A review on USFDA warning letter and violation observed in Pharmaceutical Industry

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ABSTRACT

A review on USFDA observation and finding while inspection of pharmaceutical the present review provides some important, significant observation and measure of compliance. USFDA is a regulatory body governing health products which are made (in or outside USA) and marketed in united States of America. Significant deviation from cGMP and significant violation from cGMP for both API Facility and formulations. Strictly compliance requirements under 21 Code of federal regulations (CFR). FDA observation includes but not limited to this. If not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the Safety, Identity, Strength, Purity and Quality of drug product (SISPQ), violation under [21 CFR & 211.67 (a)]. Data integrity is main issue Raised in most FDA warning letter. Corrective action and plan, level of control must be raised from raw material, packaging material (Accurate, Legible, Contamptarious, Original, attributable (ALCOA)) in process, finished dosage form, Maintain log book properly. Guidelines for Out of specification (OOS) and out of trends(OOT) must be follow if any required.

Keywords: cGMP, USFDA warning letter, Pharmaceutical Industry, violation of rules

INTRODUCTION

USFDA is an regulatory body governing health products which are made (in or outside USA) and marketed in united States of America. Significant deviation from cGMP and significant violation from cGMP for both API Facility and formulations. Strictly compliance requirements under 21 Code of federal regulations (CFR). 1) Failure to have computerized system with sufficient control to prevent unauthorized access or manipulation of data.

MOST OBSERVATION FOUND DURING INSPECTION AND COMMENTS ON COMPLIANCE REPORT .[1]

1) Failure to have computerized system with sufficient control to prevent unauthorized access or manipulation of data.

Compliance can be done by specific logging ID and Password of each employee.

2) Re-sampling and manipulation of old data

Compliance can be made by not deleting data and why Re-sampling was done must be justified and Remedial measure to prevent this.

3) Altering time in Record or changing system date and time.

Compliance can be made by not allowing manipulation in system time and lock base must be applied for robust system.

GENERAL VIOLATIONS cGMP [2,3]

cGMP Deviation regulations of finished pharmaceutical Title 21 CFR ,Part 210 and 211

This violation cause drug product to be adulterated with the meaning of section 501 (a) (2) (B) of the federal food ,drugs and cosmetics Act (21 U.S.C & 351 (a) (2) (B)) is that the method used in or the facilities or control used for ,their manufacturer, processing, packing or holding do not conform to ,or are not operated or administered in conformity with cGMP.

In addition, drug product are unapproved new drug violation of section 505 (a) of the Act [21 U.S.C & 355 (a)], these unapproved new drugs are also misbranded in violation of 502(f) (1) of the Act

If not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the Safety, Identity, Strength, Purity and Quality of drug product (SISPQ) ,violation under [21 CFR & 211.67 (a)]

Example -
Not validated cleaning methods or not adequate scientific justification
If laboratory records fails to include complete data derived from all tests nessary to assure compliance with established specifications and standards [21 CFR & 211.194]

Example
Failure to take readings and raw data or incomplete data
If not established or followed appropriate written procedure designed to prevent microbiological contamination of drug product purporting to be sterile [21 CFR & 211.113 (B) violation)

Example
A) Environment monitoring is inadequate in relation to personnel monitoring
B) technician performing air sampling at HEPA Filter in wrong way or not as per SOP

- If failed to have facilities used in the manufacture, process, packaging and holding of drug products of appropriate construction to facilitate cleaning, maintenance and proper operation. If not then violation of this (21 CFR, 211.42(a)).

  Example:- Floor titles in specific area (production, sterile or manufacture having filth or hole or cracked or inadequately repair with more gap.

- Firm has not thoroughly investigated the failure of a batch or any of its components to meet its specification whether or not the batch has already released or distributed. If not then violation of this (21 CFR, 211.192).

- If failed to follow and document at the time of performance required laboratory control mechanism. (21 CFR, 211.160(a)).

  Example :-
  1) Laboratory Analyst did not document balance weight at the time of sample weighing.
  2) Weigh print after chromatographic run.
  3) Backdated print out of sample.

- Data integrity is main issue Raised in most FDA warning letter.

LABORATORY RECORD

FDA observed deletion of data peak
HPLC – No Injection Deletion
GC – observed deletion of data
Compliance can be made by no addition or no deletion of data and all trails must be justified and if training is given to staff then no addition or no deletion and log book must state that training schedule for trails run .
Audit trail must be enable and reviewed periodically.

CORRECTIVE ACTION AND PLAN [4]

- Orginal data
- Risk assessment
- Management quality policy
- Strictly follow cGMP Norms
- Action to prevent the recurrence of cGMP deviation
- Establishment of stability study program
- Voluntary recall if the error or critical deviation at industry level after marketing or during post marketing surveillance
- Follow good documentation practices
- Follow good laboratory practices
- Medicine and pharmaceutical must also follow with specific good distribution practices
- Level of control must be raised from raw material, packaging material (Accurate, Legible, Contamptarious, Original, Attributable (ALCOA)) in process, finished dosage form. Maintain log book properly
- Guidelines for Out of specification(OOS) and out of trends(OOT) must be follow if any required

FDA Warning letter Format [5-6]

Department of Health and Human Services

Warning Letter

Acknowledgement receipt Requested

Date format (Month Date, Year)

Address of unit (Pharmaceutical)
Dear (Director/ VP or Management)

During our **DATE OF INSPECTION** inspection of your active pharmaceutical ingredient (API) and finished pharmaceutical manufacturing facility, **NAME OF INDUSTRY**, investigator(s) from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) for the manufacture of APIs and the CGMP regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your APIs and drug product(s) to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have conducted a detailed review of your firm's response dated DATE OF COMPLIANCE COMMENT RECVIED and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence (If Any).

Our investigator(s) observed specific violations during the inspection, including, but not limited to, the following:

API: CGMP VIOLATIONS
FINISHED PRODUCT: CGMP VIOLATIONS

Response to this letter, please inform this office of the actions your firm will take to prevent recurrence of this situation. Also, provide a retrospective evaluation of all lots currently in the stability program and assess whether an OOS was obtained at any testing interval.

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations may result in FDA refusing admission of articles manufactured at manufacturing site (inspected) into the United States. The articles are subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

Reply Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of violations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the drug product(s) at issue, provide the date(s) and reason(s) you ceased production. Please identify your response with FEI (UNIQUE CODE)

Please send your reply to the following address:
Compliance Officer
FDA/CDER/OC/OMPQ/DIDQ
10903 New Hampshire Ave.
White Oak Building 51, Room 4237
Silver Spring, MD 20993

Sincerely,
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

CONCLUSION

USFDA observation in pharmaceutical mainly concerned of data integrity issues and violation of 21 CFR part 210 and 211, a review provide concise observation finding which can help the industry to put more quality control parameters and outmost care in design of standard operating procedures and maintenance of raw an authentic traceable data.

↓ REFERENCES

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