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Research Article

Management of Out of Specification (OOS) for Finished Product

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ABSTRACT

Background of the study: Difficult lies at the core of drug producer successful operation. Laboratory testing, which is compulsory by the CGMP regulations are required to check that components, containers and closures, in-process materials, and finished products conform to specifications, including stability specifications. Objective of the study: The objective of the investigation procedure should clearly state when the investigation is required, and define OOS, OOT, and aberrant results. OOS results are most often generated due to laboratory or manufacturing-related errors, the setting of inappropriate specifications, or poor method development. Materials and Methods: The current work is an effort to deliberate several aspects of finding the root cause for the OOS during the finished product analysis by using HPLC. Results and Discussion: Product's individual unknown impurity was not in specification limit and, hence study carried out to find the root cause. Conclusion: After conducting detail investigation it was proved that an analyst conducted the analysis of the product after the due date to expiry.

Keywords: Laboratory errors, Flow of investigation, Phases of investigation.

INTRODUCTION

Laboratory errors

Laboratory errors occur when analysts make mistakes in following the method of analysis, use incorrect standards, and/or simply miscalculate the data. Laboratory errors must be determined through a failure investigation to identify the cause of the OOS. Once the nature of the OOS result has been identified it can be classified into one of the three categories OOS, OOT, Atypical results. The enquiry may vary with the object under investigation[1].

In pharmaceutical industry, out-of-specification (OOS) test results are results that (after rounding off) fall outside the specifications of established acceptance criteria. By analogy, measurement or test results obtained in other industries and such fields as environmental and/or food analysis, which do not comply with regulatory, specification or legislation limits, can be named also OOS test results. The problem of OOS test results was known for analysts working in quality control laboratories since the 1920s, but it was not understood until the 1990s that a lack of statistical and metrological thinking is the main aspect of the problem. In 1993, Barr Laboratories (a generic-drug manufacturer) was used by US government regarding a set of issues influencing the product quality, including the way the company dealt with OOS test results. Among the issues were averaging OOS with in-specification test result values to get a passing result, conducting multiple retests with no defined end point, performing inadequate failure investigations, maintaining an ineffective program for process validation and lacking analytical method validation, etc. Judge Wolin's ruling (the Barr Decision) was that following an OOS test result, an investigation must be initiated before any retesting can be done. Identifying OOS test results is described in the FDA Guidance as the laboratory (Phase 1) investigation[2-4].

It includes responsibility of the analyst and his or her supervisor, conditions of the testing in the laboratory, etc[5]. Identifying OOS test results using investigating tools in currently, the majority of analysts realize that the measurement uncertainty concept is very important because of necessity to balance the cost of measurements versus the product quality risk. For example, to assess compliance of a test result within legislation limits, the analyst should report not only an analyte concentration, but also the associated measurement uncertainty[6,7].

The value obtained by subtracting the uncertainty from the reported concentration is used to assess compliance with the upper legislation limit. When the compliance assessment is made on the basis of a measurement result accompanied by information on the uncertainty associated with the result, the rules Developed in the EURACHEM/CITAC Guide are applicable for identifying OOS test results. Similar rules are included in the ILAC Guidelines. JCGM Guide on the role of measurement uncertainty in conformity assessment is under development[8]. After identification of an OOS test result, it is important to determine its root causes with the purpose to avoid any repetition of the occurrence when the appearance of a next OOS test result is possible or even inevitable[9]. The FDA Guidance formulates recommendations for such incidences including

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production process review, additional laboratory testing using a pre-defined procedure, reporting testing results, and concluding the investigation with identification of the root causes. Thus, this document establishes an empirical organizational approach to the full-scale (Phase 2) investigation and decisions which can be accepted at the different stages of this investigation[10-12].

MATERIALS AND METHODS

Laboratory investigations

The investigation must be

Thorough

Timely

Unbiased

Scientifically sound

Well documented

Matters that should be investigated for assignable cause

Inadequate training of analysts

Poorly maintained or improperly calibrated equipment

Analysts not following procedures

Procedures technically not appropriate

Validated procedures

Reagents

Consumables

Cleanliness of glassware

Outcome is to

Confirm if OOS is true OOS

Determine source of OOS and

Take corrective and preventative action as appropriate.

The FDA and other regulatory agencies consider the integrity of laboratory data to be an integral part of the drug manufacturing process. Deficiencies of out-of-specification (OOS) investigations continue to be the major cause of warning letters in the pharmaceutical industry. The regulatory agencies require that OOS, out-of-trend (OOT), or aberrant results be investigated. an effective and compliant quality management system will ensure thorough, timely, unbiased, well-documented, scientifically sound investigations for OOS, OOT, and aberrant results, which will ensure, if a root cause can be assigned, the implementation of appropriate corrective and preventative actions[13]. The challenge for many firms is having a clearly outlined and well-organized process that is well understood by analysts, supervisors, and manufacturing personnel and that provides for clear, concise, complete documentation. A lack of consistency in the approaches to investigations and root-cause analyses also leads to weak, inconclusive investigations. The flow of investigation is represented in figure 1 above.

The firm’s procedure for failure investigations should discuss the types of errors that may arise and how to deal with them, describe how to investigate failures, and cover timeliness of assessments, including the following: scope, roles and responsibilities, definitions, investigation procedure (phases of the investigation), documentation, corrective and preventative action, and trend analysis. The focus of this study is an OOS investigation; however, the principles are applicable to all analytical laboratory investigations. The exact cause of analyst error or mistake can be difficult to determine specifically and it is unrealistic to expect that analyst error will always be determined and documented. Nevertheless, a laboratory investigation consists of more than a retest. The inability to identify an error's cause with confidence affects retesting procedures, not the investigation inquiry required for the initial OOS result[14]. The firm's analyst should follow a written procedure, checking off each step as it is completed during the analytical procedure. We expect laboratory test data to be recorded directly documented, use of scrap paper and loose paper must be avoided. These common sense measures enhance the accuracy and integrity of data. Review and evaluate the laboratory SOP for product failure investigations. Specific procedures must be followed when single and multiple OOS results are investigated. For the single OOS result the investigation should include the following steps and these inquiries must be conducted before there is a retest of the sample and this phase can be called by PHASE-1 investigation[15,16]. Errors showed in the stage of laboratory area and finding a root cause initially in quality control area can be done by following a regulated procedure. The analyst conducting the test should report the OOS result to the supervisor the analyst and the supervisor should conduct an informal laboratory investigation which addresses the following areas:

Discuss the testing procedure

Discuss the calculation

Examine the instruments

Review the document containing the OOS result

An alternative means to invalidate an initial OOS result, provided the failure investigation proves inconclusive, is the "outlier" test. However, specific restrictions must be placed on the use of this test.

