CGMP Trends, Data Integrity and Handling an FDA Inspection

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TRENDS IN FDA INSPECTIONS
Trends: What is FDA Focusing On?

**Data integrity**
- Electronic records systems are not Part 11 compliant
- Review of QA and QC data shows duplicate testing, and "unofficial" testing
- Paper test reports and laboratory notebooks are not controlled documents
- Lack of control over access to computerized systems
- Non-contemporaneous record-keeping
- Deletion, falsification, alteration, or other manipulation of data

**Supply chain**
- API Repackers/Relabelers
- Contract Manufacturers

**Rudimentary CGMP**
- Release testing
- Cleaning, equipment maintenance, basic sanitation
- Cross-contamination risks
- Delay/Deny/Limit/Refuse Inspection
- Complaint handling, remediation, internal investigation

**Sterility assurance**
- Aseptic technique, environmental monitoring, design
- Defective smoke studies in aseptic processing areas
- Improper investigation of Environmental Monitoring results and Personnel Monitoring results
**FDA Warning Letters Focus On Data Integrity**

- **Total CDER cGMP Warning Letters (Worldwide)**
  - 2011: 38%
  - 2012: 50%
  - 2013: 26%
  - 2014: 50%
  - 2015: 78%
  - 2016: 35%
  - 2017: 32%
  - 2018: 32%

- **CDER cGMP Warning Letters (Worldwide) Citing Data Integrity Issues**
  - Average % of Data Integrity Warning Letters 2011 – 2018: 43%

Based on Warning Letters posted to FDA database as of August 27, 2018.

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DATA INTEGRITY
Data Integrity

Regulations and Guidance

• **21 CFR Part 11**
  Electronic Records; Electronic Signatures

• **21 CFR Part 210**
  CGMP in Manufacturing, Processing, Packing, Holding of Drugs; General

• **21 CFR Part 211**
  CGMP for Finished Pharmaceuticals

• **Draft Guidance**
  “Data Integrity and Compliance with CGMP” (Apr. 2016)
Data Integrity

• The completeness, consistency, and accuracy of data.
• ALCOA: Data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate.

FDA Draft Guidance, “Data Integrity and Compliance with CGMP”
(April 2016)
Data Integrity Basics

Basic Principles
• Testing, analysis, and other activities must be documented at the time of performance.
• Backup data must be exact, complete, and secure from alteration or loss.
• True and complete copies (or other accurate reproductions) of original records must be maintained.

Computer Systems
• Have sufficient controls to prevent unauthorized access or data alteration.
• Maintain a record of any alterations made to data; the previous entry; who made the change, etc.
• Maintain a backup system if a breakdown in the primary system would result in permanent loss of records.
• Validate all CGMP-related computerized systems.
• Incidents that could affect the reliability of records or test results should be documented and investigated.

FDA Draft Guidance, “Data Integrity and Compliance with CGMP” (April 2016)
Data Integrity Basics

• Use of CGMP Data
  ◦ Any data created to satisfy a CGMP requirement must be:
    maintained for CGMP purposes (21 CFR § 211.180); and
    evaluated by the quality unit as part of release criteria (21 CFR § 211.22).
  ◦ To exclude data from release criteria decision-making, there must be a valid, documented, scientific justification.

• Audit Trail Review
  ◦ Audit trails should be reviewed with each record and before final record approval.
  ◦ FDA recommends “routine scheduled audit trail review based on the complexity of the system and its intended use.”

*FDA Draft Guidance, “Data Integrity and Compliance with CGMP” (April 2016)*
Data Integrity Basics: Paper vs. Electronic Records

• When data are generated to satisfy a CGMP requirement (whether electronic or paper), those data become a CGMP record.

• Electronic records may be used as “true copies” of paper records, and paper printouts can satisfy retention requirements in place of electronic records, if the paper printout is a complete copy of the original record.

• But, records (paper and electronic records alike) must be stored in a way that does not allow for manipulation, loss, etc.

FDA Draft Guidance, “Data Integrity and Compliance with CGMP” (April 2016)
Data Integrity Basics:
Internal Tips

Can an internal tip regarding a quality issue, such as potential data falsification, be **handled informally** outside of the documented CGMP quality system?

**NO**

Suspected or known falsification or alteration of CGMP records must be fully investigated **within the quality system** to determine:

- Effect of the event on patient safety, product quality, and data reliability;
- Root cause;
- Necessary CAPAs.
Data Integrity Basics: Remediation

• Hire a reputable third-party auditor;

• Assess scope of the problem;

• Implement a CAPA globally.
HANDLING AN FDA INSPECTION
Before the Inspection

- Have an FDA Inspection SOP.

- Have third-parties conduct mock audits.

- Foster a culture of compliance.

- FDA may request documents “in advance of or in lieu of an inspection, within a reasonable timeframe, within reasonable limits, and in a reasonable manner, and in either electronic or physical form.”

