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Investigations and CAPA: Quality system for continual improvement in pharmaceutical industry

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Abstract
United States Food and Drug Administration (USFDA) is health regulatory agency responsible for healthcare of the citizens of United State of America (USA). Investigator from the agency perform regulatory audit of drug substance and drug product manufacturing site as a part of verification of cGMP compliance. Regulatory Audit is conducted for any one or combination of three reasons (1) Pre-approval inspection (PAI) before approval of the drug product (2) Regular cGMP inspection and (3) For Cause audit. If any non-compliance is observed during audit, the investigator cites the observation on the form "FDA 483" (that is why the observations are popularly known as 483 observations). The citations related to inadequate investigation and CAPA are always topping among all the observations.
Failures are inevitable in any organization; however, it is important that organization performs a detailed investigation to identify the root cause for the reported non-compliance or failure in order to take an appropriate corrective action to avoid recurrence. Proactive organizations do not wait for the failure to be reported but take preventive action to improve the system. These organizations believe in identifying the potential non-conformity by performing quality risk assessment and taking appropriate preventive action to mitigate the risk and thus avoid the occurrence of non-compliance or failure. Proactive organization not only save money by avoiding these batch failures but also avoid potential questions / observations during regulatory audits. This proactive approach shall improve the quality metrics of the organization and reduce the frequency of regulatory audits as agency determines the audit frequency based on review of the quality metrics of the organizations.

Keywords: pharmaceutical industry, investigation, corrective action and preventive action (CAPA), risk assessment, out of specification (OOS), deviation, good manufacturing practice (GMP)

1. Introduction

Why Investigations

Failure refers to the state or condition of not meeting a desirable or predetermined specification and is viewed as opposite of the compliance. Investigation is the process of collecting and analyzing data to determine the cause of non-compliance or failure. In pharmaceutical industry, failure or non-conformity may arise due to any of the following reasons.

- Product Failure (At Release testing stage / In process testing stage / Stability testing)
- Failure of Utility [e.g. Water system – Purified water / Water for injection, Heating ventilation and air conditioning system – Heating Ventilation and Air Conditioning (HVAC), Compressed air system]
- Quality system non-compliance
- Market Complaint
- Deviation from any established standard
- Out of specification (OOS)
- Product Recall

All of the above situations in pharmaceutical industry are untoward or undesirable. Once any such situation arises, the quality unit needs to ensure that the quality issues are adequately investigated being regulatory requirement. Refer Table 1, which outlines the regulatory requirement for investigation of Indian Food and Drug Administration (FDA), United States Food and Drug Administration (USFDA) and European Union (EU) health authorities.

Table 1: Regulatory Requirement for Investigations

Nature of Quality Issue	India FDA [1]	US FDA [2]	EU Health Authority [3]
Complaints / Product return / Product recall	▪ All complaints thereof concerning product quality shall be carefully reviewed and recorded according to written procedures. Each complaint shall be investigated /evaluated by the designated personnel of the company and records of investigation and remedial action taken thereof shall be maintained.	▪ General requirements - A review of complaints, recalls, returned or salvaged drug products, and investigations. ▪ Complaint file – Investigation of market complaints ▪ Returned drug products - Investigation of returns	▪ Investigation of complaints ▪ A review of all quality-related returns, complaints and recalls and the investigations performed at the time.

Deviation / Non-conformance / Discrepancy	▪ There shall be written microbiological monitoring program for different types of water. The results shall justify the frequency of sampling and testing. Investigation shall be carried out and corrective action taken in case of deviation from prescribed limits.	▪ Master production and control records – Investigation of yield deviations; ▪ Production record review – Investigation of any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed. ▪ Responsibilities of quality control unit in investigation of errors observed during testing. ▪ Investigation of discrepancies in label reconciliation ▪ Investigation of deterioration observed in Reserve samples	▪ Documentation and investigation of any significant deviations in sampling, inspecting and testing; ▪ Documentation and investigation of any significant deviations in the manufacturing; ▪ A review of all significant deviations or non-conformances, their related Investigations.