Firms cannot frequently reject results on this basis.

The USP standards govern its use in specific cases only.

The test cannot be used for chemical testing results. An initial content uniformity test was OOS followed by a passing retest. The initial OOS result was claimed the result of analyst error based on a statistical evaluation of the data. The court ruled that the use of an outlier test is inappropriate in this case.

It is never appropriate to utilize outlier tests for a statistically based test, i.e., content uniformity and dissolution.

Determine if the firm uses an outlier test and evaluate the SOP.

Determine that a full scale inquiry has been made for multiple OOS results. This inquiry involves quality control and quality assurance personnel in addition to laboratory workers to identify exact process or non-process related errors.

When the laboratory investigation is inconclusive (reason for the error is not identified) the firm:

Cannot conduct 2 retests and base release on average of three tests

Cannot use outlier test in chemical tests

Cannot use a re-sample to assume a sampling or preparation error

Can conduct a retest of different subject from the same sample when a retest is considered appropriate.

Identifying and assessing OOS test results

Phase I: laboratory investigation

FDA regulations require that an investigation be conducted whenever an OOS test result is obtained (CFR 211.192). the purpose of the investigation is to determine the cause of the OOS result. The source of the OOS result should be identified either as an aberration of the measurement process or an aberration of the manufacturing process. Even if a batch is rejected based on an OOS result, the investigation is necessary to determine if the result is associated with other batches of the same drug product or other products. Batch rejection does not negate the need to perform the investigation. The regulations require that a written record of the investigation be made, including the conclusions and follow-up. To be meaningful, the investigation should be thorough, timely, unbiased, well-documented, and scientifically sound. The first phase of such an investigation should include an initial assessment of the accuracy of the laboratory's data. Whenever possible, this should be done before test preparations (including the composite or the homogenous source of the aliquot tested) are discarded. This way, hypotheses regarding laboratory error or instrument malfunctions can be tested using the same test preparations. If this initial assessment indicates that no assignable causes were made in the analytical method followed during analysis, a full-scale OOS investigation should be conducted. For contract laboratories, the laboratory should convey its data, findings, and supporting documentation to the manufacturing firm's quality control unit, should then initiate the full-scale OOS investigation. The purpose is to confirm or determine the assignable cause through additional laboratory work. The documented plan should be executed and the results evaluated. It must be noted that the results obtained from the practical investigation are not "reportable results" and are for the purpose of the investigation only. Examination of the retained standard and sample solutions should be used as part of the investigation. The Phase I laboratory analysis process is represented in fig 2 below.

If an assignable cause is identified, then the original suspect result is invalidated. The error is corrected, results from all affected samples are assessed, and the test is repeated. The result from the repeat test is reported and the investigation concluded. When evidence of laboratory error remains unclear, a full-scale investigation should be conducted.

Phase lA Investigation

Definition

Phase IA investigation is to determine whether there has been a clear obvious error due to external circumstances such as power failure or those that the analyst has detected prior to generating data such as spilling sample that will negate the requirement of a Phase IB investigation. The Phase IA laboratory analysis process is represented in fig 3 above and The Phase IB laboratory analysis process is represented in fig 4 below.

For microbiological analysis this may be after the analysis has been completed and reviewed during reading of the samples.

It is expected that these issues are trended even if a laboratory investigation IB.

Examples:

Calculation error

Power outage

Equipment failure

Testing error

Incorrect instrument parameters

Calculation error

Analyst and supervisor to review both initial and date correction.

Power outage

Analyst and supervisor document the event, annotate "power failure; analysis to be repeated "on all associated analytical documentation.

Equipment failure

Analyst and supervisor document the event, annotate "equipment failure; analysis to be repeated" cross reference the maintenance record.

Testing errors

for example, spilling of the sample solution, incomplete transfer of a sample; the analyst must document immediately.

Incorrect Instrument Parameters

for example setting the detector at the wrong wavelength, analyst and supervisor document the event, annotate "incorrect instrument parameter"; analysis to be repeated" on all associated analytical documentation.

If no error was noted, and none of the above conditions were met phase IB investigation must take place.

Specification

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval**.**

Regulatory Approved Specification

Specifications for release testing. If no release specifications have been established then the internal specification becomes the release specification.

Acceptance Criteria

Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures which the drug substance or drug product or materials at other stages of their manufacture should meet.

Internal Specification

Are also action limits within regulatory specifications.

Assignable Cause

An identified reason for obtaining an OOS or aberrant/anomalous result.

No Assignable Cause

When no reason could be identified.

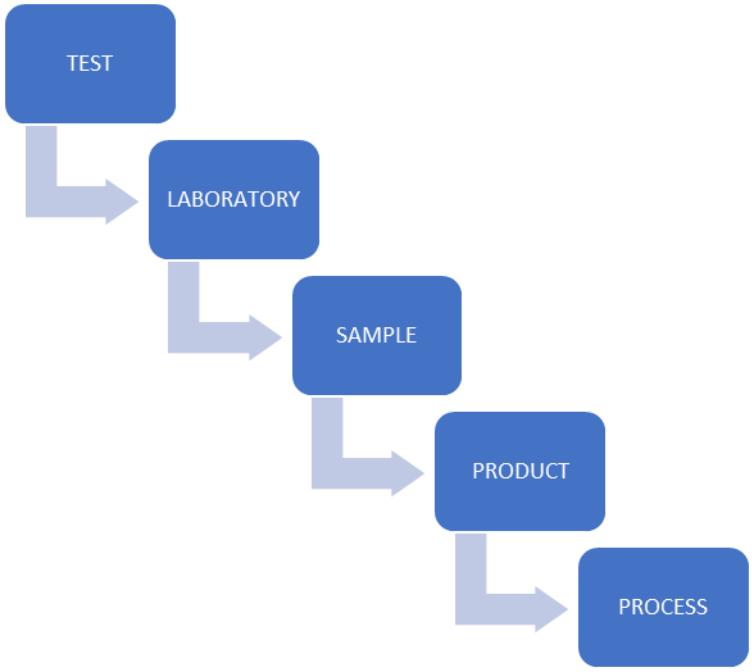

Figure 1: Flow of investigation.

Table 1: Product information.

