1. **OBJECTIVE:**

 To describe a procedure for investigation of the reported test results, that does not meet the predetermined specification.

1. **SCOPE:**

This SOP is applicable for the analytical results of Raw-materials, Packaging materials, Intermediate stages, finished products (Drug Substances) and Stability study samples, at Quality Control Laboratory API Units of \_\_\_\_\_\_\_\_.

* 1. This SOP will not apply under the following circumstances:
		1. In-process samples.
		2. Analyst qualification.
		3. Additional tests based on the Customer requirement specifications.
		4. Monograph evaluations/ Analytical Method Transfer analysis.
		5. Further study of stability sample for data collection which are OOS at previous station in same condition.
		6. Photo Stability & Transportation study (Stress Stability).
1. **RESPONSIBILITIES / ACCOUNTABILITY:**

|  |  |
| --- | --- |
| **Responsible Person** | **Responsibility/ Accountability** |
| Analyst - Quality Control  | Immediate information to the laboratory supervisor by reporting the results. |
| Laboratory Supervisor | To review the documents and to perform the OOS investigation with the co-ordination of other departments. |
| QA Designee | To issue the OOS forms on the request and inward the reported OOS.To review and co-ordinate with other departments for OOS investigation.To lead the investigation team & to initiate Phase-III. |

|  |  |
| --- | --- |
| **Responsible Person** | **Responsibility/ Accountability** |
| Head Quality control/Designee | To ensure the compliance of Phase-I and Phase-II/A investigation (Laboratory investigation) as per SOP. To support the cross functional Teams for better investigation.To propose the appropriate Preventive measure and implementation. |
| Concerned Head of the Department | To support the cross functional investigation (Phase-II & Phase-III investigations). |
| Site-Quality Head/ Designee | To ensure the compliance as per SOP.To ensure the evaluation/ assessment and completion of the OOS investigation. To ensure the batch disposition of the material. |

1. **DEFINITION :**
* **Out of Specification:** Test results that fall outside of established acceptance criteria which have been established in specifications.
* **Assignable cause:** Clear evidence, scientifically justified and documented as the cause of an OOS result.
* **Corrective Action:** Corrective Action is an action(s) taken to eliminate the cause of non conformity in order to avoid reoccurance.
* **Preventive Action:** Preventive Action is an action(s) taken to eliminate the potential non- conformity, defect or undesirable situation in order to avoid occurance.
1. **Procedure:**
	* 1. OOS shall be reported within 24 hours of observation by the Analyst through “Investigation of Out Of Specification Results” form as per the Annexure-II (CQA/A/SOP007-F02).
		2. The supervisor shall review Annexure-II which will be submitted to Quality Assurance department for allotment of OOS reference number.
		3. Designee**-**QA shall enter the OOS details in Out Of Specification log as per the Annexure-III.
	1. **OOS numbering system:**
		1. OOS number shall be assigned as per the below numbering system.

**OOS/XX/YY/ZZZZ**

Where,

**OOS:** Out of Specification

**XX:** Unit code(for API Unit-I A1, API Unit-II A2 & for API Unit-III A3)

**YY:** Two digit year code (ex: for year 2018: 18)

**ZZZZ:** Fourdigit serial number (0001, 0002 etc. for particular year)

*Ex:* OOS/A1/18/0001

**Note:**

In case of multiple batch failures in a single analysis set, one OOS number shall be assigned for all the batches however separate forms of Annexure-II shall be used.

In case of multiple test parameter failures reported for a single batch, same OOS number shall be assigned.

* + 1. In case OOS has occurred at outside testing laboratory, OOS number shall be assigned & investigation form (Annexure-II) shall be sent to the respective laboratory for investigation purpose. Alternatively, investigation report shall be accepted and considered for OOS investigation/ necessary CAPA using the vendor’s format as well.
		2. Notification to customer shall be given as per the quality agreement.
	1. **PRELIMINARY Laboratory investigation (Phase-I):**

Laboratory investigation shall be carried out by the Quality Control department Supervisor as per the OOS investigation check list available in Annexure-II (but not limited to).

 **Phase-I (a) Investigation:**

* + 1. If any obvious error found [Transcriptional / Calculation / Method parameter errors / Instrument breakdown / Power failures / (not limited to)], further investigation may not be required. The results shall be corrected and documented with appropriate CAPA.

Retesting (Triplicate analysis) shall be done if applicable.

 **Phase-I (b) Investigation:**

* + 1. If obvious error is not identified, further laboratory investigation shall be carried-out.
		2. **Analyst Interview**: Interview shall be conducted with the persons who performed the critical steps during analysis, to understand the practices & to find out the assignable root-cause. Interview details shall be captured in the OOS form of Annexure-II.
		3. During the investigation, make sure that all the solutions associated with OOS shall be retained till completion of the preliminary phase-I investigation by supervisor & Original samples (Including Standards & Impurities) shall be retained until completion/ conclusion of the reported OOS investigation.
		4. Status of impacted batches shall be evaluated/ discussed.
		5. Based on the checklist review any reportable observations notified, and then same shall be discussed for further evaluation. Impact shall be assessed and conclusion shall be drawn.
		6. As a part of investigation, re-measurement shall be carried out with retained solutions (same-vial/ same-solution/ re-dilution) unless otherwise justified (for applicable tests).