***Source*:** The authors developed it based on the resources mentioned in the reference 1,2 and 3

It is clear from Table 1 that all the above mentioned regulatory requirements are almost similar w.r.t. investigations for handling any error / deviation / complaints / product return for the pharmaceutical industry. It is important that an organization has clear standard operating procedure on investigation system for consistent approach to identify the root cause for any undesirable condition.

2.1 Related Study on Investigation and CAPA

CAPA system is the most frequently inspected sub system during regulatory audits. Inadequate investigation and CAPA system, missing root cause analysis are amongst the most frequent observations cited by regulators. It was further concluded that if proper training is not provided to employee and accurate root causes are not determined, chances of incorrect solutions may increase in the pharmaceutical industry [4].

CAPA system is a critical component of an effective QMS and it must maintain a close relationship with other quality subsystems. The ultimate goal of any regulated company must be to have a CAPA system that is compliant, effective and efficient. All relevant subsystems that may produce non-conformances must be part of the process. An efficient CAPA process is a great tool to improve quality systems and processes; the initial effort is worthwhile if it is well planned and performed correctly [5].

When a company conducts a well-documented event investigation, it informs the process of moving a therapy through development, making formulation or process changes, revising internal documentation, changing packaging configurations, or helping to make critical decisions. It can be one of the most important document a company generates as it provides the rationale and thought process for the decisions to be made when the unexpected event reported. This help to the auditor during their review that decision is made based on good science and the quality system of the organization meets the compliance requirement [6].

3. Investigation Report

Performing investigation is a skill to pinpoint and establish the exact root cause but sometime organization fails to present their findings and good work because of poorly written investigation report. Hence, writing good investigation report is an equally important skill. The report shall be written in chronology of findings and shall be self-explanatory when any person refers the document especially the investigator during the regulatory audit. Following shall be kept in mind while writing investigation report-

- **Stick to facts:** Write information which is true, and supported by documentary evidences.
- **Avoid personal comment:** Do not put in personal opinions.
- **Keep your language simple:** Language should be simple, sentences shall be short and concise.
- **Avoid vague words:** Avoid using vague words, such as “usually" or “mostly".
- **Chronological Order:** Investigation report shall be written in the chronological orders of findings, experimental details and inferences.

A good investigation report for any quality issue shall have the following titles

3.1 Quality issue definition

Defining the quality issue or problem is vital so as to know the facts about the problem, and determine the direction for the investigation. The investigation owner shall first clearly mention that what is the non-compliance (observation) giving reference of the standard requirement. Answering below questions would help in defining the quality issue properly-

- What was observed?
- Who had observed?
- When was observed?
- Where did it happen?
- How did it happen?

3.2 Objective

Objective of carrying out any investigation shall be as follows

- To identify the root cause / most probable root cause
- To perform the impact assessment
- To recommend CAPA

3.3 Scope

Scope of the investigation shall be clear whether the investigation is to be carried out limiting to the batch under investigation or other batches of same product or batches of

other drug product.

3.4 Investigation Team

Investigation team shall be cross functional team comprising of members from following functions

1. Initiating department
2. Quality Assurance
3. Quality control / Analytical Development Laboratory (ADL)
4. Formulation and Development (F&D)
5. Engineering
6. Manufacturing / Packaging / Warehouse

One person shall lead the investigation team. The team shall assemble to Brainstorm on the probabilities of the occurrence of undesired incidence and identify the tasks. The team shall list down the documents to be reviewed and team leader shall distribute the identified tasks to the team members based on their expertise and skills. The team shall re-assemble after the agreed timeline and share the findings among the team members. It is important that all findings made during review of GMP documents and investigations are documented by the team.

3.5 Hypothesis [7]

As a part of investigation, the team may write hypothesis, which is an educated guess and is a specific, testable prediction, or proposed explanation made on the basis of evidence and reasoning as a starting point for further investigation. While conducting the study to verify the hypothesis, the outcome can be in favour of hypothesis (confirm) or against the hypothesis (does not confirm). Many a times the hypothesis is written as below:

"If _____[I do this] _____, then _____[this]_____ shall be the expected outcome." (Fill in the blanks with the appropriate information from evidence and reasoning.)

