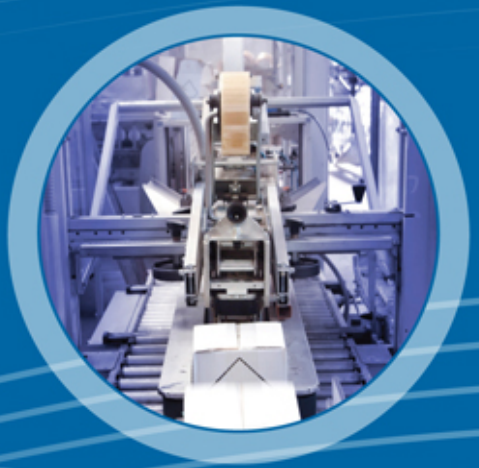
Connecting People, Science and Regulation®

Commonly Identified Non-Compliances



Carmelo Rosa
Cormac Dalton
18th September 2014

Source Data

- EudraGMDP Website
  - EudraGMDP website

- FDA Warning letters
  - FDA Warning Letters

- Do you formerly review this information?
- What actions do to take – risk management?

Hot topics

- **Data Integrity**
- **Cleaning / Cross contamination**
- **Investigations (deviations)**

Why now?

- **Data integrity**
  - Is this a recent ‘issue’?
  - No changes in GMP guide.
  - Cases of bad practice identified
  - Cases of malicious intent?
  - High focus on QC area

- **Note - data integrity is not a QC specific topic**

ICH Q7 – section 6

- Records should be maintained including:

  the name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for API's;

  the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt;

  the results of any test or examination performed and the conclusions derived from this;

ICH Q7 – section 6 (continued)

records tracing the use of materials;

documentation of the examination and review of API labelling and packaging materials for conformity with established specifications; and

the final decision regarding rejected raw materials, intermediates or API labelling and packaging material

ICH Q7 – section 6 (continued)

- **Specifically on Laboratory data**

  Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays….

- Data and meta-data generation, review, storage and archive

Data Integrity

- **Next steps**

  - What actions are you taking to:
    - raise awareness with employees / contractors
    - assess data integrity practices and weaknesses
    - mitigate any risks

Why now?

- **Cleaning / Cross contamination**

- Is this new?

- No change in ICH Q7 guidance

- PIC/S GMP Part 1 (chapters 3 and 5) are changing
  - More scientific approach to residue limits

GMP Guidance

- **Basic elements of GMP**

  - People awareness
  - Robust cleaning processes (validated and/or verified)
  - Maintaining a clean facility
  - Storage of equipment & documentation
  - Managing decommissioning activities
  - Introduction of new chemical entities to site

Investigations

- **Common phrase found under the responsibility of the QU/Production in Q7 is: "MAKING SURE" (MS):**

1. MS critical deviations are investigated, resolved, conclusions recorded

2. MS that quality-related complaints are investigated and resolved

Investigations

3. MS that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded

Investigations (deviations)

- There is a difference between documenting a deviation and investigating a deviation.
- Should all investigations be investigated:

  No___? Yes?____Why___ or Why Not___ ?
- What is a critical deviation, and why should these be investigated?

Investigations of Critical Deviations:

Q7 requires two key components:

1. Critical deviations should be investigated and documented.

What is a “critical deviation” ?

Purpose of Investigation:

- Identify the root cause, understand what happen, why, when, who is responsible/ involved, determine the impact on the quality attributes of the API, and then to implement the appropriate CAPA(s).

Investigation of Critical Deviations

- “An investigation is NOT a CAPA”
- Should evaluate historical data, previous incidents, trends, systems affected and related to the deviation
- The objective should not be to satisfy the regulator, but to find the origin or the root cause of the problem
- Need to define the scope of the problem and impact on the quality of the API, and potential risk to patient

Investigations of Critical Deviations:

Conclusions should be documented:

- How did they reach to the conclusion(s)?
- What were the contributing factors to the deviation/failure?
- What is the scientific rational and basis for the conclusions?
- What supporting documentation is available?
- What Immediate action is needed to mitigate any risk?
- What's the impact on product, systems and CAPA ?

What's a deficient investigation?

1. One that lacks supporting evidence to support the conclusions made.
2. When the conclusion is reached before the investigation is performed
3. When the investigation is focused on proving a point or theory of what happened, and not in finding the true root cause that led to the critical deviation.
4. When appropriate systems and units are not evaluated
5. When other potentially affected lots or products not assessed
6. When the quality unit not involved in the investigation

Recent regulatory deficiencies

- Manipulation and falsification of documents and data were observed in different departments
- Entries were seen to be made when personnel were not present on site

Recent regulatory deficiencies

- Cleaning procedures are not detailed to enable operators to clean each piece of equipment in a reproducible and effective manner. Cleaning procedures of the critical pieces of equipment used after final isolation of pure APIs are not validated. Analytical methods by TLC used for cleanliness verification are not validated

Recent regulatory deficiencies

- Critical deviations not investigated (disregarded or ignored)
- Process failure or laboratory OOS are not investigated.
- Breaches to integrity of data not investigated
- Failure to investigate the extent of the data integrity problems found

Example of USFDA WLs

- Failed to investigate unknown peaks found during the HPLC testing for related compounds for API XXXX

- A reviewer of the raw data reported on the "finished product report review data" worksheet that unknown peaks were observed due to vial contamination. NO investigation was performed These OOS results were not reported or adequately Investigated.

Recent regulatory deficiencies

- Failure to investigate complaints related to critical quality attributes
- Failure to investigate breaches in the integrity of the electronic data
- Failure to investigate cross-contamination events
- Failure to adequately investigate stability OOS and extend investigations to other lots

Questions / Discussion

- **Thank you !**

- Carmelo Rosa
  FDA
  Carmelo.Rosa@fda.hhs.gov

- Cormac Dalton
  AbbVie
  cormac.dalton@abbvie.com