PDA is Tackling the Data Integrity Topic

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Back to Basics!

- A **basic principle** of assuring the quality of healthcare products is the **review of data**: by industry of data from their partners, of manufacturing and testing data by an independent quality function, and of all of this data by regulators who are responsible for monitoring the products for the public.
- The **accuracy and trustworthiness** of the data, the integrity of that data, **must not be in question**, or all of the checks and balances, control measures, and quality agreements will not be effective.

Key themes from PDA-FDA 2014 Brainstorming Meeting on Data Integrity

- Culture—quality and local -- issue is huge. Good quality culture can counterbalance weak systems. Culture can influence understanding or definition of "integrity"
- Data Integrity is a disease with a spectrum like cancer; proper diagnosis is needed to identify appropriate treatments.
- Data Integrity is really a design issue. Fear or desire to make a batch pass leads to DI problems. A lifecycle problem.
- All levels and parts of the organization need to understand importance of DI and their individual roles: C suite, IT, operator level, etc. First level supervision is key.
- Natural tendency to bias and assume a root cause rather than make a thorough analysis. Assumption the equipment is broken etc.
- Companies to consider whether rewards are based on outcomes or behaviors

Data Integrity: Increased Focus of Regulatory Agencies Worldwide

Increasing trend in Health Authority Observations and Actions related to Data Integrity.

- US FDA Warning Letters & Import Alerts
- EU Non Compliance Reports
- WHO Notices of Concern and De-certification

Data integrity refers to the quality and accuracy of data over the entire data lifecycle

A = Attributable

L = Legible

C = Contemporaneous

O = Original

A = Accurate

Regulatory Guidance & Trends

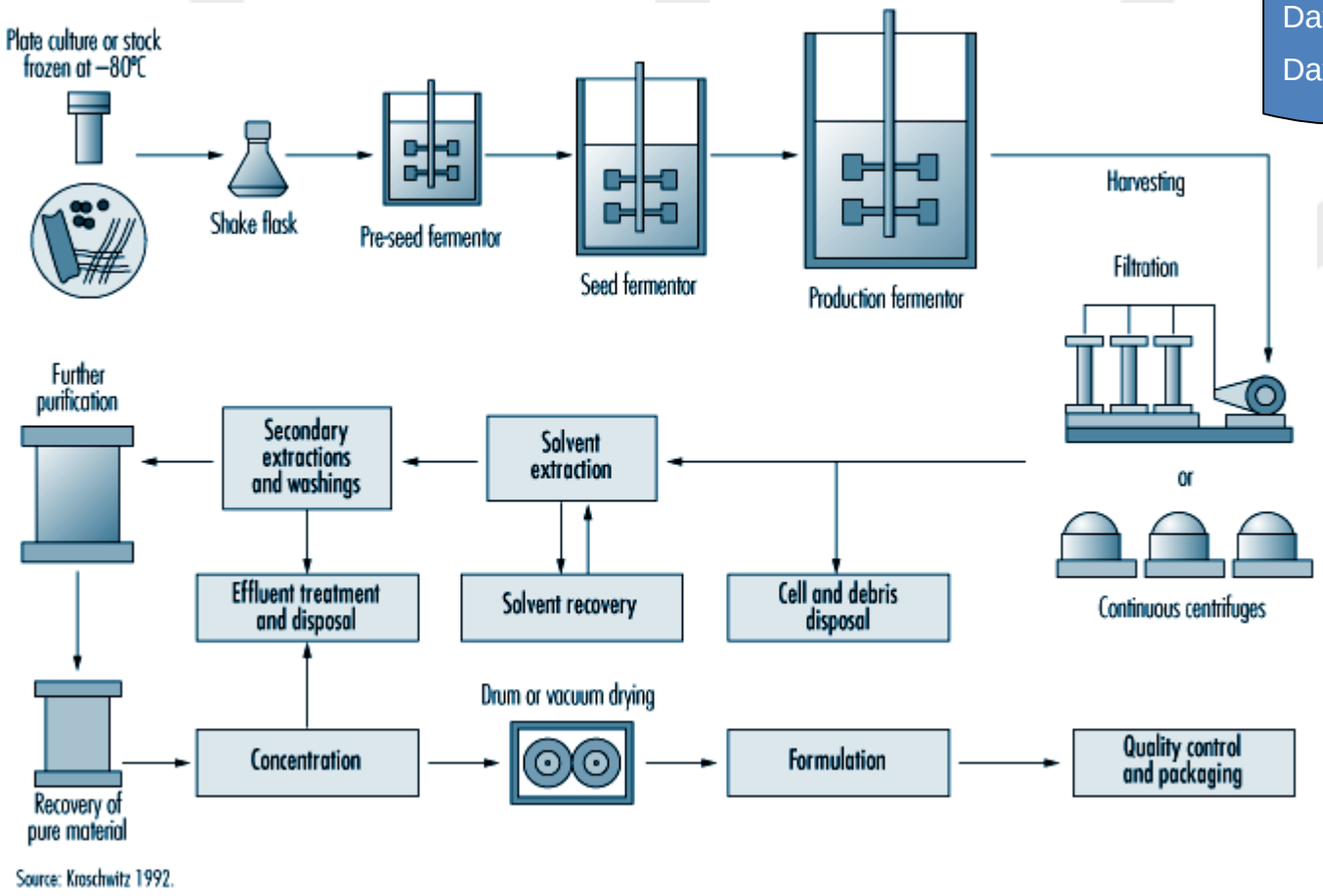
Stay Current!