3.6 Documents to be reviewed

The investigation team shall list down all the documents which need to be reviewed as part of the investigation, for example

- Batch manufacturing record
- Batch packing record
- Process validation data
- Past History- Previous OOS / deviation reports
- Existing Specification/ STP of organization, vendor and pharmacopeia
- Analytical records / results
- Instrument / Equipment calibration /qualification status
- Personnel training record
- Interview of involved personnel
- Analytical records / results
- Annual product review trends
- GMP documents related to the batch
- Stability data (exhibit & commercial batches)
- Method validation & transfer data

3.7 Investigation tools

The Investigation team shall select an appropriate investigation tool like

- Failure Mode and Effect Analysis (FMEA)
- Cause and Effect Diagram (Fish Bone Diagram/ Ishikawa Diagram)
- Why – Why analysis
- Fault tree Diagram

3.8 Investigation Findings

The Investigation team shall re-assemble to

- Discuss the findings during review of GMP documents
- Discuss the observations and make the inferences
- Discuss the outcome of the experiment planned based on hypothesis and draw conclusion
- Plan further course of action

Wherever appropriate, references of guidance for any protocol bound study shall be given.

3.9 Impact Assessment

Impact assessment is an important component of failure investigation to assess the effect or influence of failure on product quality. It has to be determined whether the quality issue is limited to the batch under investigation or multiple batches of same product or for other products or other Active Pharmaceutical Ingredient (API) batches or other areas. The decision shall be justified with scientific explanation.

3.10 Root Cause(s)

A root cause is a factor that caused a nonconformance and should be eliminated through a process or system improvement. Identifying the root cause is the main objective for carrying out investigation. Root cause can be one or multiple for the existing non-conformity. Sometimes, the exact root cause is not established even after making all the efforts during investigation. However, the investigation team shall document the most probable root cause. The most probable cause (or causes) will help to determine the corrective action(s) to avoid recurrence of the existing problem (or significantly reduce the likelihood).

3.11 Batch Disposition

Quality unit shall determine the final decision for the batch / batches / products which are impacted and clearly document whether the batch(es) are to be Released or Rejected.

3.12 Corrective Action and Preventive Action (CAPA) [8]

- **Correction:** Immediate action taken to correct the existing non conformity to avoid further damage
- **Corrective Action:** Action taken to eliminate the cause of detected non- conformity or other undesirable situation to avoid recurrence of non-conformity.
- **Preventive Action**: Action taken to eliminate the cause of potential non- conformity or other undesirable potential situation to avoid occurrence of potential non-conformity.

The difference between corrective action and preventive action can be understood with an example, where Person A and Person B own a car and their approach to maintain the car (Table 2).

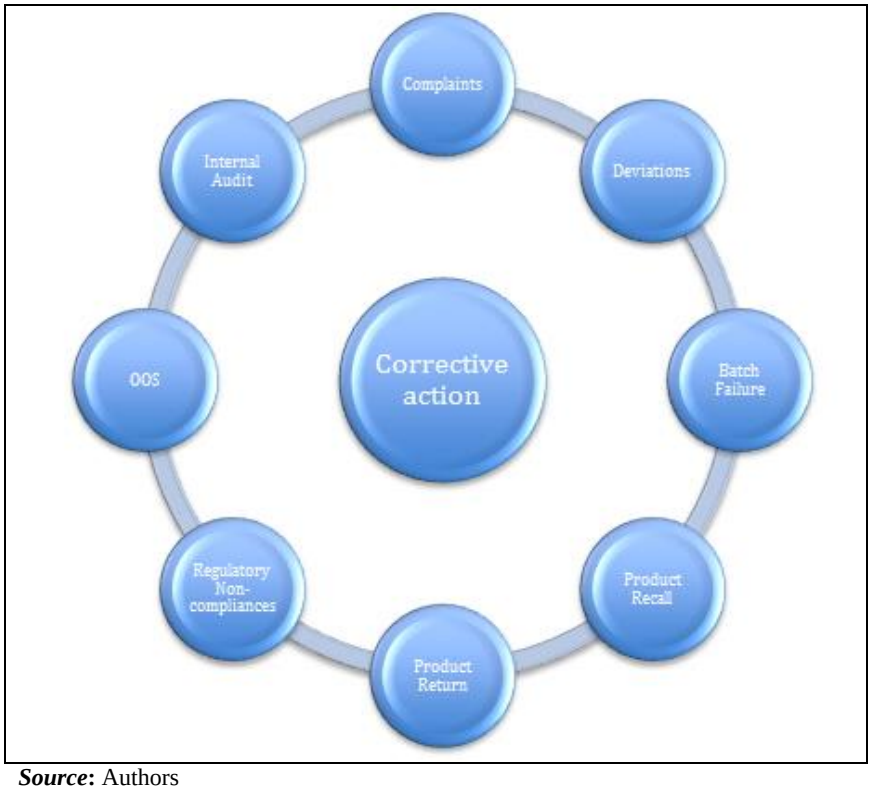
Table 2: Corrective Action and Prevention Action