*Re-measurement procedure:*

Re-measurement testing to be done to verify probable errors regarding what might have happened (E.g. Instrument malfunction, dilution errors & contamination/ etc).

The re-measurement shall be performed under the supervision of QC/QA with same analyst or second analyst as mentioned below.

|  |  |
| --- | --- |
| **Analysis to be done as a part of Remeasurement Testing** | **Suspected Laboratory Error if the Remeasurement is confirmed** |
| Re-injection of the same vial of standard and test solution | Transient Instrument malfunction |
| Re-filling of the vial with same test preparation | Contamination due to vial in case of OOS results in Impurities |
| Re-dilution of the test and/or standard preparation from the stock solution | Dilution error during final dilution of test and/or standard preparation |

Note: The obtained results shall not be considered for reporting purpose.

* + 1. Applicability of remeasurement:

Remeasurement is applicable for the techniques like chromatography where the Same vial and Original solutions are intact and possibility for remeasurement (In case of GC-HS, same vial may not be required). Whereas the techniques like non-chromatography (WC, LOD, IR, XRD & Potentiometry Assay), remeasurement shall be skipped and justification shall be documented.

* + 1. If assignable cause identified during the Laboratory investigation (re-measurement), QA Head/ Designee shall be allowed for retesting of the original sample (Three measurements) preferably by the second analyst.
		2. If assignable cause not identified during the Preliminary Laboratory investigation, QA Head/ Designee shall recommend for Full scale investigation (Phase-II - Parallel investigation of Manufacturing & extended Laboratory investigation).

Note: Phase-IIA investigation shall be initiated, whereas the remeasurement is not applicable. In such cases, parallel investigation may not be required and Phase-IIB investigation shall be initiated based on the outcome of Phase-IIA.

* + 1. For extended laboratory investigation (Phase-IIA), Annexure-II shall be followed and for Mfg investigation (Phase-IIB), notification shall be given to the Manufacturing department for further investigation (Annexure-VI).

 Note: Phase-II B (Manufacturing) Investigation is not applicable in case of Raw-materials.

* 1. **Extended Laboratory Investigation (Phase-II A):**
		1. Extended Laboratory Investigation shall be carried out with approved protocol to find out the assignable cause/ most probable causes.
		2. Protocol shall be prepared by QC as per the Annexure-V and approved by QA.
		3. During the extended laboratory investigation (Hypothesis/ Simulation study), below points shall be considered.
		4. Study shall be carried out with the available Standard unless otherwise justified.
		5. If any suspected cause identified, then only original sample measurement shall be carried-out.
		6. In case of Solution stability places a role in reported OOS; it should be proved by using Standard only.
		7. If any ambiguity in sample storage condition or doubt in sample integrity, in such cases resampling shall be done upon QA approval (with justification).
		8. Extended hypothesis study can be carried-out, until most probable causes identified.
		9. If assignable root-cause identified (during Phase-IIA), invalid the initial OOS results then propose CAPA & proceed for further retesting (Three measurements) followed by results reporting and impact-assessment.
		10. If assignable root-cause not identified during Phase-IIA/ Phase-IIB than based on the most suspected cause retesting (Triplicate analysis) shall be done with two different analysts.

Note: If first retesting analysis failed, second retesting analysis can be skipped.

* + 1. Further retesting will not be allowed, if OOS results were confirmed (OOS confirmed).

Note: If extended investigation remains unclear (No assignable cause), report the results and Phase-III investigation can be carried-out.

* 1. **Phase-IIB Investigation (Manufacturing investigation):**
		1. Phase-IIB investigation shall be carried-out by manufacturing department, upon conclusion from the Preliminary Laboratory Investigation (Phase-I).
		2. Based on the notification received from QA as per Annexure-VI, Concerned manufacturing person shall start the investigation by process review including preliminary check points. Based on the Phase-IIB investigation as per the Annexure-VIII, observation shall be documented by the Designee-Production.
		3. If assignable cause is identified during Phase-IIB investigation, then appropriate corrective & preventive action shall be taken along with impact assessment followed by batch disposition.
		4. If assignable cause/ probable cause is identified as sampling error, resampling can be done based on the QA approval.
		5. If assignable cause is not identified during preliminary investigation, further retesting (Triplicate) with original sample can be proposed based on rational (Refer Phase-II A).
	2. **Re-sampling procedure:**
		1. Before proceed for re-sampling activity, below points shall be considered/ ensured.
* Sound scientific justification must be provided for re-sampling and shall occur rarely.
* In-case of insufficient quantity of the original sample whereas other test parameters to be performed with further testing of OOS, then resampling can be done with approval from QA.
* Evidence indicates that the sample is compromised or invalid.
	+ 1. The process of resample activity should be documented (Refer Annexure-XII).
		2. Re-sampling should be performed by the same sampling 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.
		3. Analysis shall be performed in duplicate measurements, upon resample.
	1. **RETESTING & Reporting of Analytical Results:**
		1. If assignable cause identified - Retesting shall be carried-out in Three (3) measurements (3 different preparations).
		2. If assignable cause not identified - Retesting shall be carried-out on Three (3) measurements with Two analysts (Second analyst and most preferably first analyst). Total 6 measurements.
		3. Impacted batches (Other than OOS batch within same analysis set) retesting analysis shall be carried-out and assessed (Single measurement/ as per STP).
		4. Based upon the retesting analysis conclusion, initial OOS analysis set (all batch results) shall be invalidated and ‘Not considered’ stamp shall be affixed.
		5. Original Sample shall be used for retesting analysis, until unless justified (QA will decide in-case of re-sampling).
		6. *Note:* Retesting of three measurements not applicable for the test parameter of Description/ Appearance, where Single measurement is sufficient.
		7. Final result reporting shall be followed as below.

