PDA- PIC/S Q7 Training
September 18, 19, 2014
Brussels, Belgium

Frequent Deficiencies Found During API Inspections

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Topics

General Overview of frequent deficiencies found during API inspections

Inspection of API sites, conducted by PIC/S members frequently cite deficiencies:

- Laboratory controls;
- Records/investigations;
- Quality systems;
- Equipment cleaning/maintenance and;
- Process validation.

Frequent GMP deficiencies cited by USFDA during API Inspections (2012): Laboratory Controls:

(1) Lack of/inadequate method validation;
(2) Failure to have scientifically sound and appropriate specifications and test procedures;
(3) Failure to adequately investigate out of specification results;
(4) Failure to document activities at the time of performance;
(5) Failure to have adequate stability testing programs

Frequent GMP deficiencies cited by USFDA (2012): Quality Unit (QU)

(1) Failure of the QU to release/reject APIs;

(2) Failure of the QU to review and approve all quality related documents;

(3) Failure to ensure that quality related complaints are investigated;

(4) Failure to conduct regular quality reviews of the APIs;

(5) failure to evaluate the impact of changes in the quality APIs.

Frequent GMP deficiencies cited by USFDA (2012): Equipment, Cleaning, Maintenance and Validation

(1) Equipment not being properly maintained;
(2) Deficient cleaning procedures;

(3) Failure to validate cleaning procedures;

(4) Failure to clean, store, sanitize equipment to prevent contamination or carry-over that may alter the quality of APIs;

(5) Inadequate qualification of critical equipment.

Frequent GMP deficiencies cited by USFDA (2012): Records and Reports:

(1) Failure to prepare adequate batch records;

(2) Failure to include complete data of all test performed;

(3) Failure to establish written procedures related to production, quality, laboratory controls and material management.

Breaches in the integrity of data in API sites found by different PIC/S members/partners:

1. False recording of data in logbooks;
2. Falsification of batch records and test results;
3. Pretesting samples and ignoring or not investigating out of specification results;
4. Blending or mixing API batches that failed to meet the established released specifications with batches that met the required final specifications;

Breaches in the integrity of data in API sites found by different PIC/S members/partners

(5) Lacking necessary controls in handling and managing critical data;

(6) Entering manufacturing activities on records before occur

In 2011, 12 of 20 Warning Letters issued by the US FDA were issued to API manufacturers;

In 2012, 7 of 23 Warning Letters were issued to API sites (1 of the 7 was to a site that produced both, API and finished product.

As or August 2013, 6 of the 26 Warning Letters were issued to API manufacturers.

Similar findings have also been found by other PIC/S members as well as by EDQM.

In 2012, the EDQM performed 32 inspections of API manufacturers located mainly in Asia, of which 13 showed serious GMP non-compliance findings or non-compliance to the CEP (Certificate of Suitability to the monographs of the European Pharmacopoeia)

Examples of API Deficiencies Cited by FDA on WLs

Asada Miling Co., March 22, 2013

1. Failure of the QU to perform quality related activities:

   -failure to review, release, or reject API products; failure to perform annual product quality reviews; failure to have procedures to review "process validation", change management documentation, release or raw materials…"

Examples of API Deficiencies Cited by FDA on WLs

2. Failure to establish written procedures pertaining to handling of raw materials used in API production and failure to establish specifications for finished API released.

Examples of API Deficiencies Cited by FDA on WLs

- “Your firm failed to perform process validation for the manufacturing of its API products including…”
- During the inspection your firm prepared and presented a document entitled: How to Determine Process Conditions”, briefly describing your firm’s experience with parameters such as mixing duration, speed, and temperature…This document is an

Examples of API Deficiencies Cited by FDA on WLs

Inadequate replacement for executing process validation as it fails to demonstrate a robust state of control with data obtained from the API production process.”

WL Aaarti Drug Limited, July 30, 2013

1. Failure to record all quality activities at the time they were performed:

- A production employee had documented the final packaging amount of the lot, even though the final packaging was unknown, as the lot manufacturing had not been completed.
- Recording analysis time before the test had been performed.

WL Aaarti Drug Limited, July 30, 2013

2. Firm failed to review and investigate production and QC laboratory deviations

- Failure to investigate unexplained atypical peaks observed in the related substance assay results for multiple API batches….
- The source of the unknown peaks between XXX retention time was unknown, and batches were released to the US despite the detection of atypical peaks detected at the time of release (should a retrospective review/risk be assessed?)

Examples of API Deficiencies Cited by FDA on WLs (2014)

1. Failure of the QU to review batch production records before the API is released/distributed.
2. Failure to document manufacturing operations at the time they are performed
3. Failure to maintain equipment in a state appropriate for its intended use

Examples of API Deficiencies Cited by FDA on WLs (2014)

1. Failure to maintain complete data derived from all lab. test conducted to assure compliance with established specifications
2. Batch samples tested until acceptable test results were obtained
3. Atypical (OOS) results were reported, nor included in the official QU package, nor investigated

Examples of API Deficiencies Cited by FDA on WLs (2014)

4. OOS test results for residual solvents not reported.
5. Failure to document and investigate OOS results
6. Complaint investigation regarding an assay failure of the API was received in Feb 2013. The firm had failure results of January 2013, prior to receiving the complaint, and did not include these failing results in the complaint investigation.

Examples of API Deficiencies Cited by FDA on WLs (2014)

7. Disregard of OOS results, unofficial testing and trial injections, with no scientific justification for having trial injections in a stand alone testing equipment located in a separate area.

8. Practice of deleted relevant critical electronic files and test results

9. Electronic overwriting practices of questionable or failing results.

Thank You!!!!!!!!!!!!!!!!!!!

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