Person A	Person B
	
• Drives carefully • Get preventive maintenance of the car periodically • Action before the car breakdown (Untoward event) • Proactive approach	• Drives carelessly • Get car repaired only after Breakdown • Action After the car breakdown (Untoward event) • Reactive approach
Preventive Action	Corrective action

***Source*:** Authors

3.13 Potential sources of corrective actions

Following are the possible sources to initiate the corrective actions after an untoward event is reported. These untoward events in a pharmaceutical industry can be in the form of customer complaint, deviation, batch failure, Product recall, Product Return, Regulatory non-compliance, Out of specification, Internal audit observations etc. Once quality issues are reported, these need to be investigated as per regulatory requirement to identify the root cause and determine corrective action to avoid the recurrence (Reactive approach).



***Source*:** Authors

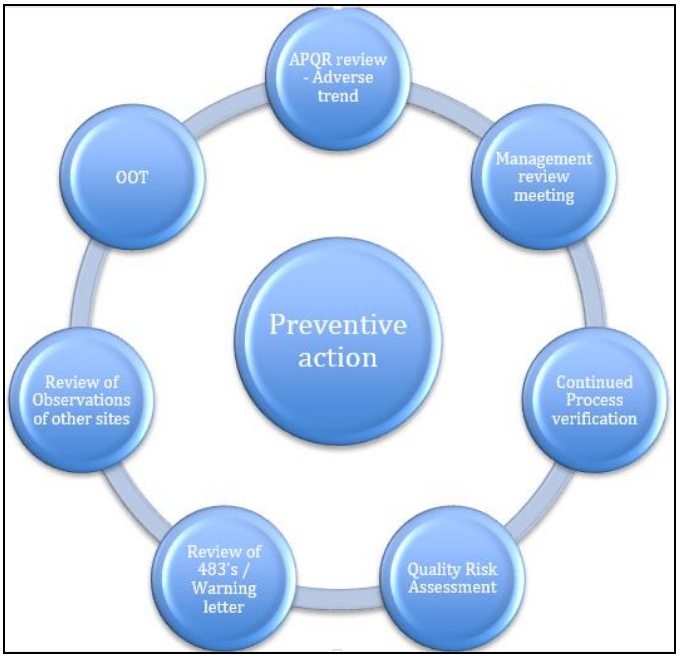
Fig 1: Possible sources of Correction actions

3.14 Potential sources of preventive action

Following are the possible sources to initiate the preventive action before the untoward event is reported. This is a proactive approach as there is no quality issue / no untoward event has been reported. Preventive actions can be initiated while assessing or reviewing the following

- Annual Product Quality review document for each Drug Product - Any adverse trend for any Critical Process Parameter (CPP) and Critical Quality Attribute (CQA) shall be investigated to identify the root cause and take

action before the non-conformance is reported.
- Management Review meetings
- Continued Process verification
- Quality Risk Assessment
- Review of 483 observation / Warning letter issued to other organization
- Review of observations reported at other manufacturing site
- Out of Trend results



***Source*:** Authors

Fig 2: Possible sources of Preventive actions

4. Case study on corrective action

The case study below is about the investigation initiated after a non-compliance event was reported. It gives an idea about the efforts made to investigate to determine the root cause and propose CAPA. Most importantly, the proposed corrective actions were considered effective when similar untoward event did not recur after monitoring the defined number of batches.