Sample type	Batch no	Material type description	Material/product name	Material code	LIR category	Lab release	Supplement information
Stability	XXX	Semi-finished	Product-x injection	XXX	OOS	Yes	I-25^0 c/60%RH-24M-3xxxx2

Table 2: Initial results.

Test performed	Batch/Lot no	Sample identity	Result
Related substance	xxx/xxxx	Inverted-25^0 c/60%RH-24M	ImpurityA: BDL[NMT 0.3%] Impurity B: BDL [NMT 0.3%] Impurity c: BDL [NMT 0.2%] Impurity E: BDL [NMT 0.3%] Individual unknown impurity-0.39%[NMT 0.2%] Total impurities-0.62% [NMT1.5%]

Table 3: Stability history.

Sample	Time point	Results
3xxx7	I-25^0 c/60%RH-12M	0.07%[NMT 0.2%]
3xxx3	I-25^0 c/60%RH-18M	0.05%[NMT 0.2%]
3xxx2	I-25^0 c/60%RH-22M	0.15%[NMT 0.2%]
2xxx1	I-25^0 c/60%RH-03M	BQL[NMT 0.2%]
2xxx4	I-25^0 c/60%RH-06M	0.06%[NMT 0.2%]
2xx61	I-25^0 c/60%RH-09M	0.07%[NMT 0.2%]

Invalidated test

A test is considered invalid when the investigation has determined the assignable cause.

Reportable result

Is the final analytical result. This result is appropriately defined in the written approved test method and derived from one full execution of that method, starting from the original sample.

Warning Level or Trend excursions

If two or more consecutive samples exceed warning (alert), or if an increasing level of counts, or same organisms identified, over a short period was identified consideration

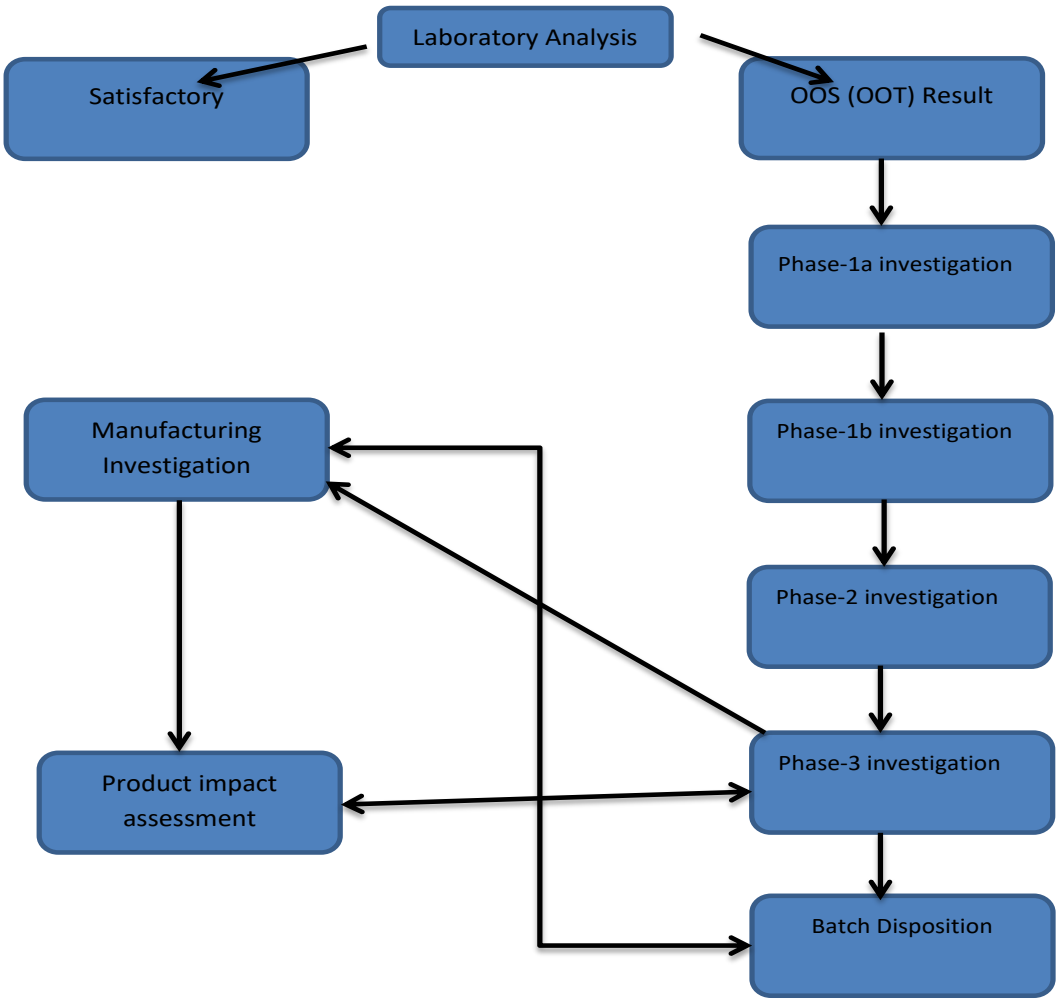

Figure 2: Phase I laboratory analysis.

Table 4: Instrument study.

Test performed	Batch/lot no	Sample identity	Result
Related substances-HPLC	xxxx	3xxx-OOS-1xxx-T3	Individual unknown impurity:0.37% [NMT 0.2%]

Table 5: Details of the chemicals used during initial analysis.

Chemicals name	Grade	Batch no	Manufacturer
Potassium dihydrogen phosphate	AR	XXXX	Merck
Dipotassium hydrogen phosphate	Emparla	XXXX	Merck
Tetrabutyl ammonium hydrogen sulphate	AR	XXXX	Spectrochem
Methanol	HPLC	XXXX	Merck
Orthophosphoric acid	HPLC	XXXX	Merck

should be given to treat the results as action level excursions.

Hypothesis/Investigative Testing

Is testing performed to help confirm or discount a possible root cause i.e. what might have happened that can be tested. For example it may include further testing regarding sample filtration, sonication and potential equipment failures etc. Multiple hypotheses can be explored.

Re-Test

Performing the test over again using material from the original sample composite, if it has not been compromised and/or is still available. If not, a new sample will be used.

