Without measurement there is no control

Data Integrity

Understanding GMP & FDA requirements and becoming compliant
Agenda

- What is *Data Integrity*?
- Standard references
  - FDA 21 CFR Part 11
  - GMP Annex 11
  - New ISPE GAMP® - Record and Data Integrity
  - MHRA
- Ethical approach
- Particle Measuring Systems’ Solution
The FDA Believes:

• Manual systems have large, inherent operational risks, and are difficult to validate.

• If it isn't documented, it wasn't done.

• If it wasn't done using an appropriate process, it wasn't done properly.
Data Integrity in Pharma industries - INTRODUCTION

Data Integrity is not a new requirement

- **UK “Orange Guide” 1971:**
  - Copies from master records to avoid transcription errors
  - Initials of people who perform each activity
  - Record of the history of each batch, from supply chain to the final package.

- **EU GMP 1989**
  - Data alteration or correction requires signature, reason, and permit of original data reading
  - Records must be completed at the time the action is taken
  - Name of person who performed and checked the action
The Data Integrity Concept

Data Integrity refers to maintaining and assuring the accuracy and consistency of data over its entire product life-cycle.
The Data Integrity Today

- Over the last few years several, FDA Warning letters (483) have been issued for Data Integrity deficiencies in the Pharma industry.
- In 2016, more than 50% of MHRA warning letters involved data integrity lapses for computerized systems compared to 2015.
- Inspector are actively trained about Data Integrity requirements control.
Global Warning Letters Citing Data Integrity

- This graph shows the increasing trend of data integrity related warning letters.
- Authorities are strongly enforcing Data Integrity related requirements.
  - FDA 483 Warnings frequently refer to:
    - Falsified Batch records
    - Discharging of raw data
Regulatory Facts

FDA WARNING LETTERS
FISCAL YEARS 2011 - 2016

DATA INTEGRITY Non Compliance

cGMP Non-Compliance in 2016

136 Regulatory Actions
35% China, 27% India, 17% USA
33% Sites had Data-Integrity Violations

Confidential and proprietary

Data Integrity Today

• Deep knowledge and understanding of the most recent Data Integrity related standards, guides, and regulations is an essential step to being:

• The Data Integrity Compliance aim is to:
  • Increase Product Quality
  • Reduce product defects and costs
  • Increase regulator confidence
  • Real-time release
  • Increase brand reputation
  • Increase process control
Standards & Guideline References
Manufacturers of finished drug products for clinical trials, bioequivalence studies, and commercial distribution, Laboratories, Contract Manufacturing, Suppliers, etc. must refer to the actual Data Integrity related guidelines in order to guarantee compliance in data management.
21 CFR Part 11
Code of Federal Requirements

21 CFR Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved or transmitted under requirements set in agency regulations.

Electronic records/signatures that meet the requirement of part 11 may be used in lieu of paper records.
21 CFR Part 11
Code of Federal Requirements

21 CFR Part 11 represents the most used and required standard for correct data management.

Main requirements include, but are not limited to:

- General Provisions
- Electronic Records
- Electronic Signatures
Data Integrity – 21 CFR Part 11

Digital Signature

Digital signature means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.

- Signed electronic records shall contain:
  - The printed name of the signer;
  - The date and time when the signature was executed; and
  - The meaning (such as review, approval, responsibility, or authorship)
Electronic Record

Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

- Electronic records must contain Data, Metadata and must be available in a readable format.
- Electronic records must be ready to retrieve during the entire period of retention.
Audit Trail

The Audit Trail is a security-relevant chronological record or set of records, that provide documentary evidence of the sequence of activities that have affected at any time a specific operation, procedure, or event.

- The FDA recommends audit trails that capture changes to critical data be reviewed with each record and before final approval of the record.

The Audit Trail shall be computer-generated and time-stamped. It must record the date and time of operator entries and actions that create, modify or delete an electronic record.
Identification Control
ID & Password

Users who intend to generate electronically/digitally signed records must be controlled upon identification rules.

- Maintain the uniqueness of password and ID Code (username)
- Ensure password periodical checks/changes
- ID privileges shall be configured individually or on a group basis; operator, supervisors, administrators shall have different levels of accessibility.
  - That is, operators should not have database management rights.
Validation

The computerized system must be validated to ensure data accuracy, reliability and consistency. The system must be capable of discerning invalid or altered records.