4.1 Quality Issue definition

The Blend uniformity results of the blend sample of XYZ Tablets USP of below batches (Table 3) did not comply with the "Blend Uniformity (BU) test" specification.

Table 3: BU results for XYZ tablet

Batch No.	Mean	Min	Max
1	83.3%	49.3%	101.0%
2	95.9%	73.6%	101.7%
3	91.4%	60.8%	99.9%
4	97.9%	77.1%	101.7%
5	99.1%	83.2%	103.1%
6	97.5%	83.2%	101.0%
Specification Limit	The mean of all test results shall be between 95.0% to 105.0% and RSD, NMT 5.0%.		

***Source*:** Authors

4.2 Investigation

Following are the highlights of investigation findings
- Initial Laboratory investigation revealed that there was no analytical error, human error, instrument error or material error. Thus, the probability of laboratory error was ruled out.
- As a part of manufacturing Investigation, Batch Manufacturing records of all the batches were reviewed for quantity of raw material dispensed, API potency calculation, manufacturing process, parameters and batch yield at the critical stages and were found to be satisfactory. Thus, the probability of manufacturing error (process, man and machine error) was ruled out.
- Review of Previous Blend Uniformity (BU) and Content Uniformity (CU) results revealed that one similar OOS was reported for low BU (It was concluded as dilution error) and no OOS for CU test was reported.
- To confirm the hypothesis (Hypothesis 1 "If the mixing is not properly done as per test procedure, it would result into low BU result"), analysis was performed by re-mixing the stock solution for sample location ID S1, S3 and S6 of Batch No 1 and results obtained are as below (Table 4):

Table 4: BU results after remixing (Hypothesis 1)

Sample ID	Initial results	Results after mixing
Batch No 1/ S1	89.3%	98.8%
Batch No 1/ S3	86.9%	98.6%
Batch No 1/ S6	46.7%	100.2%

***Source*:** Authors

Inference

These results confirmed that initially diluted samples were not properly mixed.
- Based on the above results, BU samples of 3 batches were re-prepared from original stock solution, re-filtered and injected in the HPLC system. Results obtained were as below (Table 5):

Table 5: BU results (%) after re-preparation

B. No.	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
1	88.8	99.9	92.3	65.3	64.2	49.3	99.3	72.9	101.0	99.6
2	99.5	99.6	100.4	73.6	100.3	82.8	100.0	100.9	101.7	100.0
3	93.5	89.9	100.9	100.5	100.4	101.0	98.9	99.2	100.0	99.8

***Source*:** Authors

Inference

Results of BU samples of few locations again found to be on lower side.
- To confirm the hypothesis (Hypothesis 1 "If the mixing is not properly done as per test procedure, it would result into low BU result"), analysis was performed by re-mixing the stock solution for sample location ID S1,S2, S3 and S6 of Batch No 1 and results obtained were as below (Table 6) :

Table 6: BU results after Mixing

Sample ID	Initial results	Results after mixing
S1	88.8%	99.4%
S2	99.9%	101.0%
S3	92.3%	99.2%
S6	49.3%	100.7%

***Source*:** Authors

Inference

These results confirmed that initially diluted samples were not properly mixed. These results also confirmed that initial OOS results were not due to product behavior and it seems to be laboratory error.

- However the question raised by the investigation team that, "Why there are low results on multiple occasions"? Hence, to evaluate probable degradation due to glassware, 3 volumetric flasks (10 ml) were re-shaken and solution was re-filled in the fresh vials and injected in the HPLC system. The results obtained are as below (Table 7)

Table 7: BU results after re-preparation

Sample ID	Initial results	Results of freshly filled vial
Batch No 4/ S5	60.8%	18.9%
Batch No 4/ S8	69.0%	58.6%
Batch No 5/ S6	77.1%	75.1%