- MHRA Guidance, March 2015; Draft Revision, July 2016
- FDA Draft Guidance, April 2016
- WHO Annex 5, June 2016
- PIC/s Draft Guidance, August 2016

Regulatory Guidance & Trends

- Warning Letters/Untitled Letters
- FDA 483 Observations
- Import Alerts
- EU Non-Compliance Reports
- WHO De-Certification

High Quality Decisions Come From High Quality Data



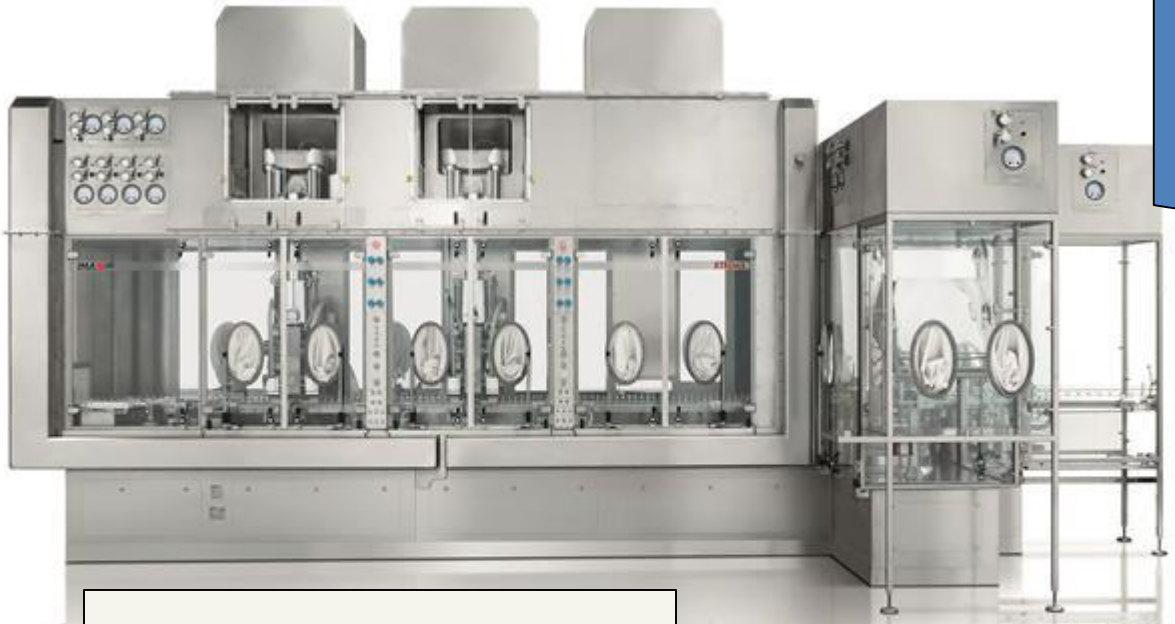
Every Step has Data In and

Data Out

Is this product safe and effective for the patient?

