REMEDIATION OF '*DATA INTEGRITY*' AND '*DOCUMENTATION*' FORM-483 OBSERVATIONS

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THIS PRESENTATION COVERS

- Lack of Data Integrity is NOT a Single ‘Disease’
- Attributes of Successful Remediation
- Observations and Corrective Actions
- FDA Specified Data Integrity Remediation

LACK OF 'DATA INTEGRITY' IS NOT A SINGLE 'DISEASE'

- **Good Documentation Practices, Paper Records**
- **Good Documentation Practices, Electronic Records**
  - Predicate Rules and Chapters / Annexes
  - 21 CFR Part 11 and Annex 11
- **Computer System Validation**
  - Laboratories, Manufacturing, ERP, Complaints
  - Not Validated For Intended Use
- **Multiple Sourced Data Associated with Same Event Not in Agreement**
- **Cannot Discern Altered or Deleted Data**
- **Data Not Available or Not Provided**

ATTRIBUTES OF SUCCESSFUL REMEDIATION

- These Problems Rarely Exist In Isolation; It's Often More **Widespread** Than You Think
- Understand The Scope Of The Issues And Take A **HOLISTIC** Approach
- Identify And Fix The **Root Cause**
- It May Be **Costly** In FTEs, Consultants, Hardware / Software
- Establish a Data Governance Program

ATTRIBUTES OF SUCCESSFUL REMEDIATION

- **Establish a Data Governance Program *Within* QMS**
  - Provides A Framework And Executive Level Ownership
  - Incorporates Remediation Into The QMS
    - Investigations and Corrective Actions
  - Permits Risk Based Evaluation and Prioritization of Activities
  - Consistency in Communication and Goals
  - Ultimately Extend to GCP and GLP Activities
  - Addressed in MHRA, PIC/S and WHO Guidance

EXAMPLES WITH REMEDIATION

Duplicate HPLC Injections, Represents Testing Into Compliance

- Evaluate ALL HPLC Injections To Ensure They Are Appropriate
- Clarify When ‘Pre-injections’ Can Be Performed And How They Are To Be Identified. Revise SOP, Train Staff, Include In Internal Audit Program

Stand Alone Instrumentation Has Shared Passwords And No Audit Trail Capability

- Upgrade Software If Possible
- Purchase New Compliant Instrumentation / Software
- Interim Fix, Use Log Book Documentation

EXAMPLES WITH REMEDIATION

Computer Systems Not Validated For Intended Use

- Identify all GXP Computer Systems
- Evaluate Validation Status of *ALL* Computer Systems
- Remember ‘Requirements’, Configuration and Testing
- Document the Evidence

Access to Computer Systems Not Controlled

- Establish And Follow The Process
- Revise As Staff Change Positions
- Ensure Appropriate Privileges Assigned

EXAMPLES WITH REMEDIATION

- **Excel Calculation Spreadsheets Not Qualified / Validated / Controlled. Often Firms Don't Know How Many They Have Or Where They Are Stored**
  - Switch To Capability Within Existing Software (For Example, Empower)
  - Minimize Their Use, If Not, Then
  - Control Their Development, Validation, Use, Revision And Retirement

EXAMPLES WITH REMEDIATION

- **GMP Documents Discarded**
  - Training
  - Discipline

- **Data Modified or Data Deleted**
  - Defer to End of Presentation

DOCUMENTATION AND PRACTICES

- **Addressing Documentation Practices Frequently Requires Changes In The Quality System**
  - Data Governance
  - Data Collection, Processing, Review
  - GMP Audit Program and Inspection Prep
  - CMOs and Contract Labs
- **Not Simply SOP Revisions and Retraining**
- **Every Employee Plays an Important Role**

EXAMPLES AND REMEDIATION

- **Electronic Data Review / Approval**
  - Paper printout is not your GMP Data
  - Clarity In Review and Approval SOP
  - Training and Expertise for Review Staff

- **Alignment Of Paper And Electronic Records**
  - Equipment Logs
  - Scale Printouts
  - Laboratory Notebooks
  - Laboratory Log-in And Destruction

FDA IDENTIFIED 'DATA INTEGRITY REMEDIATION'

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements. In response to this letter, provide the following.

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting. Your investigation should include:

* A **detailed investigation protocol and methodology**; a summary of all laboratories, manufacturing operations, and systems to be covered by the assessment; and a justification for any part of your operation that you propose to exclude.
* **Interviews of current and former employees to** identify the nature, scope, and root cause of data inaccuracies. We recommend that these interviews be conducted by a qualified third party.
* An assessment of **the extent of data integrity deficiencies** at your facility. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your facility's operations in which you discovered data integrity lapses.
* A **comprehensive retrospective evaluation** of the nature of the testing and manufacturing data integrity deficiencies. We recommend that a qualified third party with specific expertise in the area where potential batches were identified evaluate all data integrity lapses.

B. **A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include *analyses* of the risks to patients caused by the release of drugs affected by a lapse of data integrity, and risks posed by ongoing operations.**

C. **A management strategy for your firm that includes the details of your global corrective action and preventive action plan. Your strategy should include**:

* A **detailed corrective action plan** that describes how you intend to ensure the reliability and completeness of all of the data you generate, including analytical data, manufacturing records, and all data submitted to FDA.
* A comprehensive description of the **root causes of your data integrity lapses, including evidence** that the scope and depth of the current action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence CGMP-related data at your firm.
* **Interim measures** describing the actions you have taken or will take to protect patients and to ensure the quality of your drugs, such as notifying your customers, recalling product, conducting additional testing, adding lots to your stability programs to assure stability, drug application actions, and enhanced complaint monitoring.
* **Long-term measures** describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, management oversight, and human resources (e.g., training, staffing improvements) designed to ensure the integrity of your company's data.
* A **status report** for any of the above activities already underway or completed.

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Refer to: www.ungerconsulting.net for Blog entries on warning letters and form 483 analysis including data integrity issues

2015 Data Integrity: *Warning Letter Deficiencies* And *Eudra GMP Reports Of Non-compliance*. *Please email me and I'll send a copy.*