***Source*:** Authors

- Results for sample ID S5 was further dropped by 41.9%. The investigation team raised question that, "Why there is so sudden drop in the drug content"? Further upon critical observation of the glassware used for final sample preparation revealed that inner surface of these few glassware "A" is porous and these are of different make which were newly introduced in the laboratory. The investigation team suspected that low BU results are due to use of specific glassware. So it was hypothesized that "If the specific make glassware "A" are used, it shall result into low BU results" (Hypothesis 2). To verify this hypothesis, homogenous sample solution (50ml) was prepared from the original stock solution of S5 location of Batch No 4. 10 ml of stock preparation was diluted to 50 ml and this solution was injected in HPLC immediately and result obtained was 101.0%. The same sample solution from 50 ml volumetric flask was transferred in three different 10 ml of volumetric flasks (In which the results are observed low). All three solutions in the identified flasks were kept for one hour and subsequently solution of all three flasks were injected in the HPLC system using fresh vial. The results are as tabulated below (Table 8):

Table 8: Experimental Study (Hypothesis 2)

S. No	Type of sample	Results%
1	50 ml volumetric flask in which re-diluted sample solution was prepared	101.1%
2	10 ml solution held in suspected volumetric flask 1	72.3%
3	10 ml solution held in suspected volumetric flask 2	66.0%
4	10 ml solution held in suspected volumetric flask 3	69.9%

***Source*:** Authors

Inference

The degradation of API was observed in the flasks producing the low BU results and no degradation was observed in the flask which produced passing result in the earlier analysis. It was noted that all three culprit flasks were of new make recently introduced in the laboratory.

- Investigation team further discussed and realized that the same glassware "A" were used in the content uniformity test for the same product in past, however lower results were never obtained. Hence the team decided to review the difference in the method of analysis for BU and CU. The Team observed that there is difference in diluent for both the test methods. BU test requires water as diluent while CU method requires "Phosphate buffer and Acetonitrile in the ratio of 85:15 (%v/v)" as diluent (in line with United States Pharmacopoeia, USP).
- Investigation team Hypothesised (Hypothesis 3) that "If this specific make "Glassware A" is used, it shall not produce low result when "Phosphate buffer and Acetonitrile in the ratio of 85:15 (%v/v)" is used as diluent. Also to verify that the "Glassware B" produce complying results when used for analysis using diluent "Phosphate buffer and Acetonitrile in the ratio of 85:15 (%v/v) (Table 9).

Table 9: Experimental Study (Hypothesis 3)

ID of 10 ml volumetric flask	Description of flask	Result (%)		
		0 Hrs	2 Hrs	4 Hrs
Flask 1	Flask producing Low BU results	103.3	103.9	102.5
Flask 2		103.4	103.5	102.3
Flask 3		104.6	106.4	105.0
Flask 4	Flask producing passing BU results	103.4	104.3	103.1
Flask 5		103.4	103.4	102.2
Flask 6		103.4	103.6	102.3

***Source*:** Authors

Inference

No degradation of API was observed in both types of volumetric flasks i.e. Producing the low results "Glassware A" and producing passing results "Glassware B" earlier analysis using the Phosphate Buffer: ACN (85:15 %v/v) as diluent. This experiment confirmed that degradation (low results) are obtained when Glassware A are used with water as diluent.

- Further, Investigation team planned an experiment to investigate that whether the API is getting adsorbed on the inner surface of the culprit glassware "A" (Hypothesis 4). An Experiment was planned as mentioned below –

The final dilution of standard solution was filled in flask 1 and 2 which produced low results and flask 3 which produced passing results. The solution was immediately injected in HPLC system after filling the flasks (0 hrs). These flasks were retained on bench top for 4 hrs and the solution of all three flasks was injected in HPLC system (4 hr). The standard solution of all three 10 ml volumetric flasks was decanted and 5 ml of water was added. These flasks were kept on water bath at 60 °C for 30 minutes and the solution was cooled and injected in HPLC system. Refer Table 10 for the results:

Table 10: Experimental Study (Hypothesis 4)