Re-sample

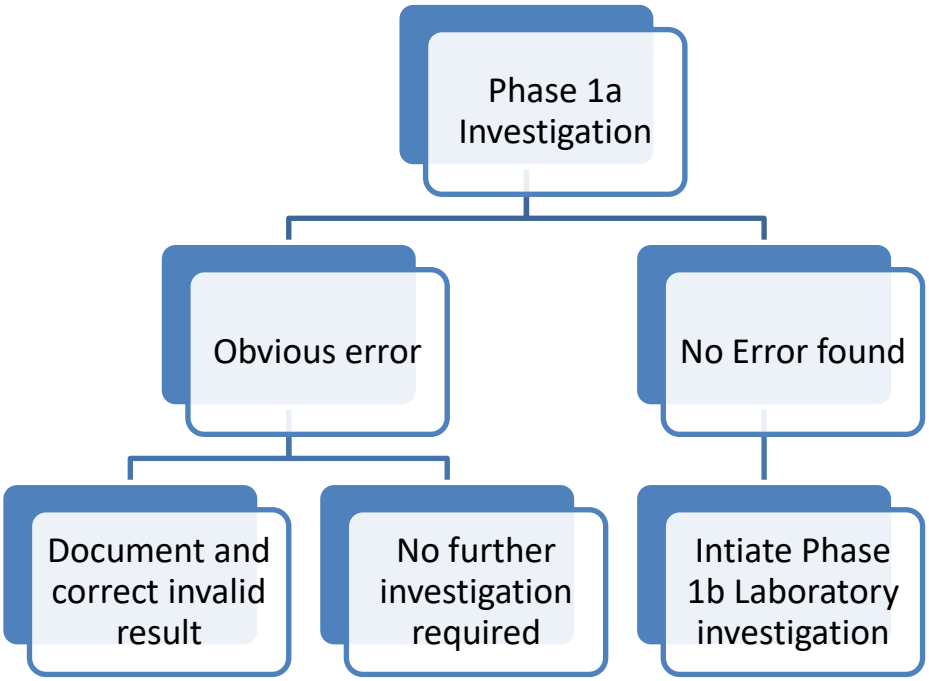

Figure 3: Phase lA Investigation.

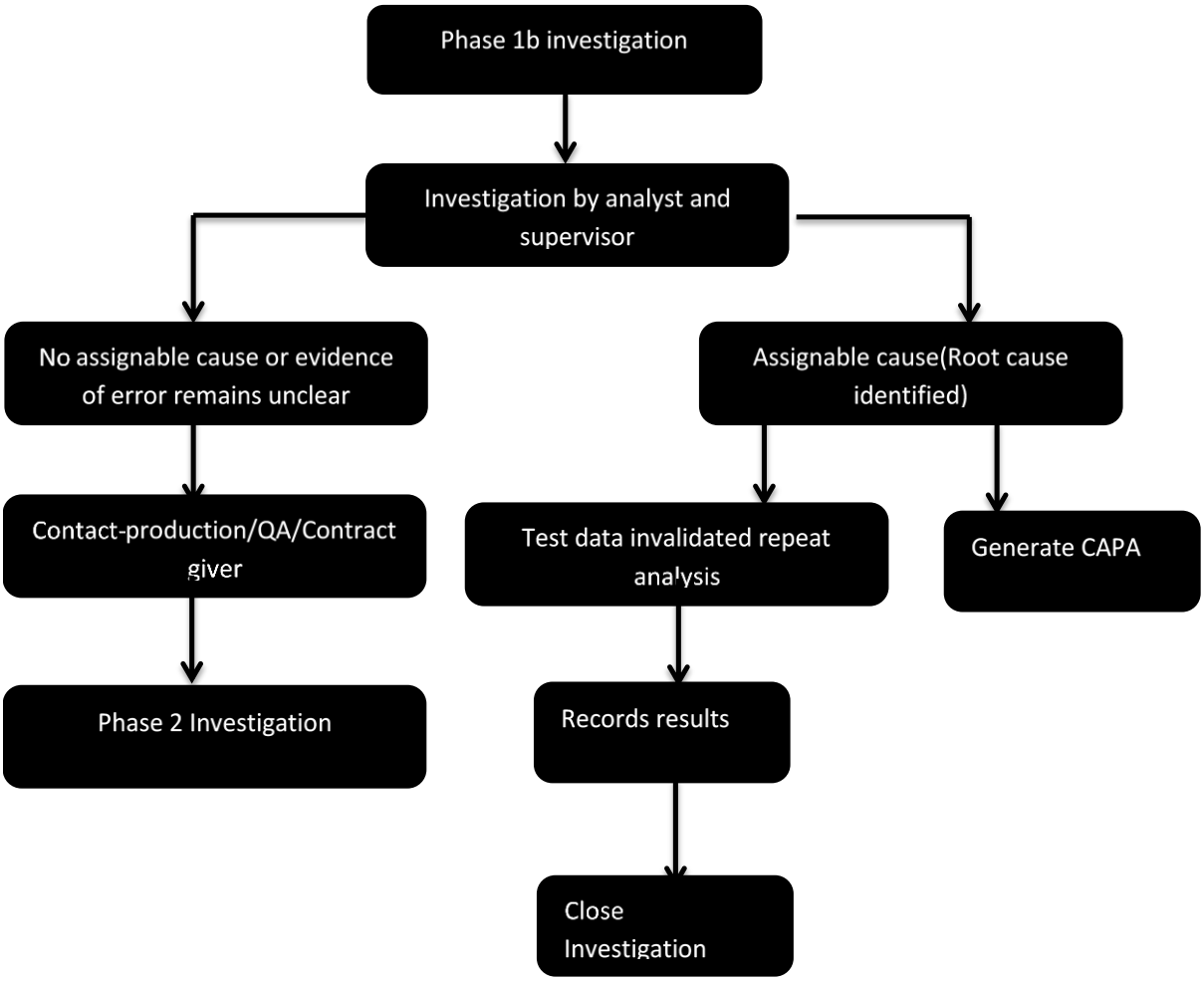

Figure 4: Phase lB Investigation.