Operator Training Records
Quality Control Checks
Media Fill Results

High Quality Decisions Come From High Quality Data



Raw Material Identity
Filter Integrity Testing
Potency Assay
Particulate Inspection

Is this product safe and effective for the patient?

Equipment Cleaning Logs
Preventive Maintenance
Sterilization Cycle Validation

Examples of Data Integrity Problems

- Security Breaches of physical plant or information systems
- Site access without secure ID.
- Uncontrolled and unrecorded access to restricted rooms such as data centers, manufacturing suites, and document storage centers
- Access to GxP computer applications not limited to authorized personnel.
- Sharing of passwords and logon IDs
- Employees logged in to unattended computer terminals.
- No requirements for periodic password updates

Examples of Data Integrity Problems

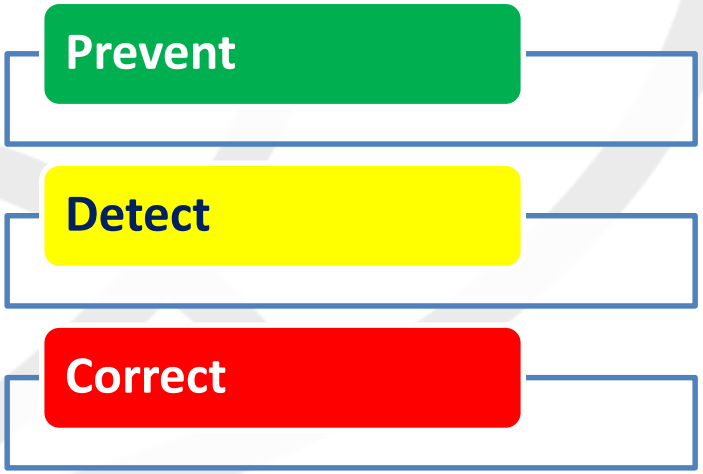
- Lack of employee ownership and accountability
  - Improper data manipulation
  - Adjustment of time clocks
  - Backdating of information
  - Creating records after the fact
  - Excluding adverse information
  - Discarding or destroying original records
- Data systems not accurate, reliable, nor fit for their intended use.
  - Uncontrolled or haphazard backup/restore, copying, and archiving of data
  - No review of electronic record by supervisory personnel
  - Audit trails not maintained nor reviewed
  - Poor process flow inhibits access to documentation systems
  - Floor operators lack access to document process exceptions

Recent FDA Inspection Findings

- Poor Documentation Practices
  - Batch records found in the trash which don't match "official" records
  - Photocopied labels with information filled out in advance of activity occurring
  - Data recorded for a microbial test with no sample plates found in the incubator
  - Microbial contamination recorded in an unofficial notebook but not found in any GMP documentation
  - Lack of second person verification of data
- Poor laboratory practices.
  - Manipulation of integration settings to achieve passing results
  - Retesting samples outside the quality system until a passing result is achieved.
  - Using multiple "trial/setup/training injections" before recording a single result.
  - Use of analytical methods not validated
  - Results can not be reproduced on subsequent aliquots
- Security Breaches of physical plant or information systems
  - Using Administrator access to override analyst results
  - Deletion of raw data or unfavorable results
  - Inspector denied access to view data recorded on a thumb drive

Elements of a Data Integrity Program

- Personnel and Training.
- Validation Program
- Security
- Audits
- Data Review and Audit Trails
- Governance
- Data Integrity Findings and Investigations
- Corrective and Preventive Actions (CAPAs)



