

Current Trends in Data Quality and Integrity Issues

Is it a Myth or tip of the Iceberg ?



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Agenda



- Objectives
- Current trends
- Recurring citations
- Common CGMP issues in Indian WLs (2015-17)
- Common explanations for DI issues
- Consequences of breaches in DI



Objectives

- Explore current inspection trends as a reflection of a defective or immature Quality System
- Identify recurring CGMP problems in order to prevent quality issues and common DI breaches (paper based and electronic systems)
- Assess if individual, group, system or quality culture issue
- Identify means of transforming an organization that has been marked by bad DI practices



CURRENT TRENDS

Compliance and enforcement actions



- Consent decrees
- Import alerts
- Seizures
- Warning letters
- Clinical investigator disqualifications
- Criminal indictments/convictions

Unapproved drugs

Health fraud

Data integrity

CGMP violations

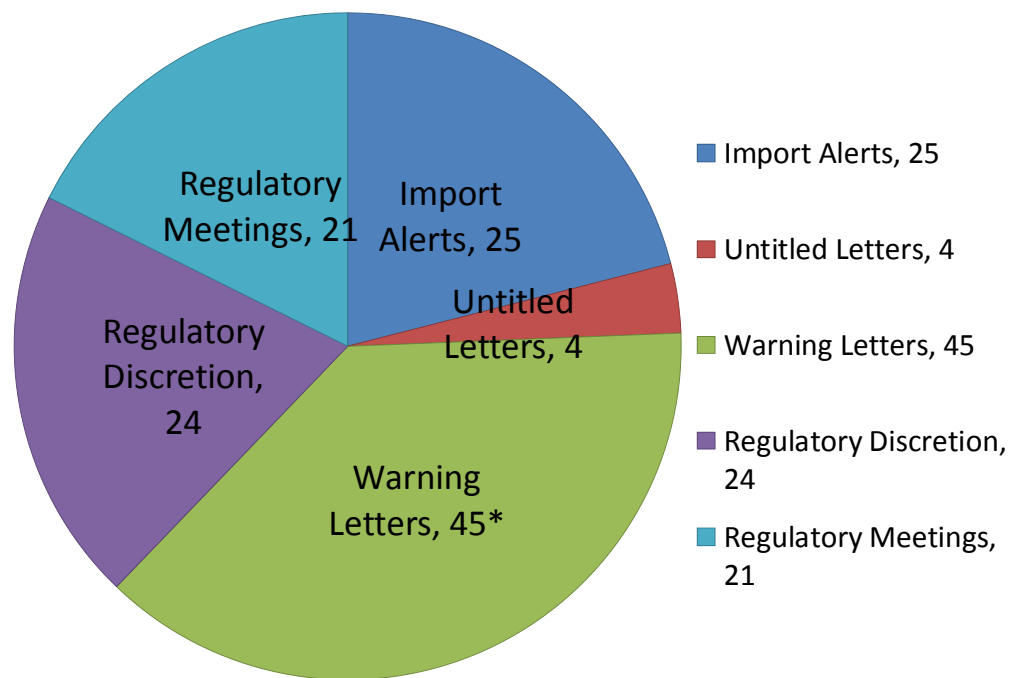
GCP violations

Enforcement and Advisory Tools



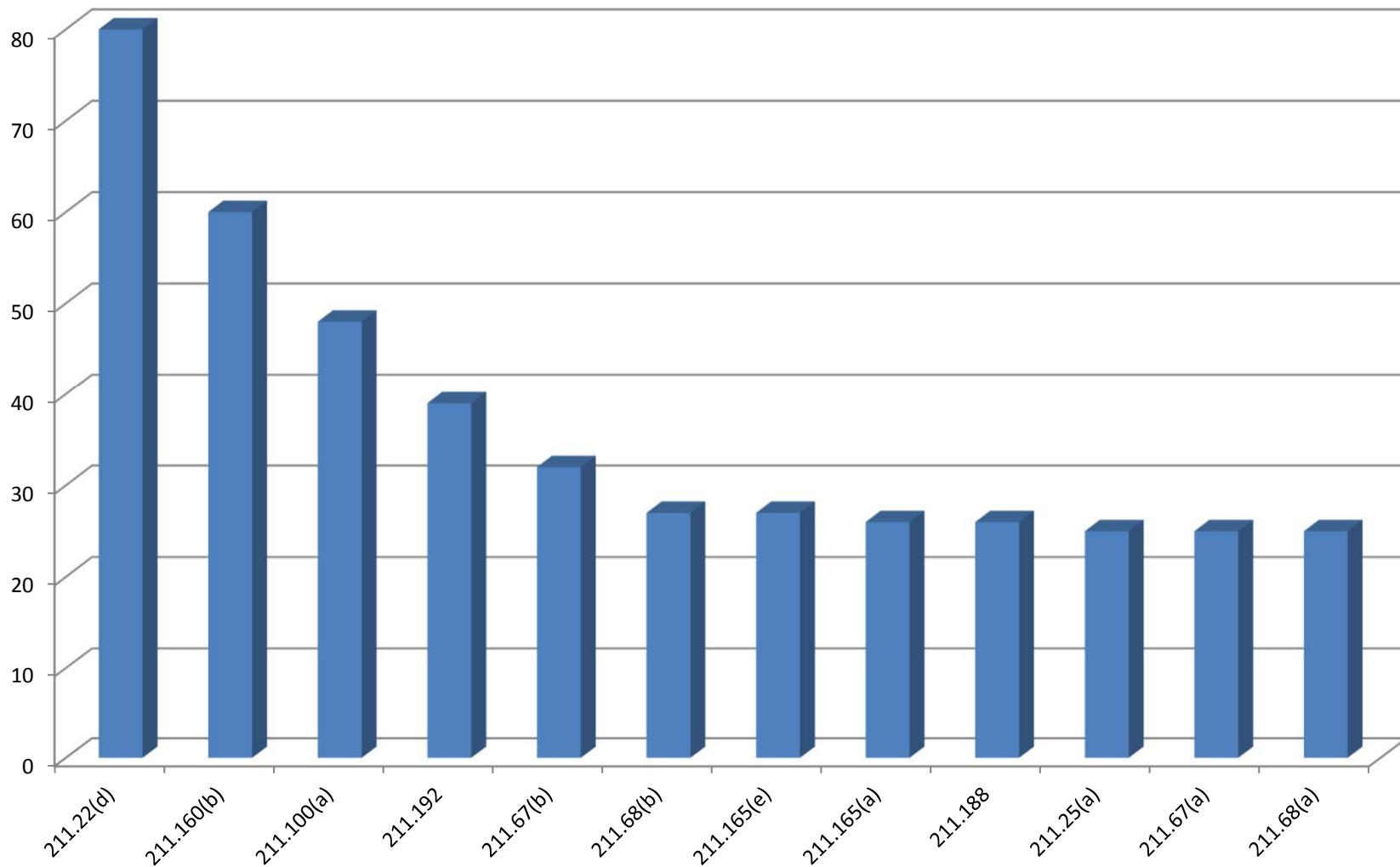
Regulatory Meetings	Injunctions
Consent Decrees	Import Alerts
Seizures	Warning Letters
Untitled Letters	Others

