAO-10-961,** “Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed”
  - **Sep 30, 2010, GAO-10-960,** Overseas Offices Have Taken Steps to Help Ensure Import Safety, but More Long-Term Planning Is Needed

Impact of FDA International Offices
FDA (CDER) GMP Warning Letters

48 Warning Letters Issued for Data Integrity Issues During Past 3 1/2 Years (2012-Jul 2015)

(Charging Companies with Violations of the Law for More than a Dozen Data Integrity Issues)
### Incidence of FDA Data Integrity Warning Letters (CDER 2012 - Jul 2015)

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<td><strong>Total</strong></td>
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*1 W/L with Sites in 2 Countries
CDER (OMPQ) Issued 71 GMP Warning Letters Charging Violations of the Law:

- 68% of WLs (48 of 71) Included Violations Related to Data Integrity Issues
- 48 WLs for Data Integrity Included 53 Manufacturing Facilities located in 18 International Countries (includes 1 site in US)
- Data Integrity Violations Ranged from Compromised Data Accuracy to Fraudulent Falsification of Records

*Note: Warning Letters Issued by FDA District Offices are Reported Separately (Not Included in This Presentation)
Out of 48 WLs Charging Data Integrity Violations:

- At least 317 Citations involved Data Integrity Issues in more than a dozen categories
- Incidence of Warning Letter Citations by Quality System is as follows:
  - 62% = Laboratory System (196/317)
  - 24% = Quality System (QA Oversight) (77/317)
  - 10% = Production System (32/317)
  - 2% = Packaging & Labeling System (7/317)
  - 2% = Materials System (5/317)
  - 0% = Buildings & Equipment System (0/317)

*Source: Tetzlaff, R. F., Personal File*
## Incidence of Data Integrity Citations by Quality System (QS) CDER Warning Letters (2012 - Jul 2015)

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<th>Integrity Issue</th>
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<td>Raw Data - Access</td>
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<td>Raw Data - GDP</td>
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Key Data Integrity Concepts
(a Few Management Reminders)
Key Concepts - Management Reminders

1. Meaning

Integrity is Not Limited to Fraud/Falsification [Information/data must Reflect What Actually Happened (Accurate, Truthful & Complete)]

2. Risks

Anticipate Potential for Integrity Lapses (at Any Moment by Any Employee in All Areas)

3. Obligations

- Fulfill Moral Obligation to Carry out Duties Per Stakeholder Expectations
- Understand Legal Obligations (& Penalties) of Non-Conformance (for Self & Company)

4. Consequences

Understand Impact of Data Integrity Lapses on Stakeholders (Patients, Customers, Regulators, Employees, Company, Self)

5. Controls

Establish Controls (Systems & Processes) to Prevent, Detect & Correct Integrity Lapses
1. Understand Meaning of Data Integrity

- **Definition**: For purposes of this Presentation, let’s use the following:
  - **Data Integrity** Means Information and Data have been Collected, Documented, Reported & Retained in a Manner that Accurately, Truthfully and Completely Represents what Actually Occurred

- **One Could Offer Many Alternate Definitions**, but it is important to understand that:
  - It also includes any instance where information or data does not represent what actually happened (including unintentional mistakes or omissions of relevant information)
1. Understand Meaning of Data Integrity

• **A Common Misconception** - Many Believe Data Integrity is Limited to Fraud or Falsification (Intentional Misconduct/Wrongdoing)

• **This is Not True** - Because Any Number of Reasons May Compromise assurances of data accuracy, truthfulness or completeness including:
  
  • **Intentional** - Fraud (Falsification or Other Misconduct)
  
  • **Unintentional** - Errors or Omissions (Mistakes), Malfunctions of Equipment/Computers, etc.
2. Recognize Risks of Data Integrity Lapses

• **Integrity Lapses have Occurred Since Earliest Recorded History**

  One of the First was in ~ 300BC

• **Greek Merchant by Name of Hegestratos**
  - **The Fraud**
    - Took out a large insurance policy known as bottomry, (essentially a loan with boat and cargo as collateral that is forfeited if loan is not paid back)
    - Hegestratos hatched a scheme to:
      - Sink his Empty Boat
      - Keep the Corn
      - Keep the Loan
  - **The Outcome**
    - Hegestratos got caught in the Act by his crew, & drowned trying to escape. His Co-conspirator was prosecuted

2. Recognize Risks of Data Integrity Lapses

• As Long as Laws & Regulations have Existed Integrity Lapses have Occurred in Every Regulated Industry

• History is Replete with Notable Integrity Lapses, including
  • Highly Publicized Incidents, and
  • Countless Lesser Know Instances

• No Reason to Expect that Integrity Lapses Will Ever be Totally Eliminated... So, Responsible Management Must...
  • Anticipate that Integrity Lapses May Occur at Any Moment (by Any Employee in Any/All Areas)
  • Exercise its duty and power by establishing effective Controls (Systems & Processes) to Prevent and Detect Lapses, and if lapses occur to Correct the root cause to minimize the potential for recurrence
"20 percent of the regulated population will automatically comply with any regulation, 5 percent will attempt to evade it, and the remaining 75 percent will comply as long as they think the 5 percent will be caught and punished."

2. Recognize Risks of Data Integrity Lapses

Trust but Verify

• This Audience includes management who are among the most highly astute manufacturers of pharmaceutical products, but...

- **When Reviewing batch production and control records, How Many will:**

  • **Accept at Face Value what is written on Forms, Records, & Reports** (without routinely double checking or verifying the accuracy or completeness by comparing data and information against source records?)

  • **Not Take Independent steps to Confirm the Accuracy or Completeness of what is Written**, because they "trust" the employees (know them to be honest and trustworthy)?

  • **Assume that their Quality Systems are Robust** and have no reason to suspect data and information may not reflect what actually happened?
2. Risks of Data Integrity Lapses

Integrity Breaches Occur When/Where Least Expected

• **Reminder** - Even with Well Designed Programs & Controls for Managing Data Integrity:
  
  • Any Individual (or group of Individuals) is Capable of Intentionally Deviating from the established requirements; &
  
  • Even Well Intentioned Persons may Make Unintentional Mistakes during the Collection, Review, Reporting & Retention of GMP data; So...
  