Data Governance

Management should develop and implement a Data Governance System to ensure Data Integrity principles, requirements, definitions and supporting processes are clearly defined, and that Data is managed in accordance with applicable

regulations, guidance and best practice throughout the Data Lifecycle

Risk management principles should be applied when developing and assigning resources for Data Governance, ensuring an acceptable level of control is in place based on the criticality and risk to data

Data Governance: Key Attributes

- Management should be responsible for the design, implementation, monitoring and maintenance of the data governance system to ensure systems and processes are compliant with data integrity requirements and principles.
- Appropriate resources should be in place to demonstrate support for the data governance system, and to ensure compliance with data integrity principles, procedures, and applicable regulations.
- Roles, responsibilities and the ownership of data should be established throughout the data lifecycle
- Procedures and controls should be established to ensure data integrity, including such that define accountability for individuals who breach such requirements

Data Governance

- Effective process and product monitoring provide early warning of emerging quality issues
- Training should be established in data integrity principles, elements and practices for all individuals responsible for data in the testing and manufacturing of drug product
- Data integrity issues should be communicated and/or escalated commensurate with criticality – to include establishing appropriate timelines to address Data Integrity compliance gaps
- Data integrity principles should be applied to outsourced activities, including contract givers and suppliers
- Self inspection should include a review of the effectiveness of the data governance system

Quality Culture

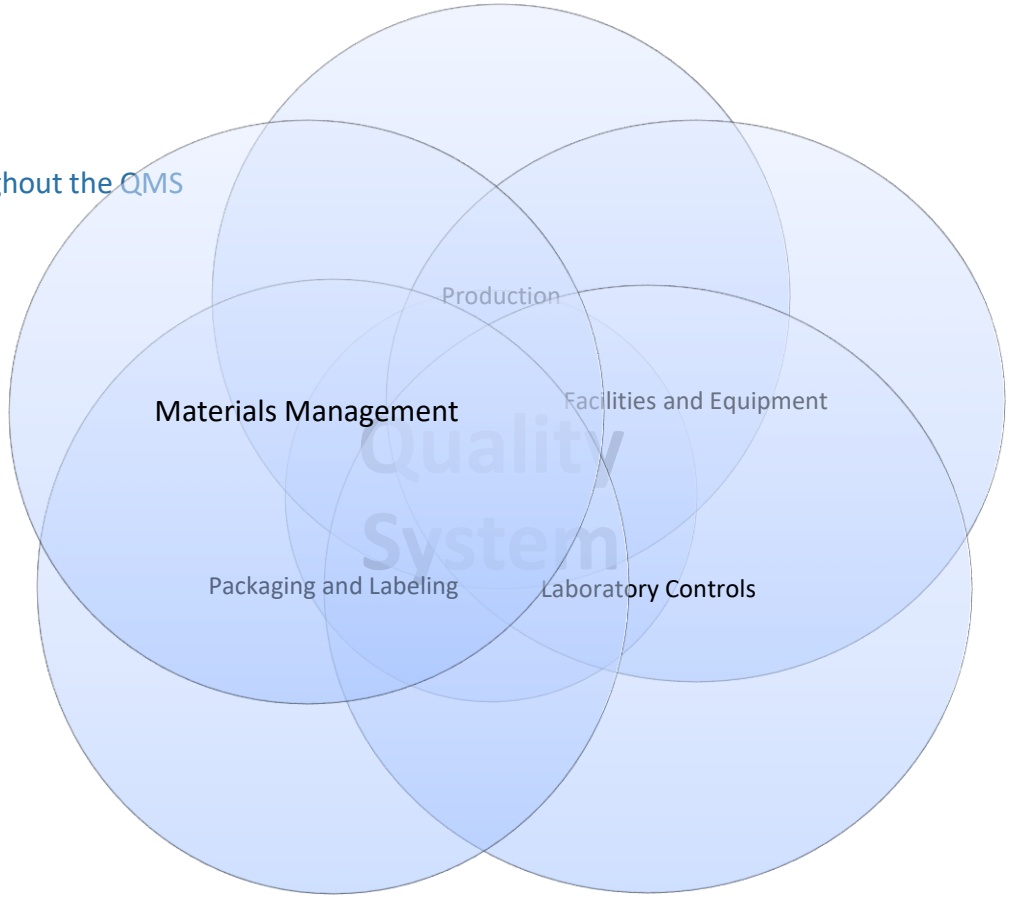
- Management controls should be established, communicated and followed to:
  - Promote transparency and timely escalation of possible data integrity gaps
  - Provide incentives and amnesty for communication of possible gaps
  - Provide a no-retaliation environment to allow for individuals to raise and investigate concerns without fear of retaliation