2017 Enforcement Actions



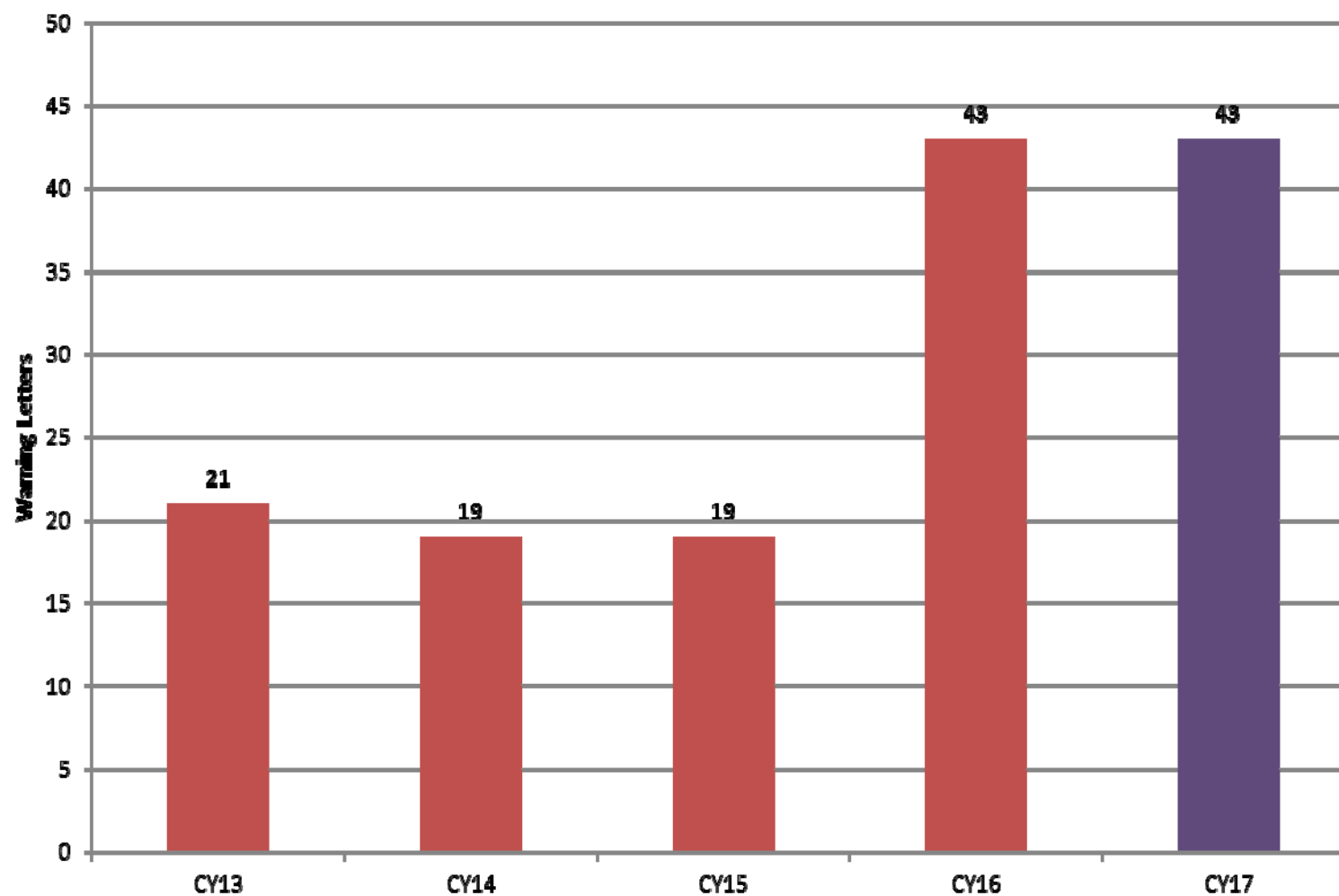
Through Sept. 1, 2017
Excludes compounding-related actions
*Domestic and Foreign