ID No. of 10ml volumetric flask	Description of flask	API Result		Recovered API after decanting the solution and filled with 5ml of water, kept on water bath at 60°C for 30 minutes (mg/5 ml) (B)	Total API content (A+B)
		0 Hrs (mg/10ml)	After holding for 4 Hrs (mg/10 ml) (A)		
Flask 1	Flask producing Low BU results in Glassware "A"	0.129	0.120 (92.3%)	0.0050mg/5ml (3.9%)	0.1250mg (96.2%)
Flask 2		0.127	0.111 (85.4%)	0.0095mg/5ml (7.3%)	0.1205mg (92.7%)
Flask 3	Passing results produced using the Glassware "B"	0.131	0.131 (100.8%)	0.000mg/5ml (0%)	0.131mg (100.8%)

***Source*:** Authors

Inference

In this experiment API was recovered from the 10ml volumetric flasks 1 and 2 (in which low BU results produced in earlier analysis). This study confirmed that the adsorption of API on the selective glassware is taking place.

4.3 Conclusion of Investigation

- The degradation of the API is found in the certain 10ml volumetric flasks when analysed as per Blend Uniformity testing method i.e. using water as diluent.
- No degradation of the API was observed in 10ml volumetric flasks (which produced low results in earlier analysis), when analysis was performed using the diluent mixture of pH 7.4 phosphate buffers and Acetonitrile in the ratio of 85:15 (%v/v), as per the Assay/CU method.
- This experimental study confirmed that the adsorption of the API on the selective 10ml glassware is taking place when water is used as diluent.

4.4 Root Cause

Review of results of experiments to verify the hypothesis concluded that the low BU results were obtained because of the fact that the API is adsorbed in the specific 10 ml volumetric flasks randomly. The adsorption of the API is observed randomly in specific 10 ml volumetric flasks only in presence of water. The low BU results were not observed when the diluent of pH 7.4 phosphate buffer and Acetonitrile was used in the ratio of 85:15 (diluent used in the assay/CU method).

4.5 Corrections

Immediate action was taken to perform the BU analysis as per approved method using newly received glass wares. The BU results are within the specification limits for next 10 batches analyzed in the newly received isolated glass wares. The detailed results are as mentioned in Table 11:

Table 11: Results of next 10 batches

B. No.	Avg. (%)	Min (%)	Max (%)	RSD (%)
1	102.5	101.4	106.6	1.5
2	102.3	101.3	103.5	0.8
3	100.3	98.6	101.4	0.9
4	102.0	99.9	105.1	1.8
5	102.6	101.3	106.3	1.6
6	102.8	100.7	104.6	1.1
7	103.1	100.9	104.8	1.1
8	102.3	100.2	104.1	1.0
9	103.2	100.5	104.8	1.2
10	103.6	101.6	105.6	1.4

***Source*:** Authors

4.6 Corrective Actions

1. Manufacturer of Glassware "A" producing lower results was discontinued.
2. The test procedure was changed in line with the Assay/CU test i.e. diluent mixture of pH 7.4 phosphate buffers and Acetonitrile in the ratio of 85:15 (%v/v) to be used in place of water.

After implementation of the above corrective actions, results of next 50 batches were reviewed and all the results were found within specification limit. This confirmed that implemented corrective actions are effective.

5. Conclusion and Discussion

Investigation of any quality issue or unexpected event in pharmaceutical industry is a GMP requirement to identify the root cause and determine appropriate corrective action to avoid the recurrence. But this is reactive approach as the actions are taken after the event is reported. In the above experiment (investigation), actions were taken after the non-compliance reported; hence preventive action is not applicable. Above case study demonstrated that a good investigation with root cause and corrective action can avoid rejection of the batches and build confidence of the regulator during the audit that batch release decision is made on good science. This approach shall be adopted by the pharmaceutical manufacturers not only as a good manufacturing and business practice; but also to meet regulatory requirement.

There are various means and processes available where any

organization can identify the potential non-conformity and take appropriate preventive action to mitigate the quality risk and avoid the occurrence of the quality issue. While designing any system, a question should be asked what can go wrong and what would be the consequences. Further attempt shall be made to eliminate the cause to avoid the occurrence of the potential issue or reduce the frequency of occurrence. This proactive approach will help the organization to save time, cost, reduce waste and quality issue and improve productivity & quality.

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