# CGMP Trends, Data Integrity and Handling an FDA Inspection

*Mark Schwartz*
*Director*
*Hyman, Phelps & McNamara P.C.*
*September 6, 2018*

Hyman, Phelps & McNamara PC

# 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

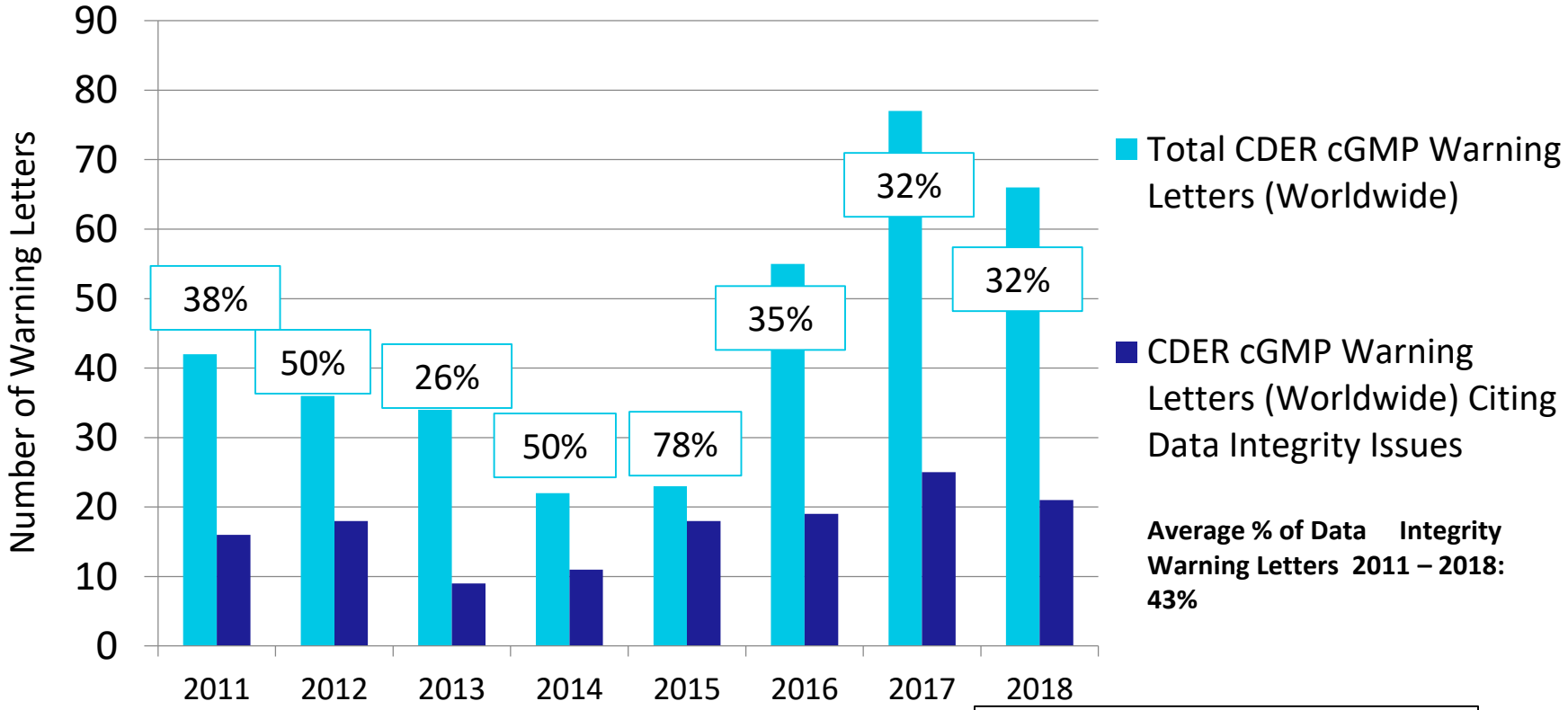
**Rudimentary CGMP**

- 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




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

# 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- **Draft Guidance**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 **a**ttributable, **l**egible, **c**ontemporaneously recorded, **o**riginal or a true copy, and **a**ccurate.

*FDA Draft Guidance, "Data Integrity and Compliance with CGMP" (April 2016)*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."

*FDCA § 704(a)(4)*

*(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
  - Immediately inform the appropriate company employees;
  - Try to correct before the inspection concludes.

- If the problem is corrected during the inspection:
  - Tell the investigator(s) when the corrective action is taken;
  - 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?