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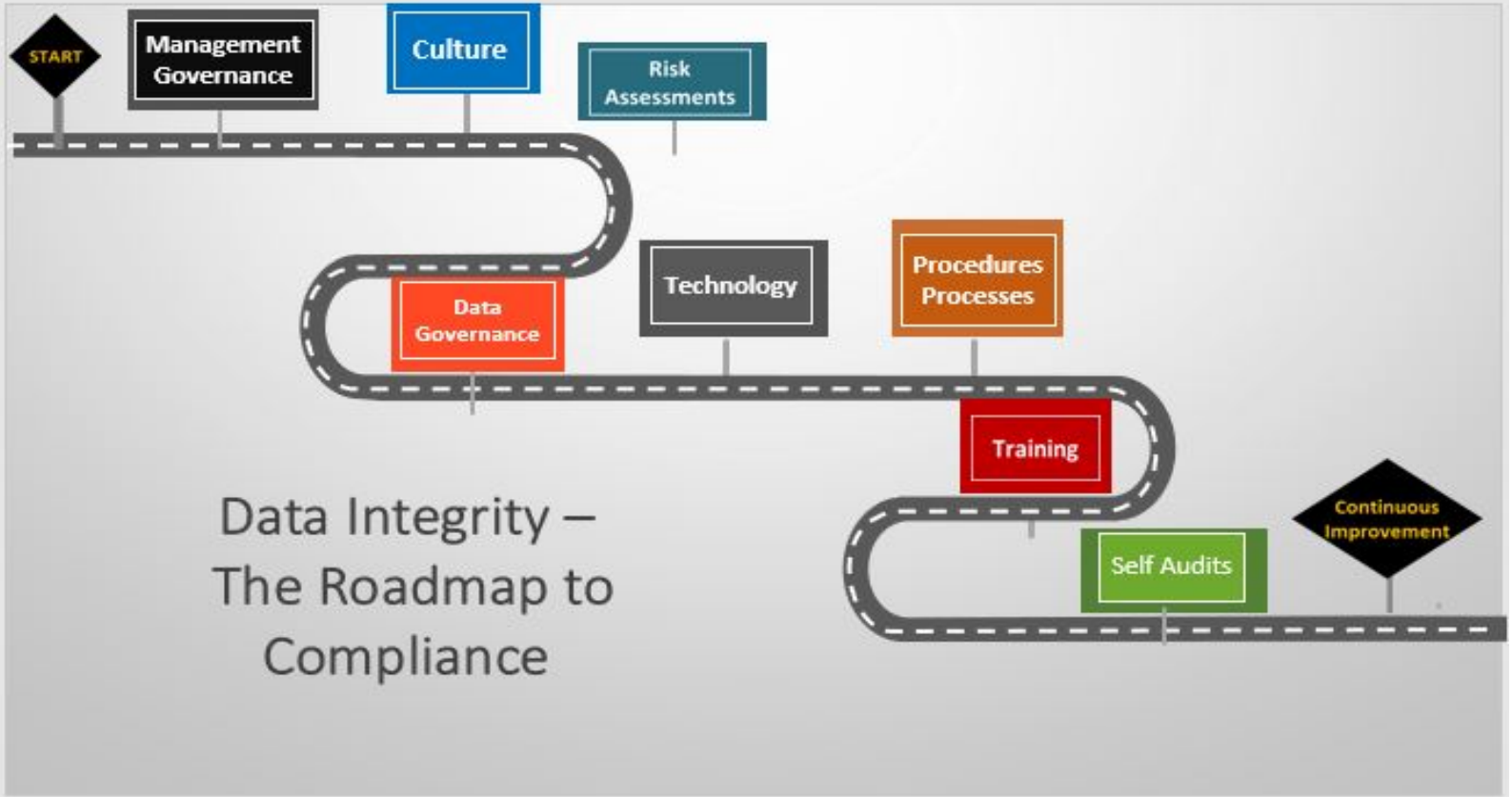
Data Integrity: The Roadmap to Compliance

Webinar Presented by Cindy Lipton
MWA Consulting, Inc.
September 25, 2019

TOPICS

- Why is Data Integrity important?
- Warning Letters/ Case Study
- Applicable Regulations and Guidance
- Roadmap to Compliance
  - Management Governance
  - Culture
  - Risk Assessments
  - Data Governance
  - Technology and Validation
  - Procedures and Processes
  - Training – ALCOA+
  - Self Audits
  - Continuous Improvement

DATA INTEGRITY – THE ROADMAP TO COMPLIANCE



DATA INTEGRITY: FDA'S POSITION

"Data integrity really sounds off alarm bells for us ... if you see data integrity problems on the surface, there is likely a lot going on underneath."

Thomas Cosgrove, director at the FDA's office of manufacturing quality

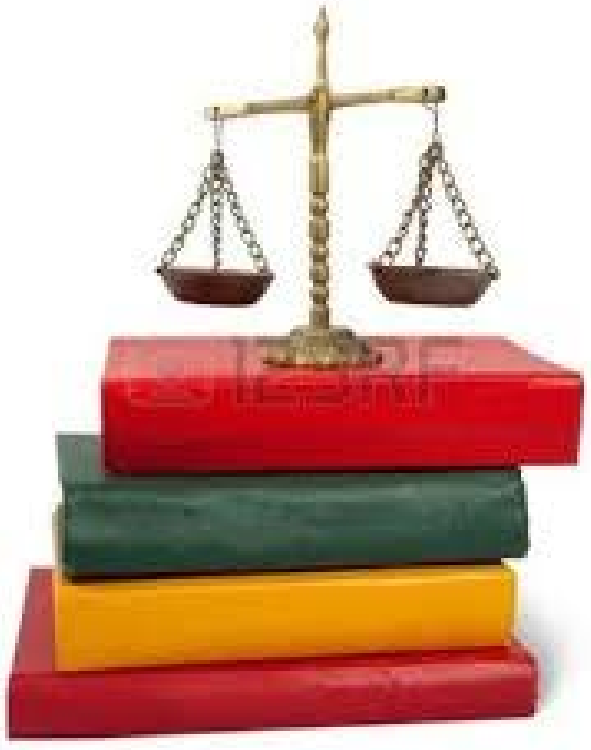
"It may sound like we're kind of bureaucratic paper-pushers, but it's more than that. It's making sure that the whole ecosystem understands that when people are working on these things that are highly technically complex, that they have to work truthfully and accurately. Because that's the foundation upon which the trust that patients put in these products is built."