  • It's Essential to Have Continuous Management Oversight of Data Integrity Controls to Ensure that all Data are accurate, truthful and complete (& Errors are Detected if they Occur)

• **Management Must Remain Constantly Vigilant for:**
  
  • Unintentional Mistakes (e.g., Errors/Omissions)
  
  • Intentional Misconduct (e.g., Fraud/Falsification)
2. Recognize Risks of Data Integrity Lapses

Understand Reasons for **Intentional** Data Integrity Lapses (Fraud/Falsification)

"It's Either **Greed** or **Need**"
Joseph T. Wells*

"It's to **Avoid** Pain or **Achieve** Gain"
David Chesney**


**David Chesney (PAREXEL Consulting) - Personal Communication
2. Recognize Risks of Data Integrity Lapses

Understand Reasons for Intentional Data Integrity Lapses (Fraud/Falsification)

- Pressure
- Opportunity
- Rationalization

Understand Reasons for Intentional Data Integrity Breaches (Fraud/Falsification)

Opportunity
- Control System Gaps
  - Allows Actions to go Undetected
- Employee Believes
  - Won't Get Caught (No One Will Ever Find Out) and
  - Consequences are Not So Severe (Worth the Risk)

Pressure
- Fear of Penalties
  - Targets
  - Deadlines
  - Metrics
- Management Signals
  - Real
  - Perceived

Rationalization
- Attitude
  - Knows it's Wrong, but:
    - Others Have Done Same or Similar
    - Perceived as "Minor Infraction - No Big Deal"
- Ethics/Honesty
  - Not Everyone is Honest
  - Ethics is in Eyes of Beholder
2. Recognize Risks of Data Integrity Lapses

Recognize Reasons for Unintentional Data Integrity Breaches (Errors)

"Everybody Makes Mistakes.... Ethics Determine the Actions that Follow"
3. Understand Obligations

Who is Responsible for Violations of the Law?

- Any Person Who **Commits an Act or Omission** That Causes the Violation

- Any Person who has Duty and Power (Responsibility) to **Prevent** the Violation from Occurring and to **Detect** the Violation if it should occur

... continued
3. Understand Obligations

- **Doctrine of Strict Liability** - Permits Prosecutions for violations of FD&C Act

- **Precedent Case**
  - 1975 U.S. Supreme Court case US Vs. Park (President of a retail food chain)
  - Supreme Court ruled persons exercising supervisory responsibility can be prosecuted for failure to **prevent** or **correct** violations of the FD&C Act

- **New Priority in 2015** - Expect to See Increase in Prosecutions of Pharmaceutical Executives

---

**1975 Supreme Court Ruling – US vs Park**

“The Act imposes not only a positive duty to seek out and remedy violations when they occur but also, and primarily, a duty to implement measures that will ensure that violations will not occur…”

“We are satisfied that the Act imposes the highest standard of care and permits conviction of responsible corporate officials, who in light of this standard of care, have the power to **prevent** or **correct violations**…”

(Emphasis added)

3. Understand Obligations

- **Legal Obligations:**
  - Responsible Management is held liable for data integrity violations (even if they are unaware of the violations) based on their failure to establish effective controls to **Prevent, Detect, & Correct** integrity lapses (**Note**: Lack of Awareness of The Violation Is Not An Excuse):
    - Management has a Legal and Moral Obligation (Duty & Power) to establish effective systems and processes to ensure the accuracy, truthfulness and completeness of data and information that is required by:
      - Applicable Laws Enforced by the Regulatory Agencies, and
      - Expected by All of it Shareholders, e.g., ...

...continued
### 3. Understand Obligations

Management **Has a Moral Obligation to Fulfill Stakeholders' Expectations for Data Integrity**

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Expectation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td><strong>Consume Safe-Effective Medicines (Every Time)</strong></td>
</tr>
<tr>
<td><strong>Prescribers</strong> (Doctors, Hospitals, Clinics)</td>
<td><strong>Administer Safe-Effective Medicines (Every Time)</strong></td>
</tr>
<tr>
<td><strong>Providers</strong> (Healthcare Distributors)</td>
<td><strong>Receive Uninterrupted Supply at Lowest Cost</strong></td>
</tr>
<tr>
<td><strong>Regulators</strong> (Local, State, Federal, Int.)</td>
<td><strong>Compliance with Applicable Laws &amp; Regulations</strong></td>
</tr>
<tr>
<td><strong>Reimbursers (Gov't)</strong> [Medicare, Medicare, Contracts, etc.]</td>
<td><strong>Receive True Claims for Reimbursement</strong></td>
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<tr>
<td><strong>Reimbursers (Private)</strong> (Insurance)</td>
<td><strong>Receive True Claims for Reimbursement</strong></td>
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<tr>
<td><strong>Shareholders</strong></td>
<td><strong>Obtain Positive Return on Investment (ROI)</strong></td>
</tr>
<tr>
<td><strong>Employees</strong></td>
<td><strong>Have Pride in Their Products &amp; Company</strong></td>
</tr>
</tbody>
</table>
3. Understand Obligations

• **Managements Role in Ensuring Data Integrity is to:**

  • Establish Effective & Robust Systems & Processes for Collecting, Documenting and Reporting Information and Data in a manner that always accurately, truthfully and completely represents what actually occurred including:

  • Instituting Policies, Procedures and Controls to **Prevent** data integrity lapses from happening

  • Effectively monitoring all data sources to **Detect** & **Correct** the root cause to minimize the potential for recurrence of data integrity lapses (if they should occur)
4. Understand Consequences

• Violating the Laws that Apply to Data Integrity Pose Serious Liabilities to the Company & its Employees

• Data Integrity Lapses Impact All Stakeholders (Patients, Customers, Regulators, Employees, Company, Etc.)

• Important to Patients/Customers Because ...
  • They Expect Products to be Safe, Effective, & in Conformance with Regulatory Requirements
  • Integrity Lapses Undermine Customer Confidence & May Result in Lost Sales
Data Integrity Lapses Jeopardize Business Success

4. Understand Consequences

• **Adverse Publicity**
  - Impact on Stock
  - Lost Sales/Customers
  - Recalls
  - Delayed Product Launch
  - Whistleblower Law Suits
  - Bankruptcy

• **Regulatory Sanctions**
  - Prosecution
  - Seizure
  - Injunction (Consent Decrees)
  - Application Integrity Agreement (AIP)
  - Corporate Integrity Agreements (OIG)
  - Fines/Restitution
  - Import Alert
  - Warning Letter
5. Establish Effective Control Systems for Data Integrity

• Why Doesn't Management of Some Companies Make Data Integrity a Priority Focus?