A new sample from the original container where possible, required in the event of insufficient material remaining from original sample composite or proven issue with original sample integrity.
Performed on the original sample not a different sample.
Can be an 2^{nd} aliquot from the same sample that was the source of the original failure.
If insufficient quantity of the original sample remains to perform all further testing then the
Procedure for obtaining a resample must be discussed and agreed by QA/Contract Giver/QA equivalent. The process of obtaining the resample should be recorded within the laboratory investigation.
The decision to retest should be based on sound scientific judgement. The test plan must be approved before re testing occurs.
The minimum number of retests should be documented within the procedure and be based upon scientifically sound principles. Any statistical review with regards to %RSD and repeatability should relate to the values obtained during method validation (accuracy, precision, and intermediate precision). The retests should be performed by a different analyst where possible. The second analyst should be at least as experienced and qualified in the method as the original analyst.
Should rarely occur.
If insufficient quantity of the original sample remains to perform all further testing then the procedure for obtaining a resample must be discussed and agreed by QA/Contract Giver/QA equivalent. The process of obtaining the resample should be recorded within the laboratory investigation.
Re-sampling should be performed by the same qualified methods that were used for the initial sample. However, if the investigation determines that the initial sampling method was in error, a new accurate sampling method shall be developed, qualified and documented.
It involves the collecting a new sample from the batch.
Will occur when the original sample was not truly representative of the batch or there was a documented/traceable lab error in its preparation.
Evidence indicates that the sample is compromised or invalid.
Sound scientific justification must be employed if re-sampling is to occur.
Most probable cause
Scientifically justified determination that the result appears to be laboratory error. Should be started as part of Phase IA and continue into Phase II if no assignable cause found.
Description of the testing should be written, and then approved by QA/Contract Giver/QA equivalent prior to initiating investigational testing.
The requirements of investigational testing listed below:
The description must fully document
The hypothesis to the test the root cause being investigated.
What samples will be tested.
The exact execution of the testing.
How the data will be evaluated
This Hypothesis testing may continue from the re-measurement of the original preparations.
Investigational testing may not be used to replace original suspect analytical results. It may only be used to confirm or discount a probable cause.

Table 6: Tests carried out.

Test performed	Batch/lot no	Sample identity	Result
Related substances-HPLC	Xxxx	3xxx-OOS-1xxx-T3	Impurity A: BDL[NMT 0.3%] Impurity B: BDL [NMT 0.3%] Impurity c: BDL [NMT 0.2%] Impurity E: BDL [NMT 0.3%] Individual unknown impurity-0.29%[NMT 0.2%] Total impurities-0.55% [NMT1.5%]
Related substances-HPLC	xxx	3xxx-OOS-1xxx-T3	Impurity A: BDL[NMT 0.3%] Impurity B: BDL [NMT 0.3%] Impurity c: BDL [NMT 0.2%] Impurity E: BDL [NMT 0.3%] Individual unknown impurity-0.35%[NMT 0.2%] Total impurities-0.62% [NMT1.5%]
Related substances-HPLC	xxxx	3xxx-OOS-1xxx-T3	Impurity A: BDL[NMT 0.3%] Impurity B: BDL [NMT 0.3%] Impurity c: BDL [NMT 0.2%] Impurity E: BDL [NMT 0.3%] Individual unknown impurity-0.42%[NMT 0.2%] Total impurities-0.63% [NMT1.5%]
Related substances-HPLC	xxxx	3xxx-OOS-1xxx-T3	Impurity A: BDL[NMT 0.3%] Impurity B: BDL [NMT 0.3%] Impurity c: BDL [NMT 0.2%] Impurity E: BDL [NMT 0.3%] Individual unknown impurity-0.48%[NMT 0.2%] Total impurities-0.78% [NMT1.5%]

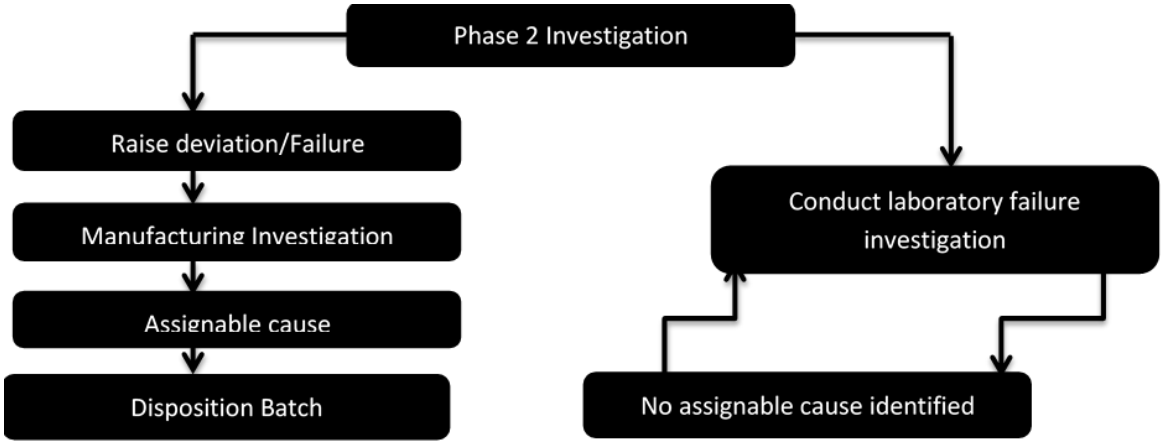

Figure 5: Phase II Investigation.

Table 7: Tests carried for related substances.

Test performed	Batch/lot no	Sample identity	Result
Related substances-HPLC	xxxx	3xxx-OOS-1xxx-T3	Impurity A: BDL[NMT 0.3%] Impurity B: BDL [NMT 0.3%] Impurity c: BDL [NMT 0.2%] Impurity E: BDL [NMT 0.3%] Individual unknown impurity[RRTO.82]-0.21%[NMT 0.2%] Total impurities-0.47% [NMT1.5%]
Related substances-HPLC	xxxx	3xxx-OOS-1xxx-T3	Impurity A: BDL[NMT 0.3%] Impurity B: BDL [NMT 0.3%] Impurity c: BDL [NMT 0.2%] Impurity E: BDL [NMT 0.3%] Individual unknown impurity[RRT0.82]-0.22%[NMT 0.2%] Total impurities-0.38% [NMT1.5%]
Related substances-HPLC	xxxx	3xxx-OOS-1xxx-T3	Impurity A: BDL[NMT 0.3%] Impurity B: BDL [NMT 0.3%] Impurity c: BDL [NMT 0.2%] Impurity E: BDL [NMT 0.3%] Individual unknown impurity[RRT0.82]--0.22%[NMT 0.2%] Total impurities-0.40% [NMT1.5%]

If no assignable cause that could explain the results can be identified during the manufacturing investigation or the assay failure investigation retesting may be considered. Part of the investigation may involve retesting a portion of the original sample.