Integration

A robust and effective QMS is intended to integrate
the objectives and requirements
(systems/processes/programs)
of GMP regulations and Data Integrity principles throughout the QMS
and
its associated systems

Based on FDA's Six System Inspection
Model, the QMS consists of the following systems:

- *Quality System*
- *Production System*
- *Facilities and Equipment System*
- *Laboratory Controls System*
- *Materials System*
- *Packaging and Labeling System*



Indicators of Potential Data Integrity Gaps

- Discrepancies between Workload, Capacity and Output
  - Equipment
  - Materials Management
  - Resourcing
- Quality Metrics show delays in closure of quality records
- Lack of documented deviations/incidents/OOS reports/Data integrity issues
- Separate quality system or laboratories for “other” markets
- Lack of detailed procedures for review of electronic data
- Computerized and automated system risks not well understood/identified and tested to confirm controls and configuration are appropriate
- Documents not submitted to Quality in timely manner (no time limits or monitoring of this timeline)
- Documents found in trash/recycle/shredder bins (location of bins in areas where documents should not need to be discarded)

Data Integrity Continuum

System Error

Individual Mistake

Individual Malfeasance

Institutional Malfeasance

GMP regulations do not require determining intent while assessing 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

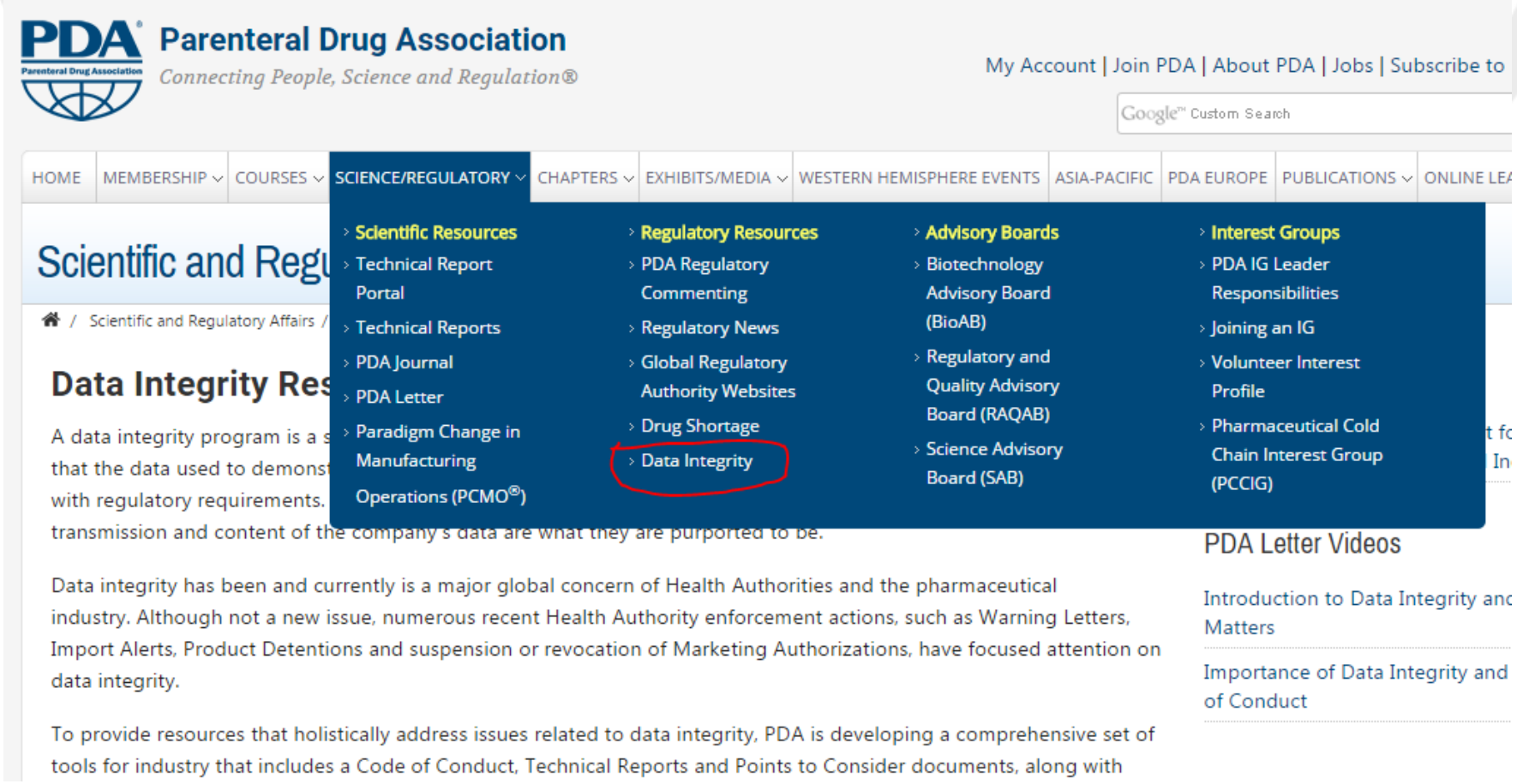
Data Integrity: Causes & Mitigation
Task Force is Working on the following .....