Finished Dosage 483 Citations Calendar Year 2017



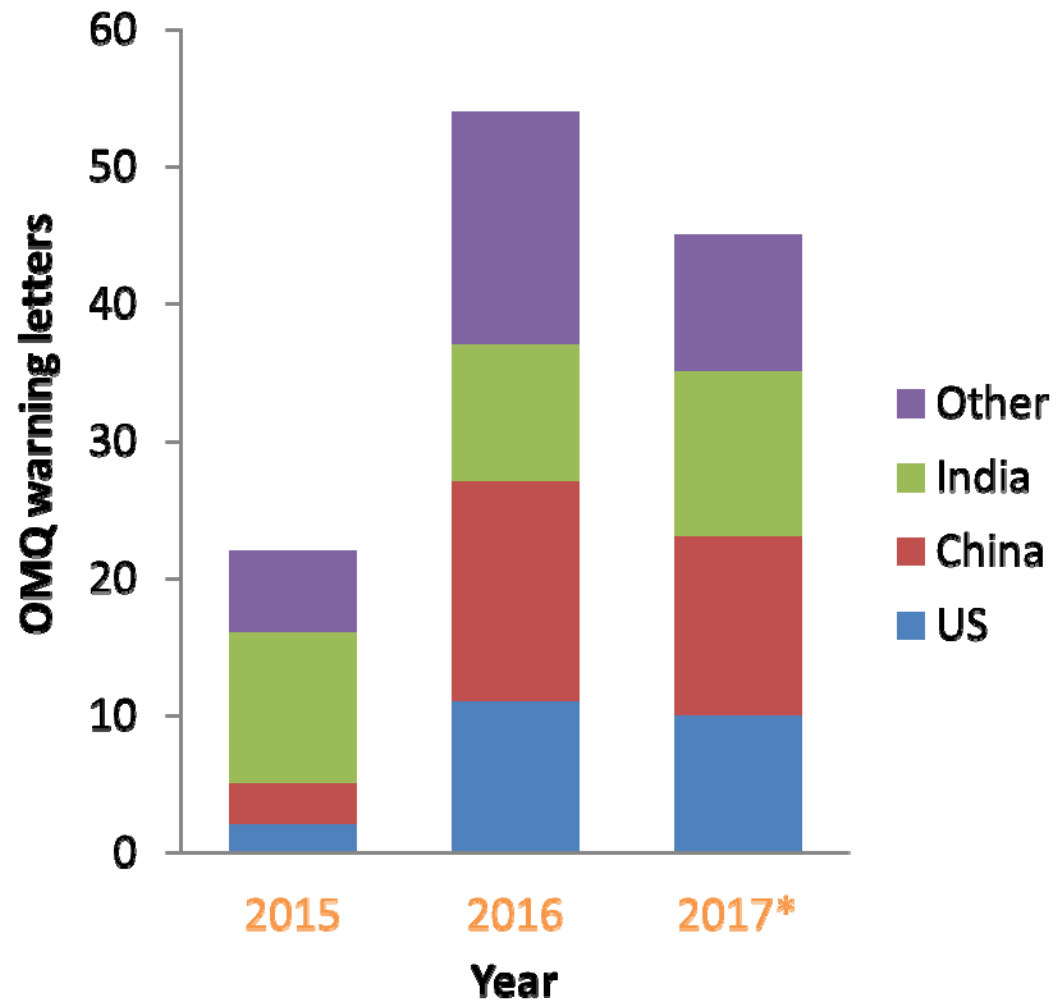


International Warning Letters Issued by OMQ Calendar Years 2013 - 2017*



*Data Source: CMS (Jan 2013 to Oct 31, 2017)

Office of Manufacturing Quality CY17 Warning Letters



*Through September 1, 2017. Compounding warning letters are not included.



RECURRING CITATIONS



Recurring Citations

- 211.22(d): The responsibilities and procedures applicable to the quality control unit are not in writing or fully followed
- 211.160(b): Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures
- 211.160(a): Failure to record and justify any deviations from required laboratory control mechanisms

“Trial” or pre-testing
of samples



Recurring Citations

- 211.192: Failure to thoroughly review any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed
- 211.194: (a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays (usually cited when data is deleted)



Recurring Citations

- 211.68(b): Failure to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records or other records
 - “The 10 ZZZXX HPLC instruments in the QC commercial laboratory were configured to send acquired data to PC without audit trails”
 - “No controls to prevent substitution or overwriting of data”



COMMON CGMP PROBLEMS CITED IN FDA WARNING LETTERS IN INDIA, 2015 - 2017

Computer Systems

- Lack of controlled access to computer systems
- “Trial”, “Test” HPLC injections of drug products for release and stability testing. Some trial injections render OOS results, but passed the “official sample”
- Some of the trial injections were deleted data
- Copying existing data as new data
- Discarding or deleting results with no justification and re-running/retesting samples to present better results

Computer Systems Cont'd

- Names assigned to each sequence injection were often changed during testing, obscuring the traceability of repeated injections.
- The data from “trial” injections was not reviewed or considered in determining batch quality.
- Electronic data of stand-alone equipment was deleted from the hard drive without creating backups. There was no audit trail or other traceability in the operating system.