  • **Naivety of Management who truly believe that:**
    • Our Quality Culture is strong, Our employees will do what is right
    • Our Employees have been trained (and told of our Zero Tolerance Policy); they are not likely to Falsify Records
    • Our Employees Know the Importance of Data Integrity

  • **Management Experience with Data Integrity Lapses is Limited (or Non-Existent)**
    • Management has not personally been made aware of data integrity Lapses for employees under his/her Span of Control (i.e., does not suspect their employees would engage in unacceptable practices), consequently ....
    • Have Not Established Robust/Effective Systems for Preventing or Detecting practices or conditions that lead to Data Integrity Lapses
5. Establish Effective Control Systems for Data Integrity

Many Companies Struggle with Deciding Optimum Control Systems for Ensuring Data Integrity

• Given the Abundance of Recent Adverse Publicity & Compliance Trends, do not Feel Comfortable (Safe & Secure) About Data Integrity Unless & Until You Have:

  • Verified the Robustness of Programs/Controls for Preventing Data Integrity Lapses & Detecting them if they Should Occur

  • Confirmed Effectiveness of the Controls Used to Continuously Monitor Employee Behavior & System Performance:

    • Never Assume that Everyone will always do what is Expected or Required (Trust but Verify)

    • Expect that Any Individual at Any time is capable of Engaging in Behavior or Practices that could cause Data Integrity Lapses
Data Integrity as a Key Quality System*

Data System Functions*

Collection: Employee Behavior (GDPs) & Electronic Acquisition

Analysis: Manual or Automated Records

Reporting: Written Reports & Electronic Records

Retention: Document & Data Control Procedures

* Advocated by Ron Tetzlaff During 39th International GMP Conf. (Athens, GA) , Mar 2015
Benefits of Data Integrity as a Key Quality System (QS)*

- **Increase Visibility and Stature** - Bring Data Integrity up to Par with other Quality Systems such as Deviations, Change Control, CAPA, Validation, etc.

- **Provide Framework for Defining Key Elements** - Comprehensively define the meaning of Data Integrity and outline the Key Requirements that need to be satisfied to ensure all GxP data are accurate, truthful and complete (i.e., becomes the standard against which all other QS must conform related to data collection, analysis, reporting & retention)

- **Establish Linkages with Other Relevant Quality Systems** - Provides mapping (linkage) of Requirements defined in the Data Integrity QS with the detailed instructions and requirements that are outlined in the various Quality Systems involved with data collection, analysis, reporting and retention
Five Key Strategies For Preventing Data Integrity Lapses
Since any Employee at any Moment can engage in behavior that jeopardizes Data Integrity, Responsible Management has a duty to implement control measures to ensure that violations will not occur in the first place, and to seek out & correct violations when they occur.

Among the Many Strategies that are available for Preventing Data Integrity Lapses, five Practical examples are Highlighted:

1. Establish a Strong Quality Culture
2. Instill in Every Employee the Meaning of Data Integrity
3. Establish Clear Expectations for Employee Behavior
4. Increase Management Presence on the Shop Floor
5. Know The Regulatory Trends (Learn from Mistakes of Others)
Definition - Quality Culture has been defined many ways, but put simply it represents the employees values, beliefs, thinking and behaviors about quality and data integrity.

Fathers of Quality Systems* - A Number of Quality Gurus Advocated Developing Quality Culture as a "Project" such as:

- Juran
- Deming
- Crosby

1. **Awareness** - Create & Maintain Quality Awareness

2. **Leadership** - Provide Evidence of Quality Leadership by Management

3. **Development** - Provide Opportunities for Self Development (Empowerment)

4. **Participation** - Inspire Action through Participation

5. **Recognition** - Provide Recognition to Reward Quality Behavior

Deming's 14 Points

1. Create constancy of purpose toward improvement of product and service.
2. Adopt the new philosophy.
3. Cease dependence on inspection to achieve quality.
4. End the practice of awarding business on the basis of price tag alone.
5. Improve constantly and forever the system of production and service.
6. Institute training on the job.
7. Institute leadership.
8. Drive out fear.
10. Eliminate slogans, exhortations, and targets for the work force.
11. Eliminate numerical quotas for the work force and numerical goals for management.
12. Remove barriers that rob people of pride of workmanship. Eliminate the annual rating or merit system.
13. Institute a vigorous program of education and self-improvement.
14. Put everybody in the company to work to accomplish the transformation.

Figure 6. Deming's 14 Points (Deming, 1986).

**Crosby**

*14 Points for Transforming Quality Culture*

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**Crosby's 14 Steps**

1. Management commitment
2. The quality improvement team
3. Quality measurement
4. The cost of quality
5. Quality awareness
6. Corrective action
7. Zero defects planning
8. Quality education
9. "Zero Defects Day"
10. Goal setting
11. Error-cause removal
12. Recognition
13. Quality councils
14. "Do it over again"

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*Figure 1. Crosby's 14 steps (Crosby, 1987).*

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*From: http://dtic.mil/dtic/tr/fulltext/u2/a256399.pdf*
**Crosby**
Quality Culture is Carefully Constructed with 4 Key Elements*

- **Requirements** - Quality means conformance to requirements (not "goodness" or "elegance")
- **Prevention** - The system for causing quality is prevention, not appraisal.
- **Performance** - The performance standard must be Zero Defects, not "that's close enough"
- **Measurement** - Measurement of quality is the Price of Non-conformance, not indices.

