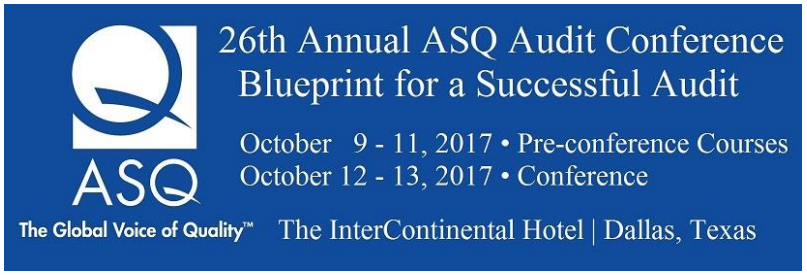

ASQ Audit Division
The Global Voice of Quality™

Data Integrity and Good Documentation Practices: Not just for the Pharmaceutical Industry

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Agenda

- Definitions
- Case Studies
- ALCOA Exercises
- Conclusion: PDCA for Data Integrity

- Resources

Definitions

Data Integrity means the extent to which all data are complete, consistent and accurate throughout the data lifecycle. Scope:

- From initial data generation and recording through processing (including transformation or migration), use, retention, archiving, retrieval and destruction
- Applies to paper and electronic data and records, within the scope of a quality management system

Good Documentation Practices (GDP) are methods for recording, correcting and managing data, documents and records, to ensure the reliability and integrity of information and data throughout all aspects of a product's lifecycle

Definitions

ALCOA

- **Attributable**: information is captured in the record so that it is uniquely identified as having been executed by the originator of the data (e.g. a person or computer system).
- **Legible, traceable, and permanent**: data are readable, understandable, and allow a clear picture of the sequencing of steps or events in the record so that all activities conducted can be fully reconstructed by the people reviewing these records at any point during the records retention period.
- **Contemporaneous**: recorded at the time data are generated or observed.
- **Original (or "True Copy")**: data in the format in which it was originally generated, preserving the integrity (accuracy, completeness, content and meaning) of the record.
  - World Health Organization: Original data include the first or source capture of data or information and all subsequent data required to fully reconstruct the conduct of the activity
- **Accurate**: data are correct, truthful, complete, valid and reliable.

Focus in Pharmaceutical Industry

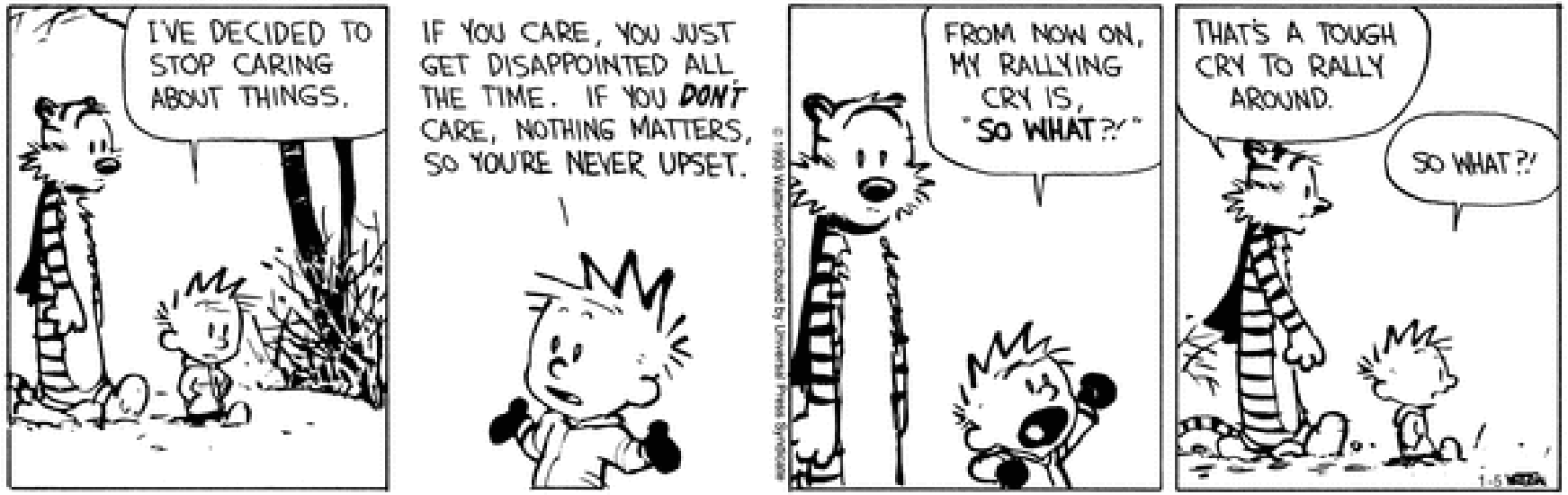
Concept not new, but “Data Integrity has been and currently is a major global concern of Health Authorities and the pharmaceutical industry.” - PDA