Malfeasance	**Quality Culture & Code of Conduct** •Elements of Code of Conduct for Data Integrity ✓ Enforcement & Discipline built into CoC •Speak-up Culture - Quality Culture Maturity ✓ Tone at the Top
Sloppiness	**Management Controls Elements Built into DI Tech Reports** ✓ Auditing & Monitoring - ✓ Accountability & Supervision ✓ Resource Allocation
Ignorance	**Knowledge, Training, & Awareness** • Technical Reports • Workshops • Training program

Data Integrity

What is PDA doing?

PDA Data Integrity Resources Page



pda.org/dataintegrity

2016 PDA Data Integrity Deliverables : Workshops, Tools & Training Courses

Date	Venue	Location
April 19-20	Millennium Gloucester Hotel	London, UK
Sept 14-15	Renaissance Washington DC, Hotel	Washington, DC
Nov 8-9	Titanic Chaussee Berlin	Berlin, Germany
Dec 7-8	Manchester Grand Hyatt	San Diego, CA

TOOLS AND TRAINING

Root Cause/Risk Assessment Matrix

PDA Education Course

PDA Data Integrity Deliverables: Publications

Publication	Title	Status
Points To Consider	Elements of a Code of Conduct for Data Integrity in Pharmaceutical Industry	Published (>1000 downloads)
Points To Consider	Fundamental Concepts for Data Integrity	Published
Book	Assuring Data Integrity for Life Sciences	Published
Technical Report	Data Integrity in Laboratories Systems	Q3/Q4 2017
Technical Report	Data Integrity: Integration into QMS	Q3 2018
Technical Report	Data Integrity in Manufacturing Systems	Q2 2018

Introduction

Data Integrity has been and currently is a major global concern of Health Authorities and the pharmaceutical industry. Although not a new issue, numerous recent Health Authority enforcement actions such as Warning Letters, Import Alerts, Product Detentions, and suspension or revocation of Marketing Authorizations has focused attention on Data Integrity. Data Integrity can result from lack of awareness of regulatory requirements, employee errors, failure to check accuracy of data, software or system malfunction, or configuration problems with electronic data handling, or malfeasance by employees. To holistically address Data Integrity, the Parenteral Drug Association (PDA) is developing a set of tools in the form of PDA Technical Reports, PDA Training Program, Data Integrity Workshops, and Points to Consider documents that can be used by industry to address this serious issue. This document presents the views of the Parenteral Drug Association (PDA) on the benefits for companies to voluntarily adopt a Code of Conduct for assuring data integrity.