*Ibid*
• "Quality means Conformance, not Elegance

• There is no such thing as:
  • A Quality Problem
  • The economics of quality; it is always cheaper to do the job right the first time

• The only Performance Standard is Zero Defects

• The only Performance Measurement is the cost of quality (COQ)"

Management Must:

1. Lead By Example [Management's Actions & Words are Always Consistent with Values (Ethics)]
2. Define Required Behavior/Conduct
3. Frequently Communicate Clear Expectations & Periodically Reinforce
4. Hold Everyone Accountable for Data Being Accurate, Truthful & Complete
5. Relentlessly Monitor Employee Actions (Behavior/Performance)
6. Recognize (Reward) Conforming Behaviors
7. Always Address Unwanted Behaviors Promptly
8. Discipline Employees who Intentionally Violate Company Requirements or applicable Laws
9. Confirm that All Data & Information has been Documented as Verified for Accuracy, Truthfulness and Completeness
10. Use Independent Experts to Periodically Verify Effectiveness of Systems, Processes & Controls for Data Integrity
Define the Data Integrity Requirements

- **Values Statements** - Establish Integrity (Ethical Conduct) as a Core Value for the Company

- **Code of Conduct**
  - Establish a Clearly Defined Meaning of Data Integrity (Ethics, Accuracy, Truthfulness, & Completeness)
  - Define the key elements necessary to ensure the reliability and integrity of data and information throughout all aspects the development and production of drug products, including the elements of:
    - Corporate Governance/Ethics
    - Employee behavior (Ethics)
  - Establish Annual Employee Recertification of Compliance to Code of Conduct...

---

Strategy No. 1 - Establish a Strong Quality Culture
Strategy No. 1 - Establish a Strong Quality Culture

Define the Data Integrity Requirements

**Requirements**
(Policies, Standards, & Procedures)

Establish the Requirements that Define:
- Meaning of Data Integrity
- Fundamental Elements (Requirements) that are necessary to **Prevent** Data Integrity Lapses, and to monitor performance to **Detect** lapses if they should occur
Key Data Integrity Elements of the Quality Culture

Designate Independent Compliance Officer
- Defined Responsibilities (including Data Integrity)
- Reports to CEO
- Provides Findings to the Board of Directors

Establish Systems for Employees to Report Concerns
- About known or suspected misconduct, wrongdoing or other data integrity issue
  - Without Fear of Retaliation
  - "Don't Shoot the Messenger"
- Telephone Hotlines (1-800 Numbers), and E-Mail (Including Anonymous Reporting)

Protect "Whistle Blowers"
- Provide Protection From Recriminations
Establish Systems & Processes for Performing Independent Investigations of:

- Employee Misconduct/Wrongdoing that calls into Question the Integrity of Data, including:
  - Designating Independent Responsible Person(s) to lead the Investigation
  - Identify Roles of Key Management including Legal Counsel (where indicated)
  - Determination of gaps in systems, processes or control procedure that failed to prevent or detect the conduct at the time of occurrence
  - Identify Root Cause and Corrective actions to prevent recurrence
  - Determine need for disciplinary action based on criteria defined in written policies, standards or procedures
Strategy No. 2 - Instill in Every Employee the Meaning of Data Integrity

Instilling Fundamental Concepts Means:

- **Awareness of:**
  - Fundamental Concepts and Principles for Ethical Conduct & Good Documentation Practices (Why All Records Must Reflect what Actually Happened)
  - Consequences/Impact of Data Integrity Lapses on:
    - Patients, Customers and other Stakeholders
    - Quality of Drug Product
    - The Company & Employees
  - Penalties for Violating Laws
    - Penalties for Company
    - Liabilities of Individuals
Strategy No. 2 - Instill in Every Employee the Meaning of Data Integrity

Instilling Meaning of Data Integrity Means:

- **Knowledge of & Adherence to Requirements:**
  - Providing Comprehensive Ongoing Learning Programs to ensure All employees are Knowledgeable of:
    - **Company Requirements** (Policies, Standards, Code of Conduct, Procedures, Methods, and other instructions)
    - **Legal Requirements** (Applicable Laws)
Strategy No. 2 - Instill in Every Employee the Meaning of Data Integrity

Good Documentation Practices Training

• Ensure All Employees have appropriate Education & Training (including Officers, Directors, Mgrs/Supv., Contractors, Temporary Employees, etc.)

• Provide Fundamentals (procedural requirements) on how to record data:
  • Recording dates and Time
  • Signing/Initialing records
  • Correcting Errors, &
  • Other details of good documentation practices, However ...

GMP Training Alone is Not Enough

• ...continued
2. Instill in Every Employee the Meaning of Data Integrity

GMP Training Alone is Not Enough Because:

• Instilling Awareness of Fundamental Concepts and Knowledge of Requirements is Far More than:
  • A few classroom Training sessions on Good Documentation Practices

• Employees have widely divergent Beliefs, Values, Thinking and Behavior (Ethics) when it comes to Data Integrity

• Employees who do not clearly Understand the Fundamental Concepts of Data Integrity may knowingly or unknowingly cause data integrity Lapses

• Employees may know what procedures say with respect to Proper Documentation Practices, but may still engage in Inappropriate Conduct for any number of reasons
Strategy No. 2 - Instill in Every Employee the Meaning of Data Integrity

Reinforce Learnings Often

- Sustain Awareness by Providing All Staff with Periodic Learnings on the Fundamental Concepts of Data Integrity & Ethical Behavior

- Reinforce the:
  - Importance of Required Behaviors
  - Consequences of Prohibited Practices

- Ensure Understanding of "Why's" Not Just "Don'ts" For Example: ...continued
Sustain Awareness Levels by:

- Addressing each of three Reasons that Account for all Data Integrity Lapses due to Employee Behavior:
  - **Inadvertent Mistakes** (e.g., data entry errors, Transcriptions, omissions, misunderstandings)
  - **Unintentionally Deviating** from a Requirement because Employee was Unaware of the Requirement (or is Unclear)
  - **Intentionally (Knowingly) Deviating** from a Requirement based on:
    - Rationalization based on Belief that the Requirement is "Not that Important"
    - To Gain some Benefit or to Avoid an Adverse Consequence (e.g., to Meet a target/Deadline or Fear of Discipline)
Strategy No. 2 - Instill in Every Employee the Meaning of Data Integrity

Instilling Awareness Means:

- Visibility of Management who Lead by Example (at All Times, No Exceptions)
- Employees Must Perceive that Actions and Deeds of Management are Always Consistent with Established Values & Standards (Requirements)
- Employees must Never Perceive that Management has Deviated from the Rules/Requirements or engaged in Conduct that does not Conform to Company Standards
- Otherwise, Credibility is Broken & the Standard will be viewed as Unimportant (Meaningless)
Strategy No. 3 - Establish Clear Expectations for Employee Behavior

Set Clear Expectations

WHO

Everyone is Responsible for Reporting All Data & Information in a Manner that accurately reflects what happened

WHAT

All Documents, Records, Reports that describe what happened or results obtained

WHEN

An accurate record of date and/or time that activities are performed or results are obtained

WHERE

Document Accurately the location(s) where activities occur or results are obtained

WHY

- Preserve Contemporaneous information about what actually happened or results obtained
- Establish the quality/safety of the drug product
- Comply with Laws that Require Accurate Records
Communicating Expected Behavior - requires:

- Making Sure Everyone Understands his/her obligation to maintain accurate, truthful & complete records that reflect what actually happened.