Dr. Peter Marks, director of FDA's Center for Biologics Evaluation and Research

DATA INTEGRITY

Many recent Warning Letters and regulatory/judicial actions by FDA directly result from data integrity issues.

- Form FDA 483
- Warning Letter
- Injunction
- Seizure
- Recalls
- Debarment / License Revocation
- Consent Decree
- Fines/Civil Penalties
- Prosecution



WARNING LETTER -STRIDES PHARMA SCIENCE LIMITED-JUL 01, 2019

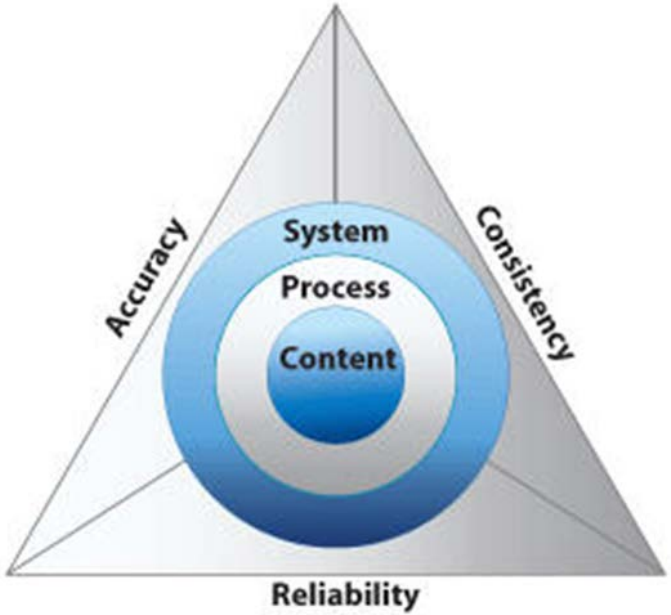
- Your quality unit (QU) lacks appropriate responsibility and control over your drug manufacturing operations.
- During the inspection, our investigator observed discarded CGMP documents and evidence of uncontrolled shredding of documents. For example, multiple bags of uncontrolled CGMP documents with color coding indicating they were from drug production, quality, and laboratory operations were awaiting shredding.
- Our investigator also found a blue binder containing CGMP records, including batch records for U.S. drug products, discarded with other records in a 55-gallon drum in your scrap yard. CGMP documents in the binder were dated as recently as January 21, 2019: seven days before our inspection. Your QU did not review or check these documents prior to disposal.

WARNING LETTER -STRIDES PHARMA SCIENCE LIMITED-JUL 01, 2019

- Your QU is responsible for the oversight of your drug manufacturing operations, including the review and approval of documents and document controls, to ensure a complete contemporaneous record of each batch of drug product manufactured. That record is retained for CGMP purposes including annual review. In addition, your QU is responsible for ensuring your production areas are adequately monitored and that employees understand your firm's procedures and their assigned tasks.
- The uncontrolled destruction of CGMP records, and your lack of adequate documentation practices, raise questions about the effectiveness of your QU and the integrity and accuracy of your CGMP records.

DATA INTEGRITY: PAPER OR ELECTRONIC

- Data Integrity applies equally to both paper and electronic systems
- Switching from paper to electronic controls, or from electronic to paper controls, does not remove the need for data integrity controls.
- Regulatory agencies expect the sponsor to:
  - Maintain records commensurate with the data integrity risk
  - Maintain an acceptable state of control
  - Employ current state of technology surrounding those controls



ALCOA PRINCIPLE FOR DATA INTEGRITY

- Attributable
- Legible
- Contemporaneously recorded
- Original (or true copy)
- Accurate

APPLICABLE REGULATIONS & GUIDANCE

GMP REGULATORY REQUIREMENTS INVOLVING DATA INTEGRITY

- Instruments must be qualified and fit for use
  21 CFR 211.160(b), 211.63
- Software must be validated
  21 CFR 211.63
- Calculations must be verified
  21 CFR 211.68(b)
- The initials or signature of the person who performs each test and the date(s) the tests were performed.
- The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.
  21 CFR 211.194(a)(8)

GMP REGULATORY REQUIREMENTS INVOLVING DATA INTEGRITY

- Data generated during an analysis must be backed up
  21 CFR 211.68(b)
- Reagents and reference solutions must be prepared correctly with appropriate records
  21 CFR 211.194(c)
- Methods used must be documented and approved
  21 CFR 211.160(a)
- Data generated and transformed must by scientifically sound
  21 CFR 211.160(a)
- Test data must be accurate, complete, and follow procedures
  21 CFR 211.194(a)