Computer Systems Cont'd

- Stability bottles and capsules were missing with no explanation. Firm concluded no repeat testing was performed but could not explain deletion of electronic data and missing testing documents.
- Disabled audit trail feature or enabled only a few days before, or during the day of the inspection
- Original injection results were found to be overwritten
- Unknown peaks deleted with no justification

GDPs

- Activities not recorded contemporaneously
- Backdating
- Fabricating data
- Copying existing data as new data

Inadequate Investigations

- Releasing failing product as if it had passed
- Testing into compliance
- Not saving electronic or hard copy data that would confirm the failing results
- Inadequate out of specification investigation
- Inadequate CAPAs
- Root cause lacking scientific evidence
- Samples retested until acceptable results were obtained
- Sample runs aborted with no justification

Microbiological Control

- Failure to establish procedures to prevent microbiological contamination
- Non-integral RABS gloves used during aseptic operations (e.g., aseptic connections, clearing fallen vials, charging primary and secondary closures, purging filling needles, critical interventions, changing EM plates, etc.)
- EM was not examined to f/u on repeated OAL results from microbial testing

Microbiological Control Cont'd

- Integral vials are not incubated during media fills
- Failure to perform smoke studies under dynamic conditions
- Thousands of alarmed events registered in the computer system monitoring differential and non-viable particles are not evaluated to determine how these events may compromise product quality
- Failure to identify the source of gram negative microorganism in critical area and to implement appropriate CAPAs.

Microbiological Control Cont'd

- Per EM records for last 20 months, no samples exceeded AL for any of the filling lines; however 12 micro plates showing contamination during walkthrough of micro laboratory.
- Poor aseptic techniques observed during the manufacture of sterile drugs
- Failure to follow SOPs related to sampling to determine microbiological quality of water eg. analytical raw data work sheet recorded that water samples were collected, when these samples were never collected

Microbiological Control Cont'd

- EM data is not reliable-records falsely indicated EM samples had been collected
- Deficient EM program
- Multiple examples of back-dating and falsification of laboratory data was reported in Micro lab

Miscellaneous

- Refusal, delay of inspection, limited access to copying or review of CGMP records
- Analyst admit the falsification of the data
- Failure to test APIs to ensure conformance to specifications (microbial and/or chemical testing). No data to support the release of the APIs
- Failure to submit FARs related to stability lots failing to meet the impurities specification
- Deficient visual inspection program



REASONS FOR DATA INTEGRITY ISSUES

Common Reasons

- Not understanding risk (to patient)
- Organization driven by production (\$) goals but communicates driven by quality (mixed messages)
 - Limited time available to complete an extraordinary amount of work- driven by \$ not by quality
 - Not assigning appropriate resources
 - No commitment from upper management to quality
- Poor or limited corporate and local quality oversight
 - Unclear expectations communicated from top to bottom and bottom to top
- Incorrect quality and organizational structure not providing the appropriate oversight
 - Not having the appropriate check and balances

Common Reasons Cont'd

- It's a common practice everywhere
- Oversimplification of the issue
- Deficient Procedures
- Immature Quality System
- Deficient training program
- Bad behavior, encouraged by poor quality culture
- Indifference to DI practices, minimizing significance





Common Reasons Cont'd

- Thought it unlikely that product could fail
- Process not science-based
- Confusing a symptom of the problem with the root cause



CONSEQUENCES OF DI BREACHES

Consequences of Breaches in Data Integrity



1. Regulatory Actions that may take years to resolve (WLs, Uls, Import Alerts, NC Status)
2. Lost of credibility, reputation, trust and confidence from patients, regulators, industry and stockholders, etc.
3. Unnecessary delays in approval of pending and new drug applications
4. Impacts business as other filers may be granted approval first

Consequences of Breaches in Data Integrity



5. Because of the time it takes to recover, companies' ability to focus on new technology and enhancement of processes and systems is affected
6. Financial impact in contractual agreements with consultants and independent parties
7. Products are usually transferred to CMOs or other sites
8. May required full organizational changes

Areas to Re-examine

Process Knowledge
Change Controls
Critical Parameters

Complaints
Returned Goods

All Systems Affected & Extent of Problem

OOS Results-
electronic and raw data

Deviations-
process/lab

Critical Parameters, In-
Process/
Finished/
Stability

Training Rejections

Feedback from "Shop Floor"

Current Staff Competencies

Raw Material Data

Results of Audits & Inspections

Process Trending Data
Retrospective Review

Q&As on Data Integrity

Draft guidance for industry



Are shared login accounts OK for computer systems?