- Ensuring that the values, beliefs, thinking and behaviors of all employees match the core values & Requirements of the Company and applicable Laws), & the Reasons Why Employee Behavior is Important to the Company & the Regulators.

- Identifying Clearly & Completely the Policies & Standards (Requirements) for Data Integrity.

- Identify those Behaviors that Constitute Unacceptable Conduct, and

- Explain "Why's" Not Just "Don'ts"
Strategy No. 3 - Establish Clear Expectations for Employee Behavior

- **Monitoring** employee behavior/actions on a continuous basis to **Prevent** data integrity lapses from happening and to **Detect** if they should occur.

- **Holding Accountable**, and Changing behaviors/actions that do not conform (Thru Additional Learning or Disciplinary Actions, as appropriate)

**Disciplinary Actions** - Establish Clear Procedures/Criteria for dealing with Data Integrity Lapses & Apply consistent disciplinary actions to serve as a deterrent (as appropriate)

Establish a process & criteria (with HR & Legal) for disciplinary actions for violations due to negligence or reckless conduct.
Strategy No. 4 - Increase Management Presence at Workstations

- **Spend More Time at Workstations, Including:**
  - Manufacturing Areas
  - Engineering and Utility Areas
  - Laboratories
  - Warehouses
  - Record Retention Areas

- **Be Seen Frequently By Employees in their Work Area**
  - Frequently Observe Employees Performing Tasks (Review of Work Products with Focus on Data Integrity)
  - Provide Regular Feedback to Staff About:
    - Importance of Data Integrity
    - Expected Behaviors
    - Prohibited Practices
    - Explain "Why's" Not Just "Don'ts"
Perform Routine "Walkabouts" in all Areas

- Make Presence Known to Subordinates
- Make it Known that You:
  - Care About Operations in All Areas
  - Want to help All Employees to Conform to the Requirements
  - Are Examining Everyone's Work, and Why (Trust by Verify)
  - Are Responsible for Verifying that All Operations are Being Conducted in Accordance with Requirements

Food for Thought
“You can observe a lot just by watching”
Yogi Berra
Strategy No. 4 - Increase Management Presence at Workstations

- **Spend More Time at Workstations**
  - Observe Employee Actions & Behaviors Related to Contemporaneous Entry of Data & Information
    - Recognize/Reward Employees Exhibiting Desired Behaviors
    - Explain the Reasons ("Whys") to those who Don't
Frequent presence of Management at Employees' Workspace tends to:

- Increase Awareness & Improve Employee Behavior when management is perceived as:
  - Caring Enough About the Importance of their work product to provide Feedback
  - Being Sincere (non-threatening, & wanting to help improve operations)
  - Providing Periodic Feedback to **All** Staff (not singling out individuals)
Establish Management Review Process to:

- **Assess Whether Workload May Potentially Impact Data Integrity:**
  - Deadline or Backlog Situations may result in Compromising Accuracy Reviews
  - Recognize Pressure Points (Be Alert for Potential Indicators & Signals), such as:
    - Delays in Performing/Completing Analyses or Reviews/Approvals (e.g., Overdue Stability Tests)
    - Backlog of Records Pending Reviews (Unusual Number or Delays)
    - Special Requests for Priority Analyses (Special Tests to be “Rushed”)
    - Employees Comments/Complaints about Workload
    - Personnel Shortages for Particular Production Tasks or Testing Samples
Learn from Mistakes of Others

- Data integrity issues are certainly not new, but
- Yet the Regulators continue to find data integrity lapses in many companies
- Such companies have not kept abreast of regulatory requirements and/or have not established Effective controls to ensure the integrity of their data

Sources

- Readily available documents provide a wealth of information about the Nature of Data Integrity Lapses being found by FDA & other Regulatory Authorities:
  - FDA Warning Letters, Import Alerts,
  - Press Releases (FDA, DOJ, OIG)
  - FDA-483s and Inspection Reports (EIRs)
  - Trade Publications (See Appendices 1 & 2)
Strategy No. 5 - Know The Regulatory Trends (Learn from Mistakes of Others)

- **Prudent Companies will:**
  - **Establish Systems/Processes to Track**
    Inspection Findings & Enforcement Sanctions for Data Integrity Issues, such as:
    - **Press Releases** - Recent Publicized Press Releases (OCI, DOJ, & OIG) Provide Valuable Insight as to the Nature of Data Integrity Violations that are Resulting in Prosecutions, Fines, Forfeitures, Debarments, Disqualifications, Consent Decrees, Application Integrity Policy, & other Sanctions
    - **[See Appendix 1 (OCI Prosecutions) & Appendix 2 (Internet Sites)]**
  - Determine whether the same/similar conditions or practices may exist in own Company, & implement Corrective & Preventative Actions
Enhance Own Systems/Processes

• Determine Whether the Potential Exists for the Same or Similar Conditions that resulted in Sanctions at Other Companies:

• Initiate Corrective Actions where indicated including

  • Modifying Systems and Processes
  • Re-training of affected Personnel
  • Verifying Effectiveness of CAPAs to eliminate Root Cause
Applications