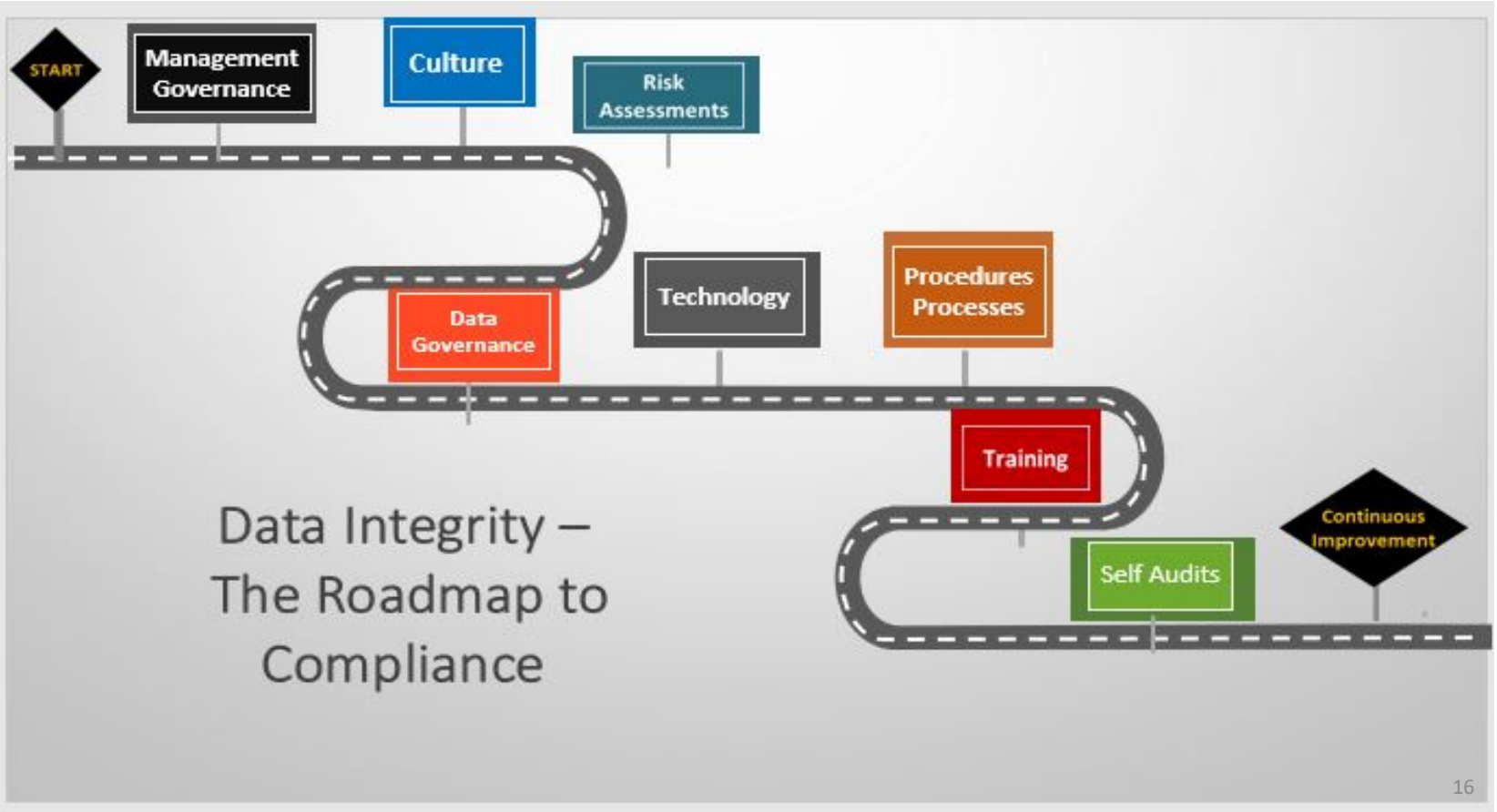
REGULATORY AND GUIDANCE DOCUMENTS FOR DATA INTEGRITY

- 21 CFR Part 11 – Electronic Records; Electronic Signatures
- EudraLex Volume 4, GMP, Medicinal Products for Human and Veterinary Use – Annex 11: Computerised Systems
- Guidance for Industry – Part 11, Electronic Records; Electronic Signatures –General Principles of Software Validation
- Guidance for Industry – Data Integrity and Compliance With Drug CGMP Questions and Answers, December 2018
- ICH Q9 – Quality Risk Management
- GAMP 5
- MHRA GXP Data Integrity Guidance and Definitions; Revision 1: March 2018

REGULATORY AND GUIDANCE DOCUMENTS FOR DATA INTEGRITY

- ISO/TR 80002-2:2017 Medical device software – Part 2: Validation of software for regulated processes
- ISO 13485:2016, Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes
- ISO/IEC 17025:2017 – General requirements for the competence of testing and calibration laboratories
- WHO published Guidance on Good Data and Record Management Practices, 2016
- PIC/S: Good Practices for Data Management and Integrity in Regulated GMP/GCP Environments (Pharmaceutical Inspection Cooperation Scheme)

DATA INTEGRITY – THE ROADMAP TO COMPLIANCE



MANAGEMENT GOVERNANCE

MANAGEMENT GOVERNANCE

- Senior management is obligated to:
  - Establish quality standards, requirements, and procedures
  - Maintain and monitor the performance of the quality system that helps to ensure the availability of safe and effective drugs
  - Maintain operational oversight to demonstrate that each product has been developed, manufactured, or tested under conditions designed to assure reliability and integrity of information and data.

FDA NEWS RELEASE

FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality

- The FDA granted this application Fast Track, Breakthrough Therapy, and Priority Review designations. Zolgensma also received Orphan Drug designation, which provides incentives to encourage the development of drugs for rare diseases.
- The FDA also awarded the manufacturer a rare pediatric disease priority review voucher, under a program intended to encourage the development of new drugs and biological products for the prevention and treatment of certain rare pediatric diseases.
- The FDA granted the approval of Zolgensma to AveXis Inc.
  - May 24, 2019

FIRST OPINION

I have spinal muscular atrophy. Critics of the $2 million new gene therapy are missing the point

By NATHAN YATES / MAY 31, 2019

The author, Nathan Yates

As someone who has lived with spinal muscular atrophy for all 30 years of my life, I was perplexed and disappointed that the recent approval of Novartis' gene therapy Zolgensma was immediately overshadowed by outrage over the drug's price: $2.125 million….

Article from StatNews

ZOLGENSMA

- Spinal muscular atrophy (SMA) is the number one genetic cause of death for infants.
- Zolgensma is FDA-approved for patients with all forms and types of SMA who are under two years of age at the time of dosing.
- Zolgensma is given through an intravenous (IV) infusion that takes about an hour. It is a one-time treatment.
- IV dosing of gene therapy can only be given to young infants under a certain weight limit.
- AveXis/Novartis is currently testing a second way of delivering gene therapy: via an intrathecal (IT) injection, which is an injection into directly into the cerebrospinal fluid through the lower back. This method of delivery could eventually make this treatment available to older and larger patients.
- Currently, this method of delivery is being studied in a Phase 1 clinical trial in children up to age five who have SMA type 2. If the results are positive, AveXis/Novartis may file for FDA approval of this delivery method as soon as 2020.