- 2016: 80% of FDA warning letters issued had Data Integrity deficiencies
- Jan 2015: MHRA issued Data Integrity Guidance for GMP
- 2016: Parenteral Drug Association (PDA) announce Data Integrity Initiative.
  - Issued “Elements of Code of Conduct on Data Integrity”
  - Had Sept 2016 conference dedicated to Data Integrity
  - Will be issuing other industry guidance on topic
- March 2016: ISPE includes special report on data integrity in magazine
- April 2016: FDA issues Draft Guidance on Data Integrity
- June 2016: WHO issued final Guidance on Good Record and Data Management Practices
- July 2016: MHRA new Draft Data Integrity Guidance to include GxP
- Aug 2016: EMA issued Q&A on Data Integrity
- Aug 2016: PIC/S issued Draft Guidance on Data Integrity

Data Integrity in Standards & Regulations

- ISO 9001:2015: *Documented information shall be controlled to ensure it is adequately protected (e.g. from loss of confidentiality, improper use, or loss of integrity)*
- Health Authorities (FDA, MHRA, WHO, etc.) well defined regulations and guidance. For example, from EU GMP, Volume 4:
  - *4.7 Handwritten entries should be made in clear, legible, indelible way.*
  - *4.8 Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.*
  - *4.9 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.*

Is Data Integrity just a pharma problem?



New England Compounding: Meningitis Outbreak 2012

- Pharmacy technicians instructed to prioritize production over cleaning and disinfecting
- Pharmacy technicians instructed to falsify cleaning records, showing rooms were properly cleaned when they had not been
- Neglected to investigate contamination found in the clean rooms
- Company distributed orders even though they were still waiting for sterility test results
- "As alleged in the indictment, these employees knew they were producing their medication in an unsafe manner and in insanitary conditions, and authorized it to be shipped out anyway, with fatal results," said Attorney General Eric Holder

64 reported deaths, >800 patients sickened

President sentenced to 9 years in prison

Other employees charged with multiple criminal acts

Led to passage of Compounding Quality Act providing increased FDA oversight

Takata: Auto Airbags 2015

- Potential danger of spraying shrapnel caused by defective air bag inflators when the air bag goes off
- Takata engineers removed some test results to artificially reduce variability in air-bag inflator performance
- "Takata provided inaccurate, incomplete and misleading information to regulators for nearly a decade," said NHTSA spokesman Bryan Thomas. "Had they told the truth, Takata could have prevented this from becoming a global crisis.“

15 deaths, 100 injuries

100 million vehicles worldwide, ~33 automotive brands

Defective airbags still in cars

Koito Industries: Airline Seats 2010

- Developed software that would display acceptable-looking readouts on screens whenever inspectors from the Transport Ministry came to observe the testing procedures
- Failed to perform a critical part of one of the tests and had applied the results of previous tests to newer products that had not been made to the same standards
- Fabricated test results for flammability and static and dynamic strength tests; Failure to meet static and dynamic strength criteria could result in injuries to the flight crew and passengers during emergency landing conditions - FAA

150,000 suspect seats installed in 1000 aircraft

EASA and FAA issued airworthiness directives to test and correct

Peanut Corporation of America: Salmonella Outbreak 2008-09

- In some cases, company officials falsified lab results, stating peanut products were safe to eat when tests showed otherwise, or when products had never been tested at all, according to court papers. - The Wall Street Journal
- The company shipped product with falsified Certificates of Analysis (COA), which attested to the purity of contaminated lots
- CEO wrote in a March 2007 email to a plant manager about contaminated products: "**Just ship it**. I cannot afford to lose another customer."

9 reported deaths, >700 consumers sickened

CEO sentenced to 28 years in prison;

others sent to prison including Plant Quality Manager

Loss of nearly $1 billion in peanut sales

Plant closed & company liquidated

Questions so far?