**Establish a Process for Routine Periodic Verification of:**

- **Accuracy of Regulatory Applications (NDA CMC & DMF), such as:**
  - Responsible Management in Respective Production & Control Departments Confirm that Current Conditions & Practices Match Commitments in Approved Applications
  - Periodically Compare Data & Information Reported in Site Annual Product Reviews (APRs) against Commitments made in Application Filings (e.g., NDA CMC, Amendments or Supplements, & Annual Reports, DMFs, etc.)
• Data integrity lapses may occur at any time for any number of reasons
• Responsible Management has a Duty to Implement Reasonable control measures for detecting events, conditions, and test results that do not conform to the requirements for collection, analysis, reporting and retention of GMP data
• Among Many Available Strategies, five Practical Examples are Highlighted for Detecting Data Integrity Lapses
  1. Increase Time at Workstations
  2. Examine the Creation & Handling of Records
  3. Conduct Independent Audits by Data Integrity Experts
  4. Review Non-Conforming Events or Results
  5. Ask Employees Where Data Integrity Improvements May be Warranted

...continued
Strategy No. 1 - Increase Time at Workstations

Observe Employee Documentation Practices at Workstations in All Areas

- Examine Cabinets, Work benches, & Desks (Drawers) and Observe Employees Performing Normal Job Functions including Review of In-process Records. Be Alert for:
  - Activities Not being Documented Contemporaneously (In Real Time)
  - Entry of Raw Data on Post-it-Notes, Scrap Paper or other Temporary format such as unofficial notepads or diaries
Strategy No. 2 - Examine the Creation & Handling of Records

**Trash**

- **Examine Trash Receptacles & Paper Recycling Containers**
  - Look for Evidence of Raw Data & Records being Discarded (e.g. weight slips, calculations, data from in-process tests, etc.)

**Workload**

- **Examine Workstations of Managers & Supervisors to Assess Workload**
  - Be Alert for Backlogs that May Impact Time Available for Verifying Accuracy & Completeness of Records & Reports
  - Accuracy Verifications may be Skipped or Rushed when Backlog Conditions Exist
Strategy No. 2 - Examine the Creation & Handling of Records

Review Attendance & Access Records

- Determine whether Managers or Supervisors are:
  - Verifying personnel were present on the Premises or in Work Areas on dates or times reflected in the production or laboratory records, e.g.,
  - Documenting Verification of Correctness of Entries on Original Batch production and laboratory Control records by Comparing Against entries in Building/Room Access Logs (paper or electronic records)
Choose Auditors with Data Integrity Experience

- **Data Integrity Safeguards** can not be Effectively Judged by the personnel who developed the systems or those who routinely monitor system performance.

- **Experienced Experts** routinely find data integrity issues that were unknown to management & had not been detected during either the daily management oversight or audits performed by its own internal auditors.

- **Utilize Independent Experts** who are experienced in Detecting Data Integrity Lapses in other facilities or in other Companies (i.e., a Fresh Set of Eyes with Objective/Independent Approach)
  - Either from Other Departments or Locations (Corporate Auditors) or
  - External Third Party Consultants
Establish Risk Based Audit Plan/Schedule

- Develop a Schedule that Provides for Coverage of All Quality Systems based on such Risk Factors as:
  - **Recent Regulatory Trends** at other Companies
  - **Laboratory System** - Lab Operations including Automated Systems for data collection, analysis, reporting and retention
  - **Quality Management System** - QA Oversight & Management of Data Integrity (Availability of systems for verifying accuracy of raw data & original records including Paper & Electronic Records
  - **Learning Management System** - Presence vs. Absence of a Training Program that focuses Specifically on the meaning of data integrity & Requirements for Employee Conduct (Ethics)
Continued

- **Production System** - Batch Production & Control Operations

- **Computer Systems** used for production, raw materials, buildings and equipment, packaging and labeling and other non-laboratory applications for data collection, analysis, reporting and retention including validation, security access controls, and data retention

- **CAPA System** - Presence or Absence of Events/Incidents involving suspected or confirmed data integrity lapses that resulted in corrective or preventive actions

- **Prior Audits** - Evaluate the Results of previous Regulatory Inspections or Internal Audits (presence or absence of data integrity focus)
Opportunities for Data Integrity Lapses - occur most often when non-conforming events happen during production or when OOS laboratory test results are obtained:

- Reasons - Misguided employees may attempt to cover up their mistakes (errors) or believe that can help the company (or self) to avoid detection by fabricating data or omitting material details about what actually happened.

- Among the Reasons for not reporting deviations or OOS test results in an accurate, truthful or complete manner include: ...continued
Reasons (Continued)

- **Disregarding Out of Specifications Results in Favor of Passing Results** - Employees attribute OOS test results to laboratory error (or Outlier) without supporting evidence or scientific justification, and then discarding original samples and test results and replacing with data from another test or another sample (Reporting Only Passing Results)

- **Trial Injections** - Performing "Unofficial" Testing to see if passing results are obtained, and if not, repeat testing until passing result is obtained (discarding the raw data and not reporting the OOS test results)

- **Unexpected Stability Results** - Disregarding OOS/OOT test results when results are inconsistent with earlier test stations (without supporting evidence), and discarding the original data/records & Substituting with Replacement Data...continued
Reasons (Continued)

- **Backlogs** - Supervisors/Reviewers of production & control records who have a large backlog may not spend the time needed to carefully verify accuracy of raw data & information reported in the records (too busy to see mistakes in first place)

- **Production Problems** - Employees may under report the incidence of product defects, Number of units rejected or other details about the circumstances or what actually happened (such as when: operations do not perform as expected or employees make errors or fail to follow required procedures)

- **Fear of discipline** - Employees who have made a mistake may fail to report the incident (or leave out material details), they believe will be held responsible for causing the Problem & will be disciplined (May Attempt to Cover-up Mistakes) ...continued
• **Timelines or Deadlines Not Being Met** - The Risk of Unsupported Conclusions (data integrity lapses) Increases when Investigations or Activities are not Closed/Approved within Established Target/Due Dates or Deadlines, Such as:
  • Deviation/OOS Investigations (Overdue)
  • CAPAs (Overdue)
  • Stability Samples (not tested by due date)
  • Calibration (Overdue)
  • Preventative Maintenance (Overdue)
  • Production Time Limits (Exceeded)
Increased Risks of Data Integrity Lapses Occur During Events involving Deviations or OOS test results because:

- Conditions/Results deviated from Requirements
- Errors (Mistakes) are at risk of not being reported (or material details being omitted) when Employees Fear being Disciplined for Causing the Problem
- Overdue activities may not be reported contemporaneously (e.g., backdating)
- Raw data or Original Records may be discarded or altered to prevent detection of a problem
- Conclusions or Decisions about acceptability of products or Root Causes may not be supported by the available information or data
- Errors may not detected due to incomplete or ineffective verification of accuracy of raw data & information reported in the records
Strategy No. 5 - Ask Employees Where Data Integrity Improvements May be Warranted

- **Ask for Feedback** - Employees frequently know where the potential problems are, but have not come forward, because "Nobody asked for their Input"
  - Often the employees will have valuable suggestions about how address the issues, but have never been asked to help with the solution
  - When Management Solicits Employee Feedback, the employee will likely:
    - Provide valuable suggestions
    - Appreciate being asked to collaborate
    - Be more receptive to eventual changes
    - Feel Ownership when Improvements are Adopted
    - Embrace the Changes rather than Resist
• Knowledge/Suspicions - When an Employee has engaged in misconduct/wrongdoing or the company has lax controls, almost always Someone else is aware of it (or at least suspects that a problem may exist)

  • Always easier for an employee to answer directed questions rather than to initiate allegations based on incomplete information or hearsay

  • When asked about Potential issues Employees will be more forthcoming (rather than to expect them to make unsolicited allegations about the company or their colleagues)
Strategy No. 5 - Ask Employees Where Data Integrity Improvements May be Warranted

Obstacles

• **Reluctance** - Employees May be Reluctant to Be forthcoming about Awareness of Data Integrity Issues for a number of reasons:
  • Fear of Self Incrimination/Disciplinary Action/Retaliation
  • Avoid "Finger Pointing" to Colleagues (being a "Snitch")
  • Suspicions may be based on Hearsay or Impressions rather than Concrete Facts (don't have enough information to be certain)
Strategy No. 5 - Ask Employees Where Data Integrity Improvements May be Warranted

- **Reporting Concerns** - Encourage Employees to Report any Concerns about Inappropriate Employee Conduct (Ethics) or Lax controls that might Impact Data Integrity or other Problems

- Encourage Anonymous Reporting if an Employee is Reluctant to discuss Issues with Management and does not want to be identified

- Stress that the most important point is to share information so the matter can be evaluated and corrected if necessary. Convey Sincerity that the Company always wants to do the right thing, and needs to Know about any instance where improvements may be needed
Some Additional Data Integrity Perspectives are Available on Video and Podcasts*

Top 5 Misconceptions About Data Integrity

Watch Ron Tetzlaff, Corporate Vice President, PAREXEL Consulting, discuss the top five misconceptions management has about data integrity lapses. View Now

6 Ways to Detect Data Integrity Mistakes

Listen to Ron Tetzlaff discuss five ways that your company can detect data integrity mistakes and rectify them. Listen Now

5 Ways to Prevent Data Integrity Mistakes

In this short podcast Ron Tetzlaff discusses five ways that your company can avoid data integrity mistakes. Listen Now

The Fundamental Concept of Data Integrity Means Data & Information are Accurate, Truthful and Complete (represent what actually happened)

Data Integrity is the single Most Important Issue for the FDA & Other Regulators, and Violations are given the Highest Priority

Management has the Responsibility (duty and power) and moral obligation to Prevent and Detect data integrity violations

Management is held liable for data integrity lapses and the consequences for data integrity violations are severe

Described were some Practical Strategies for Preventing and Detecting Data Integrity Lapses
"It isn't that they can't see the solution,
It is that they can't see the problem"

G.K. Chesterton
1874-1936
Data Integrity
Appendix 1

Some Notable Prosecutions by Office of Criminal Investigations (OCI)

OCI Prosecutions (Selected Examples)*

03-10-2015  XXX Pleads Guilty in Connection with Adulterated Infants' and Children's Over-the-Counter Liquid Drugs

02-19-2015  Medical Drug Re-Packager and Company's Senior Executives Indicted on Fraud Charges and Criminal Violations of the Food, Drug and Cosmetic Act

02-10-2015  XXX Company (Medical Drug Repacker) Indicted on Fraud Charges for Criminal Violations (and Conspiracy to violate the FD&C Act) related to non conformance to cGMP (sterile drug manufacturing) including charges of Conspiracy to violate FD&C Act

*From: OCI Press Releases on FDA Website: http://www.fda.gov/ICECI/CriminalInvestigations/ucm123086.htm
OCI Prosecutions (Selected Examples)*

02-06-2015  XXX Company Agreement to Pay $2.8 M to Resolve False Claims

12-08-2014  XXX Company & Former CEO Please Guilty to Distributing Medical Device after FDA rejected application for marketing clearance

10-29-2014  XXX company settlement to pay $6M to Resolve False Claims

10-22-2014  XXX Company settlement to pay $350M to Resolve Allegations of Kickbacks
OCI Prosecutions (Selected Examples)*

09-24-2014 XXX Company to Pay $55.6 M to Resolve False Claims re Promotion Practices

02-21-2014 Physician Sentenced to Prison for False Statement to Agent

11-07-2013 XXX Pharmaceuticals Pleads Guilty & is sentenced

11-06-2013 Members of illegal Company XXX plead guilty (misbranded drugs)

11-04-2013 XXX Company to pay more than $2.2 Billion to resolve Criminal and Civil Investigations

11-04-2013 XXX company to plead guilty & pay over $1.6 Billion to resolve allegations of misbranding & filing false claims

05-13-2013 Generic Drug Maker XXX pleads guilty & agrees to pay $500 Million to resolve False Claims Allegations, cGMP Violations & False Statements to FDA
<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-19-2012</td>
<td>XXX Company pleads guilty to Federal Charges &amp; Pays $762 Million to resolve Criminal &amp; Civil Fraud Allegations</td>
</tr>
<tr>
<td>07-02-2012</td>
<td>XXX to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data</td>
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<tr>
<td>05-07-2012</td>
<td>XXX Company to pay $1.5 Billion to Resolve Criminal &amp; Civil Investigations of off-label promotions</td>
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<tr>
<td>04-19-2012</td>
<td>XXX Company Sentenced in Connection with unlawful Promotion of XXX drug</td>
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<tr>
<td>11-22-2011</td>
<td>Justice Dept announces Nearly $1 Billion Civil &amp; Criminal Resolution with XXX Company over promotion of XXX drug</td>
</tr>
<tr>
<td>10-05-2011</td>
<td>XXX Company pleads guilty to misbranding XXX drugs</td>
</tr>
</tbody>
</table>
OCI Prosecutions (Selected Examples)*