MANAGEMENT GOVERNANCE

FDA officials said Novartis took too long to launch a formal probe into allegations of Zolgensma data manipulation. (Novartis)

MANAGEMENT GOVERNANCE

Why the FDA Dropped the Hammer on Novartis Data Manipulation Scandal

Article from Biospace

Published: Aug 21, 2019 By Mark Terry

- In early August, the U.S. Food and Drug Administration (FDA) announced that the data involved in the preclinical approval process of Novartis' gene therapy Zolgensma for spinal muscular atrophy (SMA) was manipulated.
- The therapy, which was developed by AveXis, a Novartis subsidiary, was approved by the agency in May.
- Some have wondered why the agency has hit back at Novartis so hard when the data in question didn't have any effect on the eventual outcomes of the product's effectiveness and safety.

TIMELINE

- 14 March 2019 - Data manipulation reported internally to Chief Quality officer at Avexis
- 15 May 2019 - Formal Investigation - Nonconformance opened internally
- 24 May 2019 - PDUFA Date and Zolgensma Approval
- ~28 June 2019 AveXis informed FDA “about a data manipulation issue that impacts the accuracy of certain data from product testing performed in animals submitted in the biologics license application.”
- 24 July-02 August 2019 FDA Inspection of Avexis – 483 issued
- 22 August 2019 – Avexis Data Integrity Officer Job Posting

FDA INSPECTION PERFORMED 24JUL – 02AUG 2019 – FORM 483

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

A. Non-conformance Report NCR-1922 (which was open at the time of the current inspection) was opened on 15 May 2019 due to a report that was made to the CQO (Chief Quality Officer) alleging that data derived from the AVXS-101 In-Vivo Relative Potency Assay Studies 1-10 may have been mismanaged or even potentially manipulated. Aside from evaluations of Studies 1-10 and a planned evaluation of toxicological studies under NCR-2018 there is no documentation in this NCR that an audit of all other potentially impacted data, studies, and reports was conducted or is planned to determine if there was evidence of data mismanagement or manipulation or a justification for not conducting or planning such an audit. Additionally, there is no documentation in NCR-1922 as to why the NCR was not opened until 15 May 2019 when the initial allegation is documented as having been reported on 14 March 2019.

AVEXIS JOB POSTING 3 MONTHS AFTER FDA APPROVAL

Senior Director, Data Integrity Officer, Global Quality

Employer AveXis Inc. (a Novartis Company)

Location US-NC-Durham | US-IL-Bannockburn | US-CO-Longmont | US-CA-San Diego, Posted Aug 22, 2019

Lead the drive to change human behaviors and culture relevant to ensuring Data Integrity (DI) across the AveXis network…

Ensure the implementation of effective business processes, procedures and practices in alignment with regulatory expectations and company policies for DI through its lifecycle, including GxP computer systems, hybrid systems and manual/paper systems

MANAGEMENT GOVERNANCE

Data Ethics and Senior Management

- Effective executive leadership is a critical component in maintaining a high level of data integrity.
- Understanding how organizational and technical controls are executed and applied in your business processes is critical.
- A well-defined strategy is the cornerstone of a data integrity program.

CULTURE

CULTURE

Data Integrity and Employees

- Every employee is responsible for his/her own conduct to maintain a bond of trust between the company and its stakeholders – patients, health care providers, and regulators.
- A regulator does not distinguish between human error and data falsification when assessing the impact of a data integrity failure.

CULTURE

Reporting Honest Mistakes

- People occasionally make honest mistakes.
- When people make mistakes, the firm has an obligation to assist the employee in correcting the error, and further assisting the employee in increasing their vigilance so that they don't repeat the same honest mistake again.
- We must learn from our mistakes

CULTURE

Every employee is required to:

- collect, analyze, report, and retain information and data
- in a manner that accurately, truthfully, and completely represents what occurred
- in either paper or electronic format
- in accordance with company policies and procedures, and applicable law.

CULTURE

Employee Vigilance is the Key

- People might cause data integrity issues, but they are also superior to machines when it comes to detecting them.
- Management must ensure systems are in place to monitor and correct data integrity issues.

RISK ASSESSMENT

DATA INTEGRITY RISK ASSESSMENT

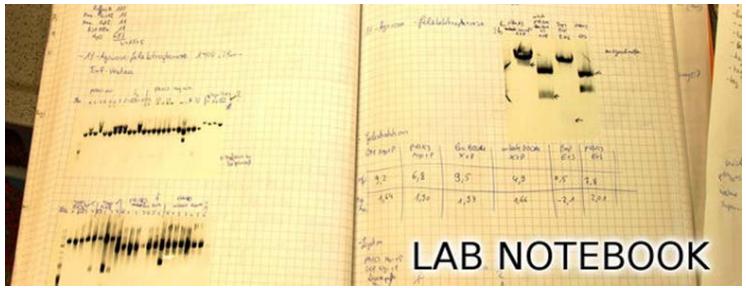
Establish data criticality and integrity risk

- What organizational (procedural) and technical (computer systems) controls are in place to ensure product quality?
- Degree of effort and resources applied to controls should be consistent with the criticality of impact on product quality and patient safety.

DATA - RISK

Data can be generated by:

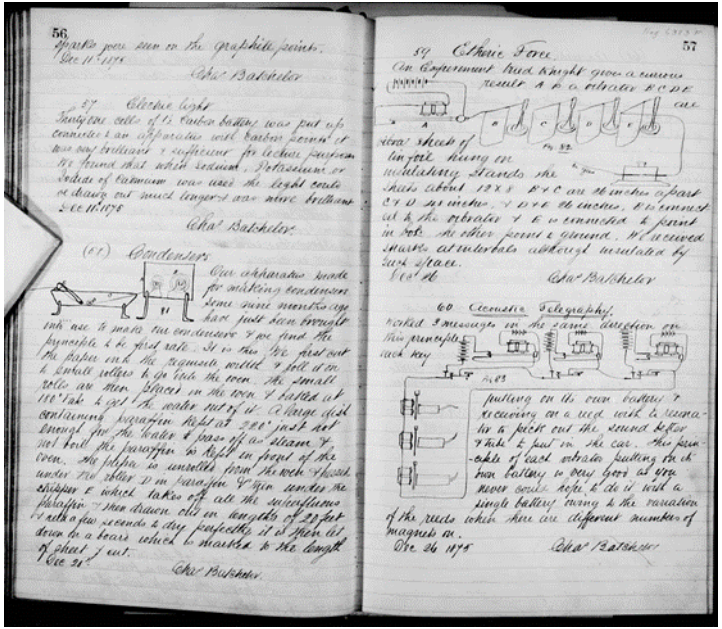
- simple manual collection methods, or
- Complex integrated systems which require validation/qualification to ensure that data processes are appropriately configured, qualified, and controlled.