ALCOA Exercises

Data Integrity Issue?

1. Raw data record not signed, no indication of who recorded/observed the data?
2. Sharing username and password to an electronic system used to record data?

ALCOA: Attributable

In practice

- Sign and date when recording data
- Sign and data reports
- Electronic systems with unique user ID

Why important

- Data traceable to person performing work
- Person must be trained/authorized to perform the work

When auditing, check:

- training records – was resource trained prior to performing activity?
- SOPs / responsibilities – is resource authorized to approve record or release lot?

"Sign here to indicate you have no idea what you've signed."

Data Integrity Issue?

1. As Jim is performing a test, he observes passing result 78 , but accidently writes failing result 76. He notices it right away, he writes overs 76 to change it to 78 . 
2. He notices it right away, he single-line crosses out 76, writes 78 and provides a explanation for the data change, initials and dates the change.

ALCOA: Legible, traceable, permanent

In practice

- Use permanent ink
- Single line cross out to correct data, with explanation of change

Why important

- At any point during record retention, allows people reviewing the record to fully understand all activities
- Illegible data give the appearance that you are trying to hide something

When auditing, check

- Overwritten data, correction fluid
- Audit trails for data changes
- Data corrections made without explanation
- Retention of records

Data Integrity Issue?

1. Jane's going to be out of the office tomorrow and returning the day after tomorrow. We really need to get this report approved by tomorrow. It's now the end of the day and edits are still being made. Jane signs the signature page and dates it for tomorrow.
2. Jane was out of the office yesterday when test results to the customer were due. Jane sets the lab equipment clock back a day and performs the tests, so that the tests are date stamped yesterday..

AL**C**OA: Contemporaneous

In practice:

- Record data at the time the data is generated or observed - Must not rely on memory

Why important:

- Backdating gives the false impression that the task had been done in a timely fashion
- Draft documents can still be modified

When auditing, check:

- Data recorded by person not performing work
- Records completely free from error
- FDA inspectors will check attendance records

Data Integrity Issue?

1. Raw material testing is recorded on a controlled form, showing calculations and any repeat testing. A summary of the data is prepared in a report and the raw material records are discarded.

ALC**O**A: Original or True Copy

In practice:

- Use official forms/records – do not record raw data on scrap paper
- Retain raw data records as originals or true copy (e.g. verified scans)

Why important:

- Data may be lost and incomplete
- May result in transcription errors

When auditing, check:

- Post-it notes or other loose paper in the record
- Uncontrolled documents
- Missing raw data

Data Integrity Issue?

1. Raw material testing is recorded on a controlled form, showing calculations and any repeat testing. A summary of the data is prepared in a report and the raw material records are discarded.
2. Before starting the production run, Jim notices that one of his instruments measuring a critical control parameter, has expired calibration. Jim is already behind on the production run, and proceeds with the run using the expired gage.

ALCO**A**: Accurate

In practice:

- Accurately enter and completely report all required data
- Do not “test into compliance”
- Calibrate, maintain, and validate (as necessary) instruments, equipment, analytical methods, etc.
- Investigate out of spec results

Why important

- Good data provides basis for good scientific decision making

When auditing, check for:

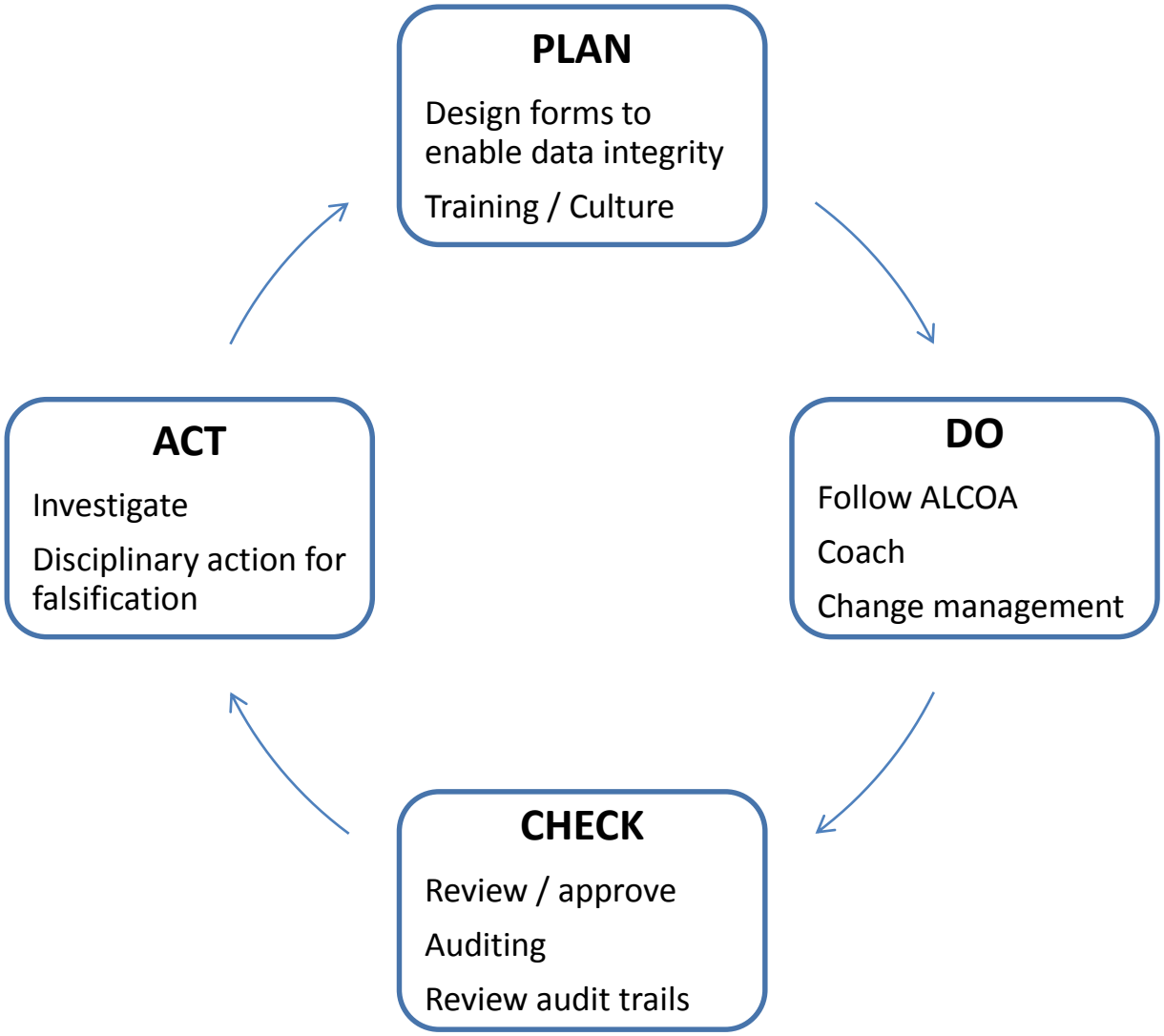
- Results that are too good to be true
- Audit trails for repeat tests – but only one reported, or others deleted

“Test into compliance” is a strategy of repeated testing until a passing result is obtained, then disregarding the out of specification (OOS) results without scientific justification.

Testing into compliance is unscientific and objectionable, and is considered falsification.

- FDA

Conclusion: PDCA for Data Integrity



Questions?

Resources: New Work Item Proposal

- A newly formed Standards Committee Writing Group will draft a TR, Data Integrity: *Guidelines for collecting, recording and retaining data within the scope of quality management systems*
- Please consider becoming involved with the **Writing Group** to draft the document, or as a **Reviewer** to review document drafts. The time commitment is approximately two years. For the Writing Group, we anticipate that there will be 2 or 3 meetings a year (remote and face to face).
- Please contact ASQ Standards (standards@asq.org) with your interest in being part of the Writing Group or as a reviewer. Please include a biography, no longer than 250 words, on why you will be able to contribute to the development of the data integrity guidance.

Resources: Pharma guidelines

- Medicines and Healthcare products Regulatory Agency (MHRA) publication “GxP Data Integrity Definitions and Guidance for Industry: Draft version for consultation July 2016: http://academy.gmp-compliance.org/guidemgr/files/MHRA_GxP_data_integrity_consultation.pdf
- Parenteral Drug Association (PDA) data integrity resources: https://www.pda.org/scientific-and-regulatory-affairs/regulatory-resources/data-integrity (“Elements of a Code of Conduct for Data Integrity in Pharmaceutical Manufacturing” is available free)
- World Health Organization (WHO) “Annex 5: Guidance on good data and record management practices” http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

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