  \textit{FDCA § 704(a)(4)}

  \textit{(FDASIA 2012)}
Arrival of the Investigators

The receptionist should:

• Ask the investigator(s) to sit in the lobby;

• Immediately contact management;

• If management is unavailable, ask investigator to either wait or return when management personnel are in the facility;

• Refuse to sign anything, allow inspection of documents, or give out copies of documents.
During the Inspection: Receiving the Investigator

The inspection team (escorts) should:

• Ask to see the investigator’s credentials;

• Ask to see the Form 482;

• Try to determine if any investigator is from FDA’s Office of Criminal Investigations;

• Tell the investigator that other employees are not authorized to speak for the company.
During the Inspection: FDA’s Authority

FDA may inspect:

- facilities where drugs are manufactured or stored;
- equipment;
- finished and unfinished materials;
- containers;
- labeling; and
- records relating to CGMPs and pre-market approval applications.
During the Inspection: 
FDA’s Authority

**FDA may NOT**

- Inspect:
  - financial data;
  - sales data (other than shipping data);
  - pricing data;
  - personnel data (except for qualifications of technical and professional personnel);
  - research data (other than data relating to certain new drugs, devices, and other products subject to specific reporting and inspection requirements);
  - internal audit reports; and
  - internal reports and memos on factory inspections.

*FDCA § 704(a)*

- Breach sterility or intervene with the production process.

*Any request to inspect areas or data beyond the investigator’s authority must be made in writing.*
During the Inspection:
FDA’s Authority:
Photography and Videotaping

• FDCA does not indicate that photographs must be permitted.

• FDA Guidance states (at page 7): Conditions or practices effectively documented by photographs include “evidence of rodents or insect infestation; faulty construction or maintenance of equipment or facilities; product storage conditions; product labels and labeling; and, visible contamination of raw materials or finished products.”

• “Impeding or resisting photography by an FDA investigator may be considered a [unlawful] limitation if such photographs are determined . . . [t]o be necessary to effectively conduct that particular inspection.”

• Guidance does not require companies to allow videotaping

*FDA Guidance, “Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection” (October 2014).*
During the Inspection: Do’s and Don’ts

Do:

• Record the purpose of the visit (e.g., routine inspection, complaint follow-up, pre-approval inspection, anticipation of enforcement or regulatory action);
• Escort the investigator(s) at all times;
• Funnel all requests for documentation, data, or product samples, etc. through the escort;
• Determine a schedule of events or (at a minimum) the areas to be covered and approximate time of day;
• Allow authorized employees to answer questions that are not inappropriate or leading;
• Tell the truth;
• Ask for clarification when necessary;
• Consult with counsel before signing any affidavit.
During the Inspection:  
Do’s and Don’ts

Do not:

• Joke with the investigator;
• Volunteer information;
• Argue or make threatening remarks.
During the Inspection: Availability of Employees

- FDCA does not mandate that employees must continue working or be made available when investigator arrives.

- However, FDA Guidance states (at page 6) that it is unlawful to “impede the investigator,” including when “[a] facility sends staff home for the day and tells the FDA investigator that the facility is not producing any product.”

- Guidance also states (at page 6) that a facility that “orders the discontinuation of all manufacturing for the duration of the FDA inspection without a reasonable explanation” also has “refused” to permit observation of the manufacturing process and thus prevented investigators “reasonable access” to areas “FDA is entitled to inspect.”

*FDA Guidance, “Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection” (October 2014).*
During the Inspection:
Problems and Corrective Actions

• Ask investigators to identify problems noted during the course of inspection so that they may be corrected as soon as possible.

• When the investigator notes a problem
  o Immediately inform the appropriate company employees;
  o Try to correct before the inspection concludes.

• If the problem is corrected during the inspection:
  o Tell the investigator(s) when the corrective action is taken;
  o Ask the investigator(s) to either not mention the problem on the Form 483 or to indicate that the problem was corrected during the inspection.
During the Inspection: Close-Out Meeting

- Investigators will offer close-out meeting;
- Usually includes presentation of FDA Form 483;
- Take time to pose questions, seek clarification, and to the extent necessary, challenge the observations;
- Corrective actions can be noted on the 483;
- Do not make admissions, argue, or give a final response to the observations.
After the Inspection

**Do NOT** commit to any corrective action unless employees are certain the commitment can be met.

**Do** follow up to assure that required actions are completed expediently.

**Do** prepare a **483 Response** (i.e., responses to any Form 483 observations):

- Respond within 15 working days;
- Do not wait to receive the EIR;
- Be as thorough and detailed as possible;
- If FDA receives your response more than 15 days after the 483 is issued, the Agency may issue a Warning Letter without reading your 483 Response.
After the Inspection:
Corrective Action

- If it’s not documented, it didn’t happen.

- Meetings with FDA can help, but usually are most constructive if they follow written submissions.

- Do not solicit guidance about something you should already know.

- Determine root causes; identify systemic issues; address issues globally.

- If you are unclear what corrective action is appropriate (and can’t find out), it is appropriate to ask FDA, but BEWARE.

- It can also be appropriate to ask if corrective action is sufficient, but, again, this can open the door to unhelpful suggestions/directives from FDA.

- When EIR is received, review carefully, and communicate any corrections.
Questions?