04-14-2011  XXX company sentenced for false & misleading Statements related to XXX drug clinical tests

03-10-2011  XXX Former CEO of XXX Pharmaceutical, Pleads Guilty to Misbranding Drugs and Agrees to Pay United States $1.9 Million as Fines and Forfeiture

03-02-2011  XXX Pharmaceuticals To Pay $164 Million For Criminal Violations

02-28-2011  XXX Pharmaceuticals Pleads Guilty, Sentenced for Off-Label Marketing of XXX

01-28-2011  XXX Pharmaceuticals Corporation Sentenced for Off-Label Drug Marketing

12-15-2010  Pharmaceutical Companies to Pay $214.5 Million to Resolve Allegations of Off-Label Promotion of XXX Drug
<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>11-09-2010</td>
<td>Pharmaceutical Company Lawyer Charged with Obstruction and Making False Statements</td>
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<td>10-26-2010</td>
<td>XXX Will Plead Guilty and Pay $750 Million to Resolve Manufacturing Deficiencies at Puerto Rico Plant</td>
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<tr>
<td>09-30-2010</td>
<td>XXX Pharmaceuticals Corporation to Pay $422.5 Million for Off-Label Drug Marketing</td>
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<tr>
<td>09-15-2010</td>
<td>Drug Maker XXX Pleads Guilty: Will Pay More Than $313 Million to Resolve Criminal Charges and False Claims Act Allegations</td>
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<tr>
<td>09-01-2010</td>
<td>XXX Agrees to Plead Guilty and Pay $600 Million to Resolve Allegations of Off-Label Promotion of XXX</td>
</tr>
<tr>
<td>Date</td>
<td>Event Description</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------------</td>
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<tr>
<td>05-21-2010</td>
<td>XXX Pharmaceutical Pleads Guilty to Illegal Promotion of XXX and is Sentenced to Criminal Fine of $6.14 Million</td>
</tr>
<tr>
<td>04-05-2010</td>
<td>XXX Company pleads guilty to not reporting Safety problems to FDA</td>
</tr>
<tr>
<td>09-29-2009</td>
<td>XXX Former Biotech CEO, Convicted of Wire Fraud</td>
</tr>
<tr>
<td>09-02-2009</td>
<td>U.S. Attorney News Release: Justice Department Announces Largest Health Care Fraud Settlement In Its History</td>
</tr>
<tr>
<td>06-18-2009</td>
<td>XXX Company, Manager sentenced for off label marketing of drug</td>
</tr>
<tr>
<td>06-16-2009</td>
<td>XXX company &amp; 4 Executives sentenced for unlawful clinical trials</td>
</tr>
<tr>
<td>04-15-2009</td>
<td>XXX company to pay $302 M to resolve allegations of misbranding of medical devices</td>
</tr>
<tr>
<td>Date</td>
<td>Description</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>03-30-2009</td>
<td>XXX Company, Manager pleads guilty to off label marketing of drug</td>
</tr>
<tr>
<td>01-15-2009</td>
<td>XXX Company to Pay $1.415B for Off Label Marketing of Drug</td>
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<tr>
<td>09-29-2008</td>
<td>XXX Company to Pay $1.415B for Off Label Marketing of Drug</td>
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<tr>
<td>03-27-2008</td>
<td>XXX Company to Pay $4 M for Off Label Marketing of Drug</td>
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<tr>
<td>09-31-2007</td>
<td>XXX Company to Pay $515M to resolve allegations of illegal marketing &amp; pricing</td>
</tr>
<tr>
<td>03-08-2007</td>
<td>XXX company employees admit Fraud</td>
</tr>
</tbody>
</table>
Appendix 2

Internet Sources Related to Data Integrity

FDA Office of Criminal Investigation (OCI)
Department of Justice (DOJ)
Office of Inspector General (OIG)
Office of Research Integrity (ORI)
EU & Various Others
Some Key Internet Sources - FDA

Prosecutions (Office of Criminal Investigations) - Press Releases
http://www.fda.gov/ICECI/CriminalInvestigations/ucm123086.htm

Debarment (List of Individuals)
http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm

Disqualification Proceedings (Clinical Investigators)

Application Integrity Policy (List of Companies)
http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134453.htm

Import Alerts (66-40 - Drug GMPs)
http://www.accessdata.fda.gov/cms_ia/importalert_189.html
Warning Letters

All Centers
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

CDER (OMPQ)

Districts
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm
Some Key Internet Sources - DOJ

**Home Page**
http://www.justice.gov/

**News**
http://www.justice.gov/justice-news


**Case Highlights**
http://www.justice.gov/publications/case-highlights
Some Key Internet Sources - OIG

**News Room**

**Corporate Integrity Agreements**

**Corporate Integrity Agreement (Listing by Company)**

**Enforcement Actions**
http://www.oig.hhs.gov/fraud/enforcementactions.asp

**False Claims**
https://oig.hhs.gov/fraud/enforcement/cmp/false_claims.asp

**Kickbacks**
https://oig.hhs.gov/fraud/enforcement/cmp/kickback.asp
Some Key Internet Sources - ORI

**ORI Home Page**
https://ori.hhs.gov/

**Administrative Action Report (Debarment)**
http://ori.hhs.gov/ORI_PHS_alert.html

**PHS Administrative Action Bulletin Board**
https://ori.hhs.gov/phs-admin-action-bulletin-board

**Misconduct Case Summaries (2005-2015)**
https://ori.hhs.gov/case_summary

**Case Summaries**
https://ori.hhs.gov/ori-updates-0
Some Key Internet Sources - EU & Others

Health Canada (Legislation & Guidelines)

ANSM (France)
http://ansm.sante.fr/Mediatheque/Publications/Informations-recentes

ANVISA (Brazil)
http://portal.anvisa.gov.br/wps/portal/anvisa-ingles

PMDA (Japan)

TGA (Australia)
https://www.tga.gov.au

Eudralex - European Commission (Vol 1-10)
...continued
Some Key Internet Sources - EU & Others

**MHRA Homepage**

**Guidance (Data Integrity)**