• Computerized systems must generate an accurate, complete and human-legible copy of the records.
• Access limitation using ID / Password combination
• Having the appropriate education, training, and experience for those who develop, maintain, or use electronic record/electronic signature systems is essential to guarantee data integrity.
Data Integrity and Compliance With CGMP Guidance for Industry

- Data Integrity and Compliance with CGMP Guidance for the Industry
- Is currently a DRAFT Guidance
- Intended to clarify the role of data integrity in current good manufacturing practice CGMP
- Expects data to be accurate and reliable
- Does not establish legally enforceable responsibilities. Describes the Agency’s current thinking. Is suggested and recommended but not required.
The FDA Guidance provides a clear Question and Answer paragraph, intended to give clarification to commonly used terms:

**What is Meta Data?**
- The information to understand the data
- Example: 300 means nothing without knowing it is counts per cubic meter for a particle counters

**What is an Audit Trail?**
- Secure, computer-generated, time-stamped records
- Who What When and Why of the record
Data Integrity and Compliance With CGMP Guidance for Industry

The FDA Guidance provides a clear Question and Answer paragraph, intended to give clarification to commonly used terms:

- **Static and dynamic record formats**
  - “Static” is used to indicate a fixed data document such as a paper record or electronic signature.
  - “Dynamic” means a record that allows interaction between the user and record content, such as entering values manually in the systems database.

- **What are the systems in “computer or related systems”?**
  - ANSI defines systems as people, machines and methods organized to accomplish a set of specific functions.
  - Compute hardware, software, peripherals, networks, cloud infrastructure, operators and documents (manuals, sop’s etc.)
• In the European Union (EU), EudraLex is the collection of rules and regulations governing medicinal products (for human use as well as for veterinary use).
• Annex 11 is part of the European GMP Guidelines and defines the terms of reference for computerized systems used by organizations in the pharmaceutical industry.

• It’s important to note that Annex 11 is not a regulation, like the FDA 21 CFR Part 11 rule.
Eudralex GMP Annex 11

- The guidelines set forth by the Commission of the European Committees are not too distant from their US counterpart created by the FDA (21 CFR Part 11).
- Among other things, Annex 11 defines the criteria under which electronic records and electronic signatures are managed.
21 CFR Part 11 and Annex 11 (EU) Summary

The central consideration of both of these regulations are to ensure the records are entered correctly, cannot be tampered with, can be stored for the retention period as well as retrieved (in full) at any time during use and during the retention period.

Focus

- Accuracy of records
- Integrity of records
- Security of records
- Retrieval of records
21 CFR Part 11

- Part 11 has recently been modified to provide a more rational framework for implementation; however, the rule still applies if the electronic record is in a **high risk** area as defined by the data’s potential impact on human health.
The Must-Have SOP

<table>
<thead>
<tr>
<th>System Maintenance SOP</th>
<th>• Appropriate maintenance is carried out in a controlled way</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Security SOP</td>
<td>• Control of secure access (intrusion)</td>
</tr>
<tr>
<td>Logical Security SOP</td>
<td>• User and password policy</td>
</tr>
<tr>
<td>Incident and Problem Management SOP</td>
<td>• How to manage and communicate possible problems</td>
</tr>
<tr>
<td>System Change Control SOP</td>
<td>• How the change may affect your process</td>
</tr>
<tr>
<td>Disaster Recovery SOP</td>
<td>• Ensure data protection and recovery of process</td>
</tr>
<tr>
<td>Backup and Restoration SOP</td>
<td>• Control of regular data backup</td>
</tr>
</tbody>
</table>

Main Focus Area

- **The Features of Your System**
  - There are a range of features that are required by Annex 11 when implementing a computer system to manage electronic records.

- **Standard Operating Procedures**

- **System Validation**
  - Demonstrate that your system does what it should do.
The acronym ALCOA stands for the following attributes:
- Attributable
- Legible
- Contemporaneous
- Original
- Accurate

Data Quality should be focused on doing tasks right the first time, and report the results immediately.

Data Quality = Product Quality
The ALCOA

**Attributable**
Who acquired the data or performed an action and when was it acquired?

**Legible**
Data must be in a legible format and permanent during the entire retention time.

**Contemporaneous**
Documented at the time of the activity.

**Original**
Raw data or source data must be available in original form or true copy.

**Accurate**
Data must contain context/meaning and metadata.
BIG DATA and QUALITY

Velocity + Volume + Variety + Veracity + Viability = Value

Velocity
Frequency of data generation
- 300 hours of video uploaded to YouTube every minute (estimate)
- 2,400,000 search queries per minute on Google
- 4,170,000 posts liked on Facebook per minute

Volume
The growth of world data
- 1 terabyte holds the equivalent of roughly 210 single-sided DVDs.