RISK MANAGEMENT: PROCESS FLOW MAPPING

- Process flow maps key data integrity processes:
  - What actions are performed?
  - How are those actions performed?
  - How are they recorded?
  - What decisions are made?
  - Is the process manual or automated?
  - Possible risks associated with the step (e.g., how could fraud be prevented or detected)?
  - What checks exist to ensure data integrity?

DATA INTEGRITY FOR A PAPER SYSTEM



Involves demonstrating that procedures and policies are in place that control paper-based data systems.

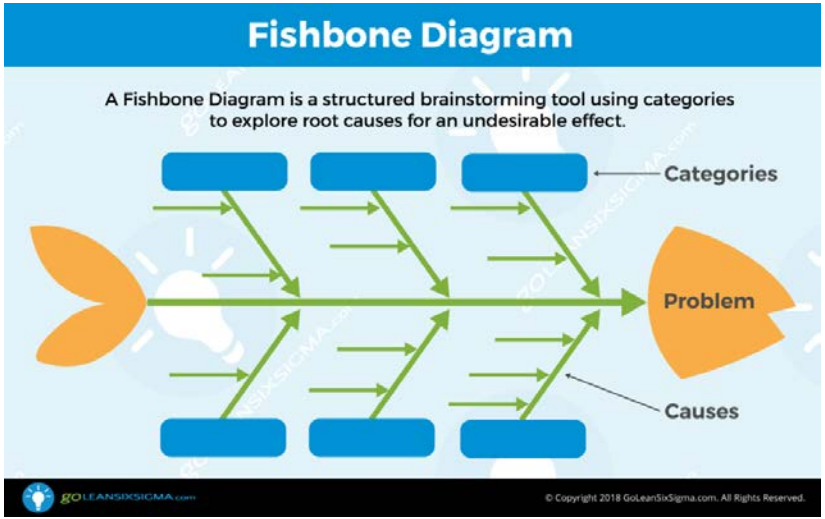
- Document control
- Execution of production batch records
- Manual recording of laboratory data
- Change management
- Nonconformance / deviation / CAPA management
- Risk management

RISK ASSESSMENTS

Risks to Data

- It is much easier to change electronic records than paper records.
- Regulatory agencies have thus placed greater emphasis on electronic data integrity in recent years, especially breaches on data security.

RISK ASSESSMENT



- Determine risks
- Determine severity, probability, detectability
- Perform risk analysis
  - Failure modes effects analysis (FMEA)
  - Root cause analysis
  - Ishikawa (fishbone) analysis
- Detection is key

RISK MANAGEMENT

EudraLex - Volume 4, GMP Guidelines, Annex 11

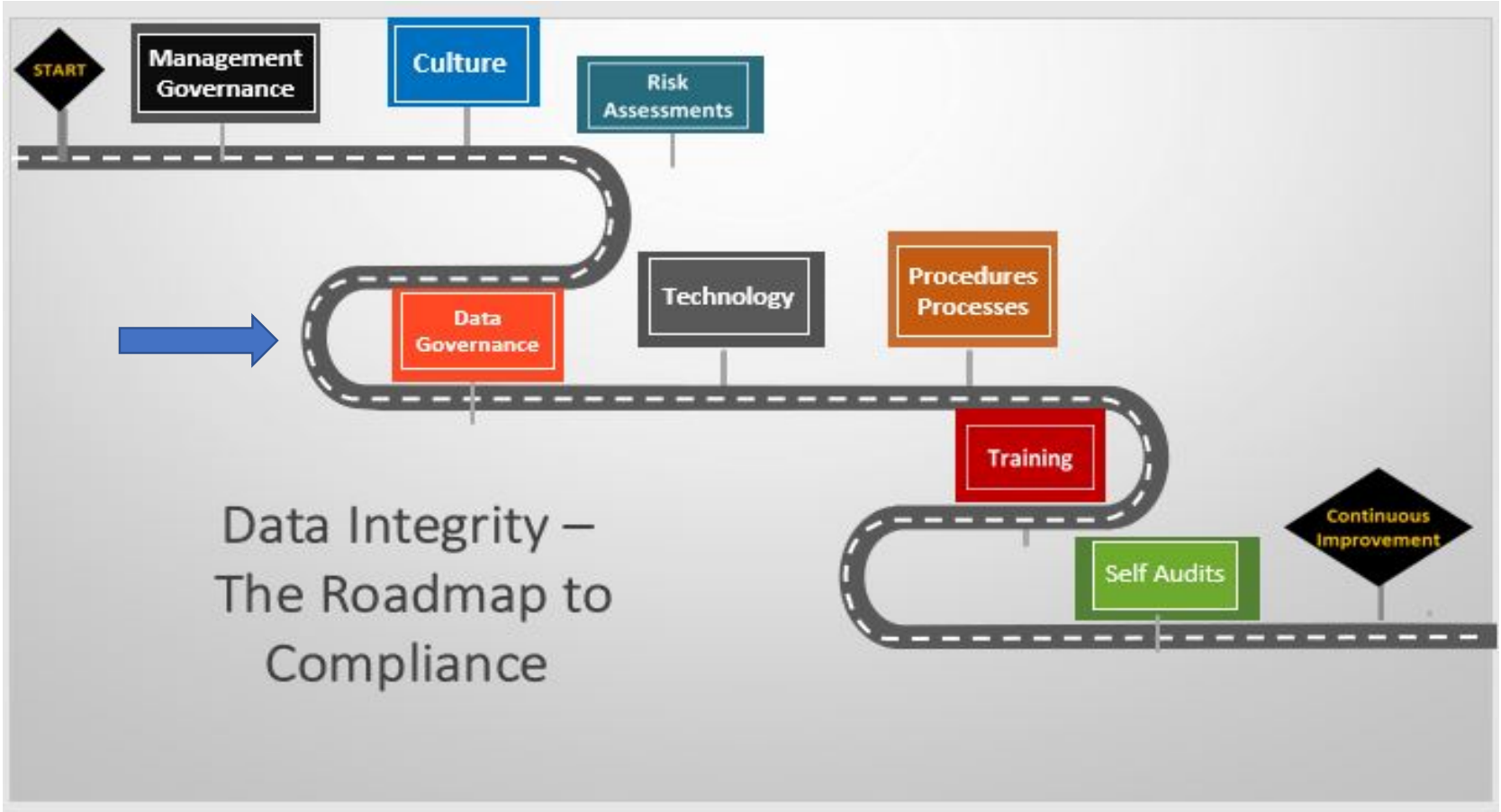
General: 1. Risk Management

- “Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.”