Averaging

The validity of averaging depends upon the sample and its purpose. Using averages can provide more accurate results. Averaging cannot be used in cases when testing is intended to measure variability within the product, such as powder blend/mixture uniformity or dosage form content uniformity. Reliance on averaging has the disadvantage of hiding variability among individual test results. For this reason, all individual test results should normally be reported as separate values. Where averaging of separate tests is appropriately specified by the test method, a single averaged result can be reported as the final test result. In some cases, a statistical treatment of the variability of results is reported. For example, in a test for dosage form content uniformity, the standard deviation (or relative standard deviation) is reported with the individual unit dose test results.

Outlier test

An outlier may result from a deviation from prescribed test methods, or it may be the result of variability in the sample. It should never be assumed that the reason for an outlier is error in the testing procedure, rather than inherent variability in the sample being tested.

Hypothesis Testing (Applicable to Phase IA and Phase II)

Should be started as part of Phase Ia and continue into Phase II if no assignable cause found.

Description of the testing should be written, and then approved by QA/Contract Giver/QA equivalent prior to initiating investigational testing.

The requirements of Investigational testing listed below:

The description must fully document

The hypothesis to the test the root cause being investigated.

What samples will be tested.

The exact execution of the testing.

How the data will be evaluated

Table 8: Triplicate analysis.

Test performed	Batch/lot no	Sample identity	Result
Related substances-HPLC	xxxx	3xxx-OOS-1xxx8/1st triplicate	Individual unknown impurity [RRTo.80]:0.20% (NMT: 2.0%)
Related substances-HPLC	xxxx	3xxx-OOS-1xxx8/1st triplicate	Individual unknown impurity [RRTo.80]:0.18% (NMT: 2.0%)
Related substances-HPLC	xxxx	3xxx-OOS-1xxx8/1st triplicate	Individual unknown impurity [RRTo.80]:0.22% (NMT: 2.0%)
Related substances-HPLC	xxxx	3xxx-OOS-1xxx8/2nd triplicate	Individual unknown impurity [RRTo.77]:0.06% (NMT: 2.0%)
Related substances-HPLC	xxxx	3xxx-OOS-1xxx8/2nd triplicate	Individual unknown impurity [RRTo.77]:0.07% (NMT: 2.0%)
		3xxx-OOS-1xxx8/2nd triplicate	Individual unknown impurity [RRTo.77]:0.10% (NMT: 2.0%)

This Hypothesis testing may continue from the re-measurement of the original Preparations.

Investigational testing may not be used to replace an original suspect analytical Results. It may only be used to confirm or discount a probable cause.

Phase II Investigation

Conducted when the phase I investigations did not reveal an assignable laboratory error. Phase II investigations are driven by written and approved instructions against hypothesis. Prior to further testing a manufacturing investigation should be started to determine whether there was a possible manufacturing root cause. Phase II Investigation represented in fig 5.

Phase IB Investigation – Initial Investigation conducted by the analyst and supervisor using the Laboratory Investigation Checklist.

Contact Production/Contract Giver as appropriate.

For microbiological analysis where possible once a suspect result has been identified ensure all items related to the test failure are retained such as other environmental plates, dilutions, ampoules/vials of product, temperature data, auto pipettes, reagents – growth media. No implicated test environmental plates should be destroyed until the investigation has been completed.

The Analyst and Supervisor investigation should be restricted to data / equipment /analysis review only

On completion of the Analyst and Supervisor investigation re-measurement can start once the hypothesis plan is documented and is only to support the investigation testing.

This initial hypothesis testing can include the original working stock solutions but should not include another preparation from the original sample (see: re-testing)

The checklist may not be all-inclusive, but should be a good guideline to cover the pertinent areas that need to be covered in any laboratory investigation:-

Correct test methodology followed *e.g.*.. Version number.

Correct sample(s) taken/tested (check labels was it taken from correct place).

Sample Integrity maintained, correct container and chain of custody (was there an unusual event or problem).

How were sample containers stored prior to use.

Correct sampling procedure followed e.g. version number.

Assessment of the possibility that the sample contamination has occurred during the testing/ re-testing procedure (*e.g.* sample left open to air or unattended).

All equipment used in the testing is within calibration date.

Review equipment log books.

Appropriate standards used in the analysis.

Standard(s) and/or control(s) performed as expected.

System suitability conditions met (those before analysis and during analysis).

Correct and clean glassware used.

Correct pipette / volumetric flasks volumes used.

Correct specification applied.

Media/Reagents prepared according to procedure.

Items were within expiry date

A visual examination (solid and solution) reveals normal or abnormal appearance

Data acceptance criteria met

The analyst is trained on the method.

Interview analyst to assess knowledge of the correct procedure.

Examination of the raw data, including chromatograms and spectra; any anomalous or suspect peaks or data.

Any previous issues with this assay.

Other potentially interfering testing/activities occurring at the time of the test.

Any issues with environmental temperature/humidity within the area whilst was conducted.

Review of other data for other batches performed within the same analysis set.

Consideration of any other OOS results obtained on the batch of material under test.

Assessment of method validation.

Phase III Investigation

If the batch is rejected then there still needs to be an investigation.

To determine:

If other batches or products are affected.

Identification and implementation of corrective and preventative action.

The phase 3 investigation should review the completed manufacturing investigation and combined laboratory investigation into the suspect analytical results, and/or method validation for possible causes into the results obtained.

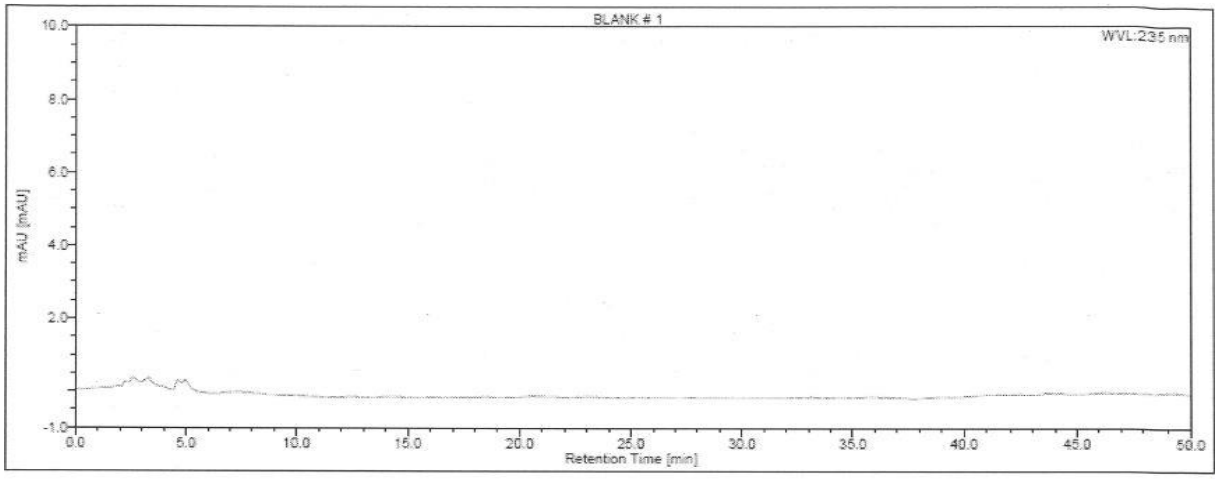

Figure 6: Blank Chromatogram

Blank chromatogram proves that is not contaminated by showing any desired peak area and represented in fig 6.