Variety
Structured and unstructured data - types of Big Data
- Web and social media
- Machine to machine
- Big transaction data
- Biometric
- Human-generated

Veracity
Establishing trust in data
- 1 in 3 business leaders don't trust the information they use
- Uncertainty due to inconsistency, ambiguity, latency and approximation

Viability
Relevance and feasibility
- “Can we use mobile phone data to monitor cross-border tourism?”
- Hypothesis: validation to determine if the data will have a meaningful impact
- Long-term rewards and better outcomes from hidden relationships in data

Value
Return on investment

Costs
Risk of simply creating Big Costs without creating the value

Insights
Sophisticated queries, counterintuitive insights and unique learning

Confidential and proprietary
The impact of record and data integrity issues can be significant on a regulated company. It can result in recalls of products, warning or untitled letters, import alerts, injunctions, seizures, Application Integrity Policy Invocations/legal action, and ultimately the potential for patient harm.

These regulatory actions can also have a significant financial impact.
This Guide addresses paper records, electronic records, and hybrid situations, while encouraging a move away from hybrid situations, wherever practical.

This approach is intended to encourage innovation and technological advances while avoiding unacceptable risk to product quality, patient safety, and public health.
• Data integrity is fundamental in a pharmaceutical quality system which ensures that medicines are of the required quality.
• A robust data governance approach will ensure that data is complete, consistent and accurate, irrespective of the format in which data is generated, used or retained.
Data Integrity and Computerized systems

Data Integrity Definitions and Guidance

Diagram to illustrate the spectrum of simple machine (left) to complex computerised system (right), and relevance of printouts as ‘original data’

Simple  ------  Complex

pH Meter  Filter Integrity tester
UV Spec  HPLC systems
FT-IR  CAPA System

LC-MS  LIMS system  ERP System

No software  Simple software  Complex software

Printouts Could Represent Original data  Printouts not representative

(diagram acknowledgement: Green Mountain QA LLC)
THE MHRA MESSAGE

“A senior management resolution for the new financial year might be put to good use by reviewing the suitability of current performance metrics and engaging with front line staff in an attempt to understand the challenges of their day to day operations. By doing so, employees feel connected with management and feel that their voices, however inexperienced they may be, are heard and valued.”
Ethical Approach
Ethic Approach

From the PDA Journal:

- **Prevention**
  - The prevention of data integrity breaches can be addressed with three primary elements: Personnel and Training, a Validation Program, and Security.
  - Company standards of ethical conduct, when followed, ensure that each employee acts with integrity in the execution of their work.
  - Each employee is responsible for the validity and integrity of their data and documentation, whether it is a paper-based or electronic system.
Ethic Approach

• Avoid potential breaches of ethical behavior such as (but not limited to) the following:
  • Improper data manipulation
  • Adjustment of time clocks
  • Backdating of information
  • Creating records after the fact or without actually executing the procedure
  • Excluding adverse information
  • Sharing of passwords
  • Discarding or destroying original records
Without measurement there is no control

Conclusion
Conclusion

- It is imperative that everyone in the company understand they are ultimately responsible for data integrity.
- Data Integrity is a significant component of the Quality Management System.
- Inspectors around the world have made it very clear that good intentions are no defense against compromised data.
- The pharmaceutical industry must strongly consider any preventive or corrective action to improve the product quality through enhanced data integrity and ethical behavior.
Turning Data into Novelty...

NOVELTY

FUTURE

BUSINESS MODEL

WISDOM
Strategies

BUSINESS DECISION

KNOWLEDGE
Organized Info.

BUSINESS PROCESS

INFORMATION
Meaningful Data to Company

DATA
Collected facts and observations

STORE & MANAGE

PAST
EXPERIENCE

CONTROL
Act on it

SIMULATION
Make sense of it

MODELING
Make it relevant
Thank you for attending!

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For more information, comments or feedback, contact your Particle Measuring Systems local representative or navigate to our Customer Service webpage.
Thank You.

• References:

US-FDA
www.fda.gov

Health Canada
http://www.hc-sc.gc.ca

PDA
www.pda.org

ISPE
www.ispe.org

Novatek International
www.ntint.com

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