IDENTIFY GAPS

- System gaps
- Performance gaps
- Equipment gaps
- Part 11 gaps

DATA INTEGRITY – THE ROADMAP TO COMPLIANCE



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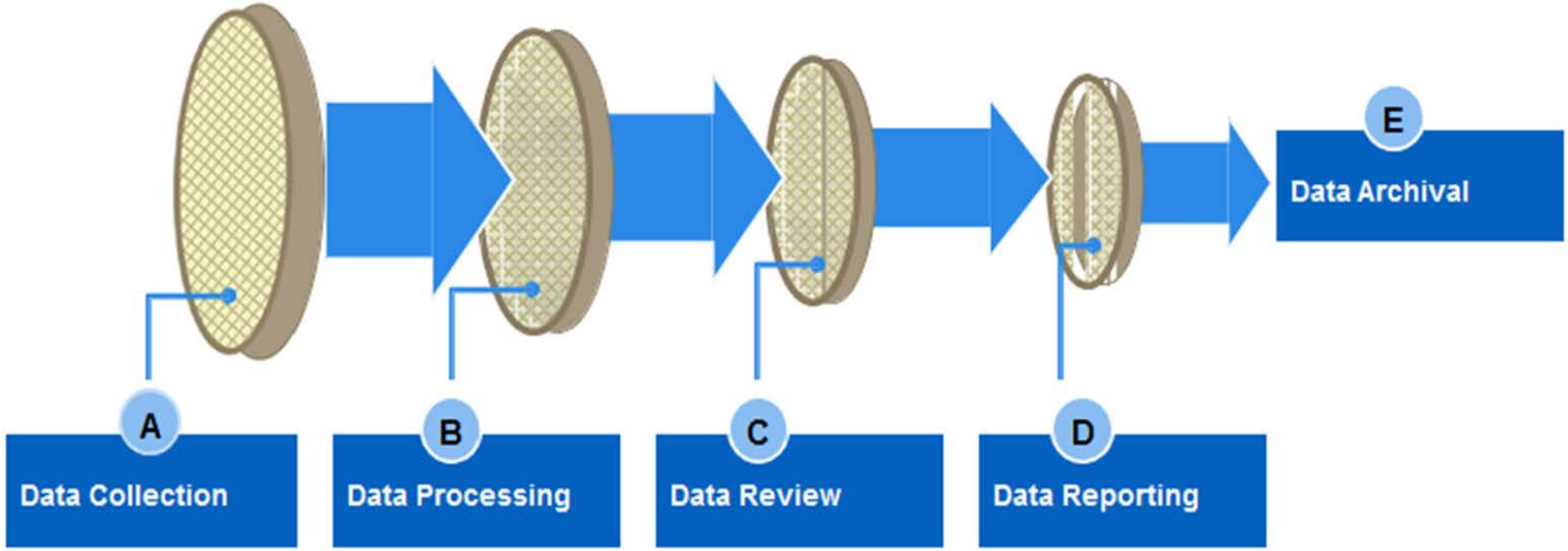
DATA GOVERNANCE

The total set of arrangements, systems, etc., that ensure that data are recorded, processed, retained, and used as intended.

- Data governance ensures a complete, consistent, and accurate record throughout the data lifecycle.
- Data governance should address data ownership throughout the lifecycle.
- Data governance should consider the design, operation, and monitoring of processes/systems, including control over intentional and unintentional changes to the information.

DATA GOVERNANCE LIFECYCLE



DATA LIFECYCLE

All phases in the life of the data, from initial generation and recording, through processing.

- This includes transformation or migration, use, data retention, archive/retrieval, and destruction.
- Procedures for data destruction should consider criticality of data and regulatory requirements.

DATA INTEGRITY - PDA

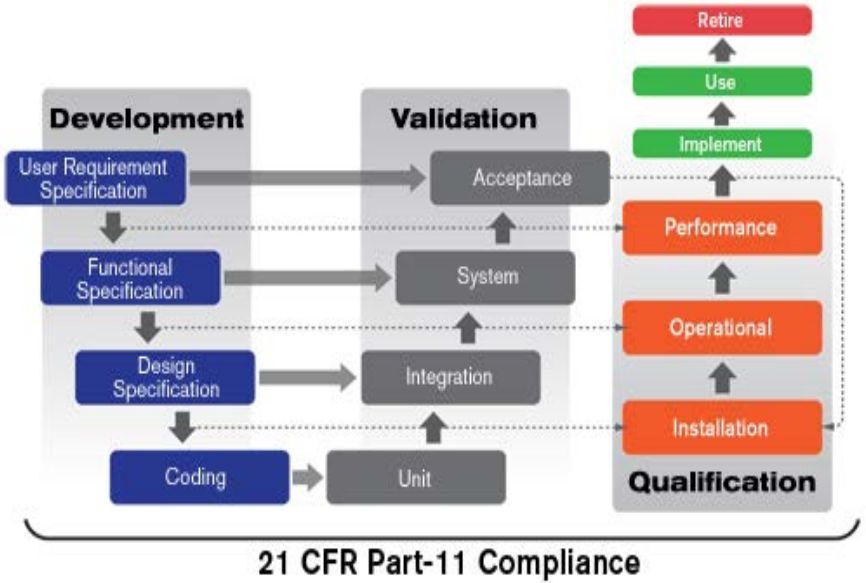
- Data integrity is the accuracy and consistency of stored data, indicated by an absence of any alteration in data between two updates of a data record.
- Data integrity is imposed within a system at its design stage through the use of standard rules and procedures and is maintained through the use of error checking and validation routines.