How to Use this Document

This document was developed by a team with expertise in the fields of quality, regulatory affairs, auditing, and manufacturing and reviewed by attorneys specialized in food, drug and labor law. This document is written for easy adoption, in part or in its entirety, by companies, if they so choose, without the need for extensive rewriting of the document. Therefore, the terms 'shall' and 'must' have been used to permit the Code to be enforceable by the company, if adopted. This document is intended to reinforce a culture of quality and trust within the pharmaceutical industry. It is not intended to be a regulatory standard or guidance, nor is it intended to supersede any country specific or local laws and regulations governing labor, privacy and/or employee rights.

In order for the language used below to be as globally applicable as possible, the document scope has been limited to drug and biological medicinal products. The same or similar concepts could be applied for device and combination products manufacturing. PDA is providing this document and these concepts as a service to members and an example of best practices to the pharmaceutical industry. Please see Section 2 below for more details on how to use this code. Section 3 begins the code of conduct provisions.

Elements of a Code of Conduct for Data Integrity

Scope and Purpose

- Developed by a team of quality and regulatory experts with input from attorneys.
- Ready to use language that can be incorporated into existing company codes of conduct or supplier quality agreements.
- Written to apply to GXP activities for drug and biological products

Elements of a Code of Conduct for Data Integrity

Key Elements and Sections

- Senior Management must establish quality standards and requirements.
- Every employee has a duty to engage in conduct which results in data that are accurate, truthful and complete.
  - Data Collection, Analysis, Reporting and Retention
  - Electronic Data Acquisition Systems and Access Security
  - Auditing and Investigations
  - Internal Reporting Responsibility and Disciplinary Actions
  - Notifying Regulatory Authorities
  - Outsourced Services and Purchased Raw Materials
  - Employee Training
  - Glossary of Terms

PDA PAPER

PDA Points To Consider: Fundamental Concepts in Data Integrity

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Executive Summary

The purpose of this document is to describe behaviors, including the elements and controls, to ensure the integrity of GxP data in pharmaceutical manufacturing operations. Fundamental concepts such as ALCOA (attributable, legible, contemporaneous, original, and accurate) and the prevent/detect/respond approach to a data integrity program are defined and discussed. This paper was developed through the Parenteral Drug Association (PDA) Data Integrity Task Force and reviewed and approved by the PDA Regulatory and Quality Advisory Board as well as the PDA Board of Directors.

Data integrity is a significant component of a company's Quality System, providing foundational assurance of the data a company uses to operate in compliance with regulatory requirements and to demonstrate its products are safe and effective for their intended use. Through data integrity the company recognizes its responsibility to prove the origin, transmission, and content of the company's data and that data is what it is purported to be. To holistically address Data Integrity, the PDA is developing a set of tools in the form of PDA Technical Reports, PDA Training, Data Integrity Workshops, and Points To Consider documents that can be used by industry to address this serious issue. This document serves as an introduction to that suite of tools to follow.

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The Importance of Data Integrity throughout the Product Lifecycle

Nearly every GxP activity at a company generates some form of data or documentation. GxP regulations require companies to put systems in place to ensure the completeness and accuracy throughout the lifecycle of these records, including, but not limited to

- Creation and recording
- Processing and transferring
- Use, reporting, replication, and distribution
- Archival, backup, restoration, obsoleting, and retirement