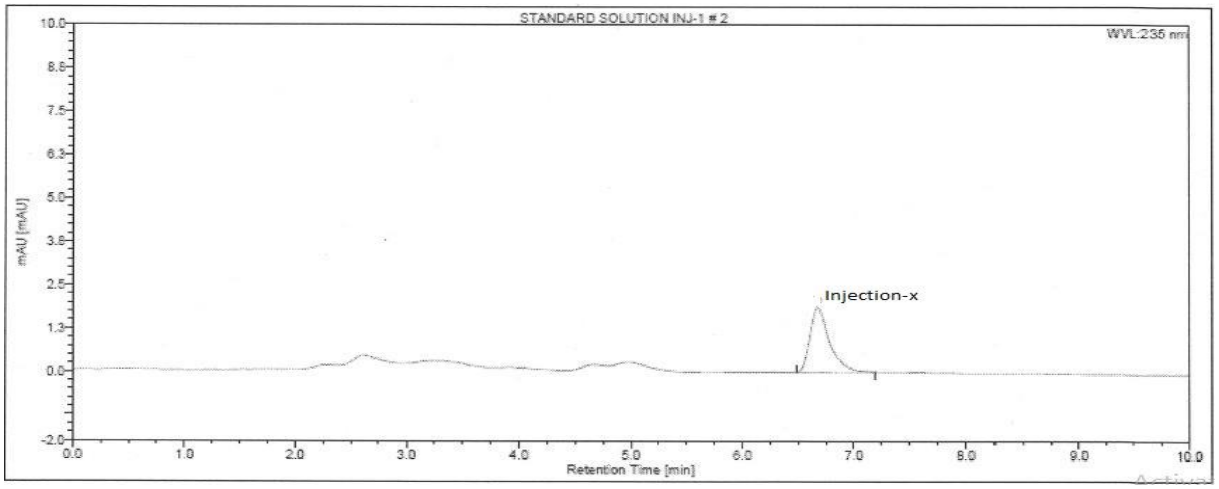

Figure 7: Standard chromatogram

Standard chromatogram proves that pure compound gets desired peak area and standard is not contaminated and represented in fig 7.

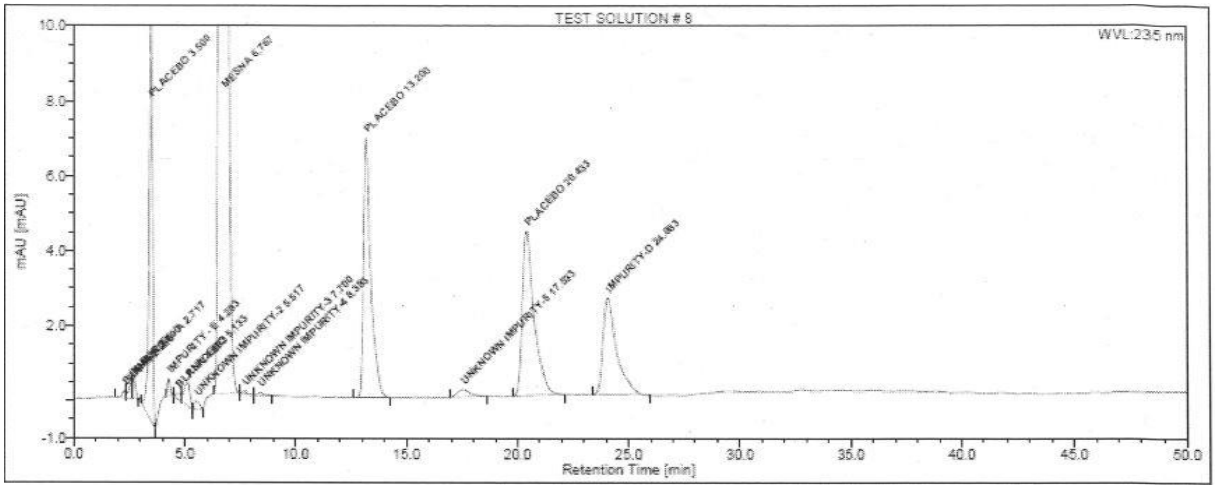

Figure 8: OOS Chromatogram

Chromatogram shows the peak area of the unknown individual compound.

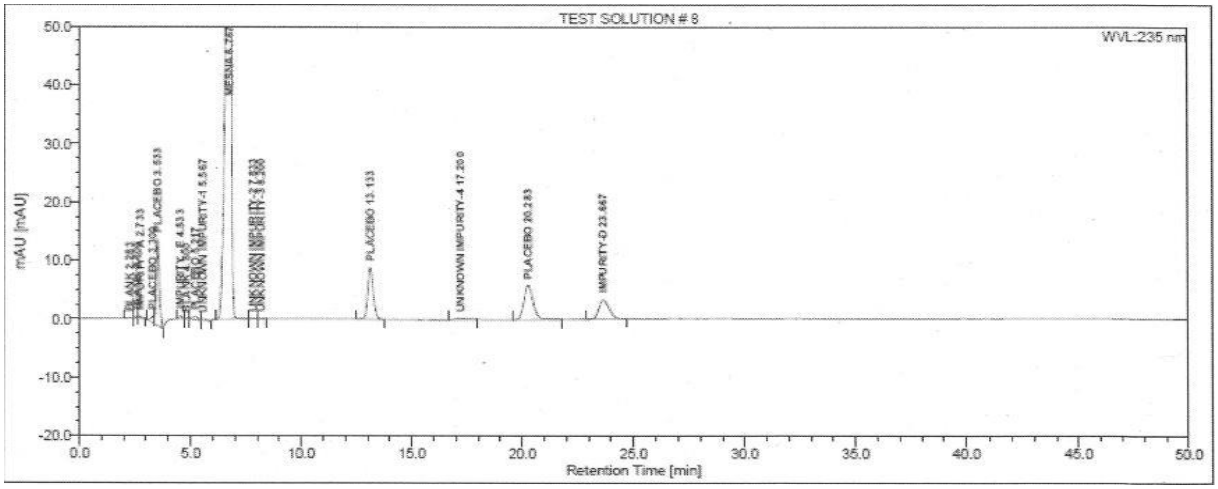

Figure 9: Hypothesis Chromatogram

Hypothesis Chromatogram proves that there is no instrument error and chemicals error.