TECHNOLOGY AND VALIDATION

VALIDATION DEFINITION

- The process of establishing documented evidence demonstrating that a procedure, process, or activity carried out in production, testing, or other operations maintain the desired level of compliance at all stages and is capable of consistently delivering the desired outcome over the lifecycle of the product and process.

COMPUTER SYSTEMS VALIDATION



- Involves both software and hardware validation.
- FDA guidelines and GAMP 5 define processes for software testing, verification, testing, validation, and life cycle management through system retirement.
- Also covered are approaches to hardware selection and qualification.
- Data integrity, including database validation and management, are also treated.

DATA INTEGRITY MUST BE DEMONSTRATED DURING SOFTWARE /HARDWARE VALIDATION

- One of the main purposes of validation software / hardware is to demonstrate that the computerized system captures, processes, records, and stores data reproducibly and accurately.
- This involves validating the database structure (schema), the data storage devices, and the backup software / hardware / media.

VALIDATION FOR GOOD DOCUMENTATION PRACTICES (GDP)

- Validation ensures that GDP principles are embedded in the data acquisition, processing, reporting, storage, archival, and retirement operations.
- The same GDP principles involved with paper data systems are also employed in electronic data systems. ALCOA +
- Database validation is critical, as well as validation of critical associated systems such as:
  - backup/recovery
  - offsite storage
  - cloud storage
- Vendors of critical data support systems must be qualified

DATA STORAGE IN THE CLOUD

If data are stored in the cloud, and/or offsite at an internet / cloud provider, the vendor must be qualified, including auditing of:

- their software / hardware / networking systems
- infrastructure
- network topology
- quality systems
- security features to ensure that user data are properly secured and retrievable

SOFTWARE IS NEVER "PART 11 COMPLIANT" OUT OF THE BOX

- The best a software provider can do is make the software "Part 11 ready", meaning that the key functionalities for Part 11 compliance are present in the source code
- It is up to the user to:
  - Determine that the functionality fulfills the need for Part 11 compliance within their organization
  - Validate applicable functionality within their quality systems, workflows, and processes
- Beware of software providers who say their software is "Part 11 compliant"
- The compliance burden is on the user to validate the software for Part 11 compliance.

PART 11 VALIDATION

- 21 CFR Part 11 treats three (3) main topics:
- Electronic data integrity, governance, and retention
- Audit trails
- Electronic signatures and authentication

PROCEDURES AND PROCESSES

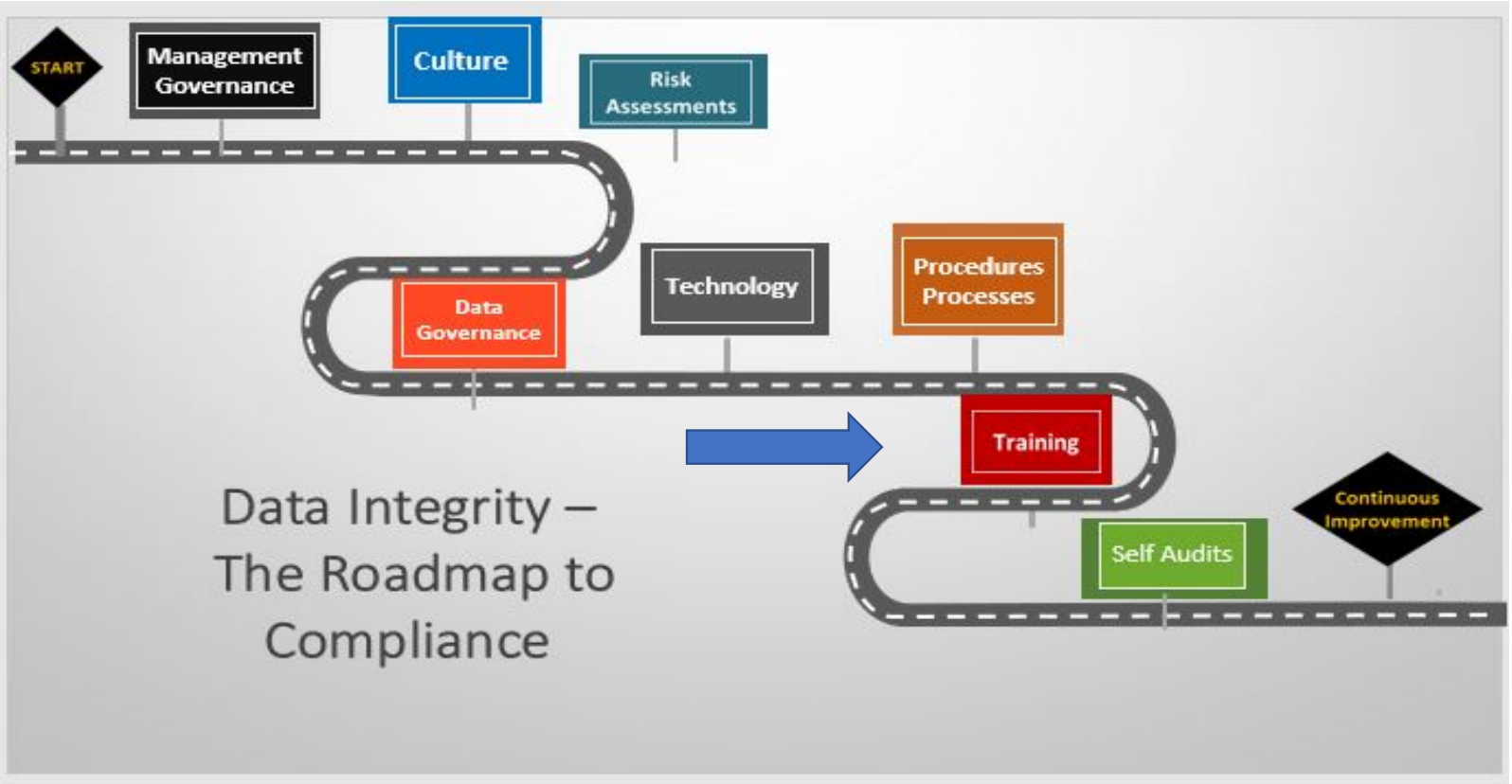
DATA INTEGRITY SOP SHOULD TREAT THE FOLLOWING