Are electronic signatures OK for master production and control records?



Can we use actual samples to perform system suitability testing?

Detailed discussion online:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm>



FDA compliance information online:

www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm081992.htm

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EXAMPLES OF WARNING LETTERS

2015, 2016, 2017



Citations in 2017 WLs

1. Omitting and replacing the name and address of API manufactured in COA
2. Numerous complaints related to ophthalmic product not investigated for leakage, under fill, unreliable process.
3. Insects, rust, damage, drug residues...in equipment identified as clean.
4. Products released without testing
5. Critical parameter failures not evaluated



Citations in 2017 WLs

6. Failure to establish and follow appropriate procedures designed to prevent microbiological contamination (e.g. smoke studies deficient, turbulence, critical interventions not simulated, damaged garments).
7. Deletion of filter integrity tests by operators
8. Unreported OOS results tested by GC
9. Raw material failed the integrity tests, and a passing result was accepted without any investigation of the failed result.



Citations in 2017 WLs

10. Firm delayed scheduling FDA inspection by indicating there was a strike, but FDA obtained evidence the firm was manufacturing drugs
11. Firm limited FDA's inspection
12. Failure to provide batch records
13. Numerous OOS results w/o adequate investigation or appropriate root cause
14. Computers used in the lab., not validated



Citations in 2016 WLs

1. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards. (21 CFR 211.194(a))

Our investigators observed colony counts for environmental and personnel monitoring that did not match your official records.

WL October 2016



Citations in 2016 WLs

2. Firm routinely re-tested samples without documented justification and deleted analytical data.

3. Failing and atypical results were not adequately investigated.

Citations in 2016 WLs

4. HPLC audit trails showed multiple integrations modifications during stability tests for unknown impurity content without appropriate documentation, justification and investigation.

The QA manager agreed they were inappropriate.

The FDA investigator requested the chromatograms to be reprocessed using appropriate parameters, the results were OOS



Citations in 2016 WLs

5. Firm's QU allowed the use of adulterated XVYYY, USP from a sister site found with egregious CGMP violations and placed under import alert.
6. The production manager admitted that he falsified signatures of other employees.
7. Mold-like substances observed on walls in drug processing area.
8. Complaints not investigated
9. Original product quality complaint records found in trash (did not match the official complaint log).

Citations in 2015 WLs

1. Failure to exercise controls over data systems. Analysts could delete lab results – March 2015
2. Trial HPLC injections and retests of samples without reporting original results – March 2015
3. Trial HPLC injections, disregarding test results, and reporting only results from additional tests – January 2015
4. Quality Control Personnel created unauthorized folders on computerized laboratory systems without appropriate oversight – January 2015



Citations in 2015 WLs

5. “firm routinely re-tested samples without justification and deleted analytical data”

6. “We observed systemic data manipulation across your facility, including actions taken by multiple analyst, on multiple testing equipment, and for multiple drugs”

Citations in 2015 WLs

7. Failure to maintain backups of chromatograms that would provide “dynamic” data – May 2015
8. Failure to maintain access controls – May 2015
9. Fabricated impurity data – June 2015
10. Audit trail disabled...because the audit trail was disabled, neither your quality unit nor laboratory staff could demonstrate the data was complete



Citations in 2015 WLs

11. Raw data for 17 of the 61 injections was deleted from the reported sequence as if the injection had never been performed.

Citations in 2015 WLs



12. Failure to retain HPLC raw data – February 2015
13. Selective discarding of HPLC data – February 2015
14. Failure to prevent unauthorized access or changes to data – February 2015
15. Unreported product failures, labeled “trial” HPLC injections. Similar failures for gas chromatography, ultra violet spectroscopy and moisture analyses – January 2015
16. Failure to control access to data systems – January 2015

Citations in 2015 WLs

17. Completed batch production records days after operations ended. Also released lots before Quality Unit approvals
18. Failure to maintain original manufacturing data, contained in “rough notes”
19. Failure to control access to data systems
20. Lack of access controls to prevent manipulation of data
21. Lack of audit trails for lab instruments
22. Turning off audit trail
23. Altered results of identity test results