To conclude the investigation all of the results must be evaluated.

The investigation report should contain a summary of the investigations performed; and a detailed conclusion.

For microbiological investigations, where appropriate, use risk analysis tools to support the decisions taken and conclusions drawn. It may not have been possible to determine the actual root cause therefore a robust most probable root cause may have to be given.

The batch quality must be determined and disposition decision taken.

Once a batch has been rejected there is no limit to further testing to determine the cause of failure, so that corrective action can be taken.

The decision to reject cannot be reversed as a result of further testing.

The impact of OOS result on other batches, on-going stability studies, validated processes and testing procedures should be determined by Quality Control and Quality Assurance and be documented in the conclusion, along with appropriate corrective and preventive actions.

RESULTS AND DISCUSSION

Material

OOS observed during analysis of Calcitriol API, assay by HPLC method.

Product-x injection 100mg/ml (10ml), related substances test result for individual unknown impurity found to be OOS and product information is shown in table 1 below and initial results are also shown in table 2 below.

Comments

Product-x injection, related substances by HPLC test result for individual unknown impurity found to be an OOS[RRT:2.59]

As per stability protocol at the time point analysis considered as 24th month stability study, but actual time point is 26th month analysis, because the product was expired.

This sample was analysed after expiry, this batch [xxxx] was manufactured was expired prior to analysis. But the sample when analysed on 22nd month it showed a satisfactory results and stability history are shown in table 3 below.

From the above product history no findings are observed, hence further investigation shall be carried out as per the LIR sop.

Phase-1

To find the instrument error the sample and standard are re-injected to equipment as per Injection profile in STP.

This result proves there is no instrumental error occurred during the initial analysis and study of instrument is shown in table 4 above.

Hypothesis study

Hypothesis study-1: analysis shall be performed by using same column and same chemicals which were used for initial analysis to establish the contribution of the column and product degradation due to chemicals or regents.

Hypothesis study-2: Analysis shall be performed by using new column and same chemicals which were used for initial analysis to confirm the contribution of the column, used for initial analysis.

Hypothesis study-3: Analysis shell be performed by using same column which was used for initial analysis and new chemicals to confirm the contribution of the chemicals, used for initial analysis.

The above hypothesis studies are planned to evaluate the contribution from old column and chemicals, regents used for initial analysis and details of the chemicals used during initial analysis are shown in table 5 below.

All the hypothesis study analysis, procedure shall be carried out as per the current STP.

Sample is not available to perform the hypothesis study; hence additional sample shall be received from stability contingency through additional sample request from approved QA and tests carried out through HPLC are shown in table 6 below.

Phase-2

Test plan:

To eliminate/confirm the initial OOS results planned to perform the triplicate analysis as per the LIR procedure.

Existing sample is not available to perform the triplicate analysis hence additional samples shall be collected from

stability contingency through additional sample request form and Tests carried for related substances are shown in table 7 below.

Test Plan

Triplicate analysis shall be performed in PDA detector to identify the cause of OOS result observed with respect to RRT 0.82.

Laboratory sample is not available to perform the triplicate analysis; hence additional sample shall be collected from stability contingency through additional sample request from approval by QA and Triplicate analysis results are shown in table 8 below.

CONCLUSION

When product-x injection were analysed in laboratory for the assay of individual unknown impurity, initially for all the months it shows the results in specification limit. Based on the initial OOS investigation proceed to investigation phase-II as per LIR procedure, to find the instrumental and solvents error hypothesis study conducted and it proves no instrument error and solvent error. Further investigation proceeds to investigate root cause, retesting of product-x injection were carried out. As the samples were not there triplicate analysis carried out by requesting QA. Triplicate analysis results were reviewed and observed that, unknown impurity at RRT 0.82 result found instead of unknown impurity RRT 2.55. Based on these variation results of unknown impurities RRT 2.55 & 0.82, the root cause for initial OOs could not be identified. Hence to confirm the OOS result observed due to unknown impurity at RRT 0.82, further investigation proceeds. Then the results are discussed with R&D and further triplicate analysis shall be performed by using PDA-Photo diode arey detector to identify the root cause observed at RRT of 0.82. Hence by conducting triplicate analysis by using PDA detector, the retest OOS result with respect to individual unknown impurity at RRT 0.80 is proven. Product-x injection 100mg/ml[10ml], related substance by HPLC test results for individual unknown impurity found to be an OOS[RRT:2.59] As per stability protocol at this time point analysis considered as 24th month stability study, but actual time point is 26th month analysis, because the product was expired before only. As part of investigation, standard and sample and solutions are re-injected, the result of individual unknown impurity found to be an OOS and it is comparable to the initial OOS result. Based on the re-injected results proves there is no instrumental error occurred during the initial analysis. The result of hypothesis analysis is comparable to initial OOS results with respect to any other individual impurity and also it proves that the chemical and column used for the initial analysis are not contaminated. Hence to confirm the initial OOS result, analysis shall be performed in triplicate. As part of investigation performed the triplicate analysis to identify the root cause for initial OOS due to any other unspecified impurity (about RRT2.55) Triplicate analysis results are reviewed and observed that, unknown impurity at RRT 0.82 result found OOS instead of unknown impurity RRT 2.55. Based on these variation results of unknown impurities (RRT 2.55 & 0.82) the root cause for initial OOS could not be identified. Hence to confirm the OOS result observed due to unknown impurity at RRT 0.82, further investigation shall be performed. Triplicate analysis performed two times, due to during 1st triplicate analysis PDA-detector 3D field were not used to identify a purity of peak at RRT of 0.80 hence once again performed the triplicate analysis, by using PDA-detector 3D field to identify a peak purity at RRT of 0.80peak.

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