- ALCOA + complete, consistent, enduring and available
- Metadata
- Audit trail and audit trail review
- Static and dynamic data formats
- Backups
- Computer or related systems
- When data can be excluded
- Computerized systems validation, access, permissions, and authentication
- Blank forms control
- Originals and true copies, including laboratory instrument printouts
- Part 11, electronic signatures and wet signatures
- Suspected breaches in data integrity and/or ethics
- Personnel training, ethics, and awareness

ELEMENTS OF A CODE OF CONDUCT FOR DATA INTEGRITY

- Applicability
- Data Collection, Analysis, Reporting, and Retention
- Electronic Data Acquisition Systems
- Electronic Access Security Measures
- Auditing of Quality System for Data Integrity
- Investigations of Wrongful Acts
- Reporting Wrongful Acts
- Disciplinary Actions for Employees Due to Wrongful Acts
- Notifying Regulatory Authorities about Data Integrity Issues
- Data Integrity of Outsourced Services and Purchased Raw Materials
- Employee Training

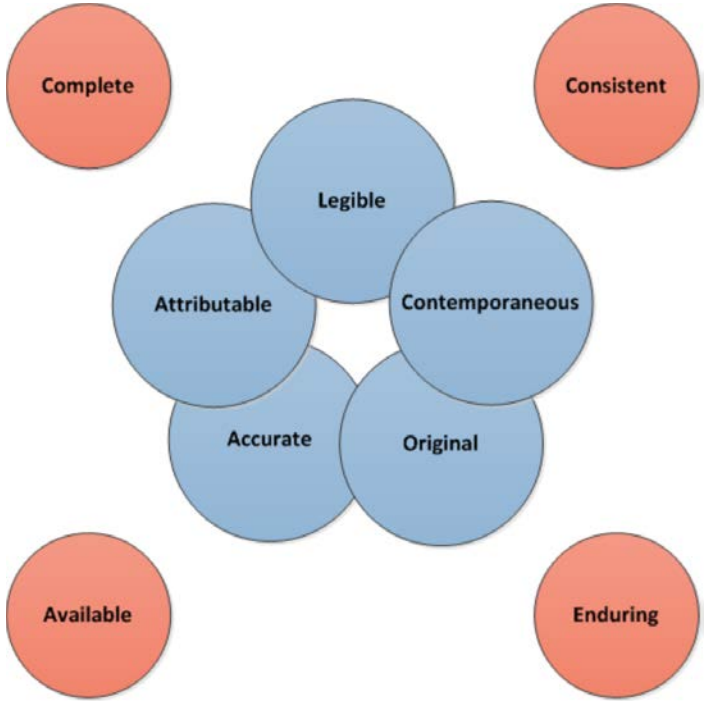
DATA INTEGRITY – THE ROADMAP TO COMPLIANCE



EMPLOYEE TRAINING

- Firm establishes and maintains training in data integrity, Code of Conduct, and reporting requirements for suspected breaches.
- Firm enforces the policy that all employees received data integrity training before being allowed to participate in GXP activities, and that all employees receive annual refresher training.
- Management reviews, annually at a minimum, employee records to confirm initial and ongoing data integrity training.

TRAINING AND ALCOA +



Firms should train personnel in data integrity principles (like we are doing right now!) and in the importance of data integrity

Management needs to create a work environment that encourages an open reporting culture for errors, omissions, and aberrant results.

Management is responsible for the implementation of systems and procedures that minimize the risk to data integrity, and for identifying risk according to ICH Q9.

WARNING LETTER - INDOCO REMEDIES LIMITED - JUL 16, 2019

- While multiple batch records of (b)(4) mg tablet included handwritten values routinely within process parameters, the values recorded by the programmable logic controller (PLC) of your compression machine were frequently outside your established process parameters. For example, (b)(4) mg batch (b)(4) had compression force values handwritten (b)(4) in the batch record ranging from (b)(4) (your limit was (b)(4)).
- …
- An inspection conducted by the (b)(4) in March 2018 found similar discrepancies between the compression force values in batch records and PLC data.

WARNING LETTER -INDOCO REMEDIES LIMITED - JUL 16, 2019

- Your response acknowledged discrepancies including missing data, "mis-matched data," non-contemporaneous entries, and other inconsistencies in your batch records. It also acknowledged inadequate procedures for compression machine setup and adjustments during operations intended to maintain process control, and a lack of documentation of these critical activities.
- Your response is insufficient. The integrity of all data within your manufacturing records is called into question by the actions of your staff involved in compression operations. You did not commit to perform a comprehensive retrospective evaluation of the integrity of data throughout your manufacturing operation.

WARNING LETTER -INDOCO REMEDIES LIMITED - JUL 16, 2019

- Process Controls
- Your firm does not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. See FDA's guidance document Process Validation: General Principles and Practices for general principles and approaches that FDA considers appropriate elements of process validation at Process Validation Guidance.
- CGMP Consultant Recommended
- Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant highly qualified in data integrity as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements.
- Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

SELF AUDITS – AUDITING OF QUALITY SYSTEM FOR DATA INTEGRITY

- Need to conduct internal audits, or parts thereof, specifically for data integrity issues.
- Audits are regular and periodic, using independent auditors qualified by education, experience, and training to evaluate data integrity.
- Employees conducting internal audits maintain current awareness of applicable laws and directives regarding data integrity.

CONTINUOUS IMPROVEMENT

- If you define the problem correctly, you almost have the solution - *Steve Jobs*

- Without continual growth and progress, such words as improvement, achievement, and success have no meaning - *Benjamin Franklin*

SUMMARY OF TRAINING

- Why is Data Integrity important?
- Warning Letters/ Case Study
- Applicable Regulations and Guidance
- Roadmap to Compliance
  - Management Governance
  - Culture
  - Risk Assessments
  - Data Governance
  - Technology and Validation
  - Procedures and Processes
  - Training – ALCOA+
  - Self Audits
  - Continuous Improvement

QUESTIONS

THANK YOU

THE MWA TEAM

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