Key Elements

- Executive Summary
- Purpose
- The Importance of Data Integrity throughout the Product Lifecycle
- Current Regulatory Trends and Recent Issues in Data Integrity
- Data Management Systems Considerations
- Globalization and Cultural Factors
- Elements of Data Integrity
- Holistic Approach to a Data Integrity Program through the Data Lifecycle
- Personnel and Training.
- Validation Program
- Security
- Audits
- Data Review and Audit Trails
- Governance
- Data Integrity Findings and Investigations
- Corrective and Preventive Actions (CAPAs)
- Conclusion

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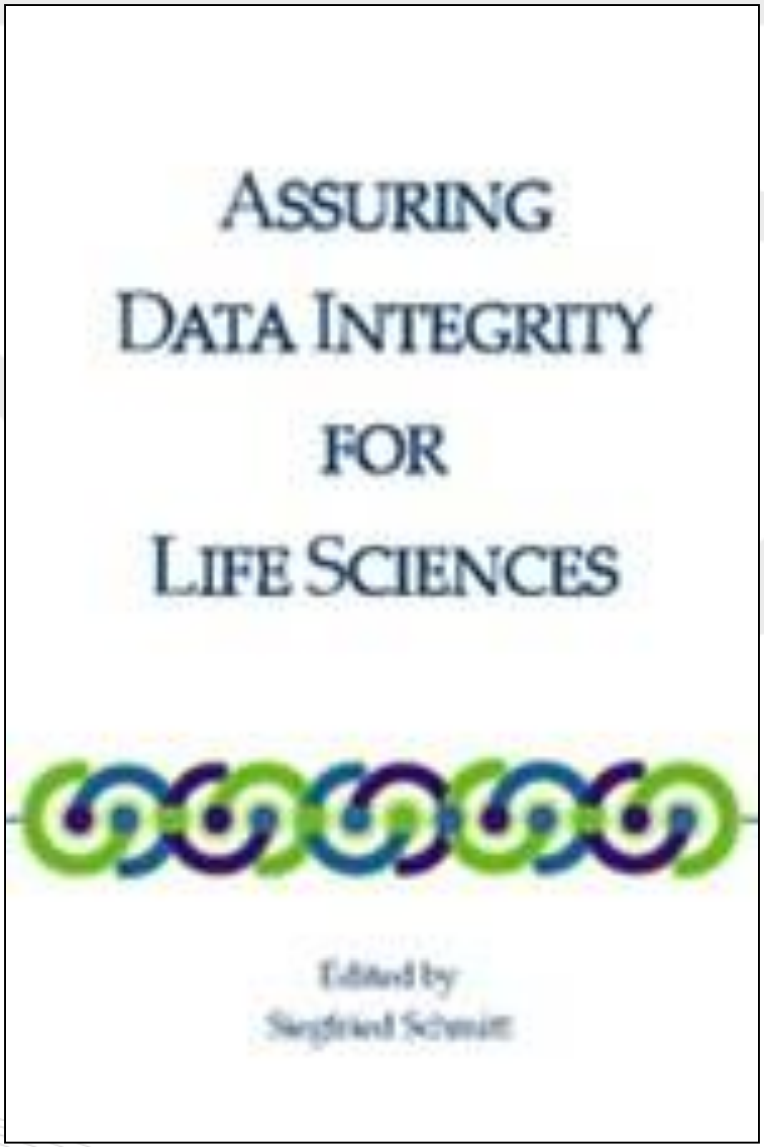
PDA/DHI Book



Data Integrity Task Force: Expected Outcomes

- Harmonized standards to comply with regulatory expectations for maintaining data integrity,
- Defining mechanisms for detecting non-compliance and outlining a clear methodology for remediating gaps.
- Serves both industry and regulators in creating and defining solutions for the increasing number of failed inspections where firms lack the needed controls to ensure data integrity and lack the expertise to detect and resolve non-compliance
- Methodology for restoring confidence in a system and organization to avoid revenue loss and regulatory impacts.

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  - Chief Compliance Officer, Faith & Royale Consultants
  - Co-Chair PDA Data Integrity Task Force

Questions?

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- More Info.:

  https://www.pda.org/scientific-and-regulatory-affairs/regulatory-resources/data-integrity