Average results shall be considered for reporting in case of quantitative analysis (All individual results shall comply).

Note: For Assay test parameter, %RSD shall be NMT-2.0%. If % RSD not complies, further investigation shall be based on QA recommendation/evaluation.

* 1. **Phase-III Investigation:**
		1. If assignable cause is not identified during the Phase-II investigation, then report all the results (Confirmed OOS) and initiate Phase-III investigation. Annexure-XI shall be used.
		2. As part of Phase-III investigation, review the manufacturing investigation and combined laboratory investigation and reported OOS shall be escalated to PDL/ADL for further investigation to find-out the root-cause and preventive measures.
		3. The impact of OOS result on other batches shall be evaluated.
	2. **STABILITY SPECIFIC PROCEDURE:**
		1. Out of Specification (OOS) procedure shall be same as regular analysis. However, Cross Functional Investigation (Phase-II & Phase-III) shall be lead by QA.
		2. Additional samples can be withdrawn for investigative analysis based on the pre-approved protocol with proper justification (Phase-IIA), protocol shall be approved by QA Head/ Designee.
		3. During the investigation, further station Stability samples can be tested if the product bound to be failed. This activity can be done with pre-approved protocol only.
		4. In case of confirmed OOS in stability study, further study (upcoming station analysis) may continue for data collection purpose and OOS shall not be reported for same batch at same condition.
	3. **Batch Disposition - Conclusion:**
		1. All test results, shall be reported and considered in batch release decisions.
		2. If assignable cause not identified and OOS found to be invalid, batch disposition decision shall be taken by QA & considering most probable cause determined once after completion of the full scale investigation (Phase-II) (Where the OOS result not reflecting the quality of the batch).
		3. Upon the batch disposition decision, OOS investigation shall be closed with reference CAPA number by QA Head/ Designee (if applicable). Hence, further implementation of proposed Corrective actions & preventive actions shall be tracked.
	4. **Raw materials/ Packing materials Specific procedure:**
		1. Any batch rejected either due to non-conformance to the Quality standards, OOS shall inform to the Purchase department (as per Annexure-X) for further notification to the respective vendor.
		2. QA Designee shall log vendor non-conformance as per the Annexure-IX.

 Vendor non-conformance shall be numbered as ‘VNC/AA/YY/XXX’.

 *Where*,

 VNC – stands for Vendor non-conformance.

 AA – stands for location Code (API Unit-I A1, API Unit-II A2 & API Unit-III A3).

 YY – stands for last two digits of current calendar year (18 for 2018).

 XXX – stands for serial number starting from 001, 002, 003…

 E.g. First vendor non-conformance of year 2018 for API Unit-I, shall be numbered as VNC/A1/18/001.

* + 1. Based on the above notification (Annexure-X), QA designee shall be taken follow-up for response of said non-conformance w.r.t. the KSM.
		2. After getting response from vendor, evaluation of response shall be done by Head QA/Designee.
		3. If vendor response is not received within 60 days, then non-conformance form shall be closed with recommendation for upcoming lots monitoring.
		4. In case of any quality issues, reanalysis/ joint analysis shall be decided by Head QA/Designee.
		5. Decision of batch disposition shall be taken by Head QA/Designee.
		6. For Packing material, Phase-I investigation shall be carried out as per Annexure-VII.
	1. **Timeline for OOS completion:**
		1. OOS investigation shall be completed within 30 calendar days from the date of OOS reported, unless otherwise justified (Phase-I & Phase-II).
		2. Phase-I Investigation (Laboratory) shall be completed within 3 calendar days from the date of OOS reported, unless otherwise justified.
		3. Designee of Laboratory/ Mfg. shall request Quality Assurance with proposed timelines for further extension. Extension request shall be made before its actual timelines.
		4. Phase-III investigation shall be completed within 30 calendar days from date of Phase-III initiation.
	2. **Evaluation of OOS investigations:**
		1. Summary of OOS shall be prepared by Quality Assurance on half-yearly basis for effectiveness of the investigations and impact evaluation.
		2. Investigation/ report shall be amended in-case of customer / regulatory observations.
		3. Investigation report shall contain the following information (but not limited to).
* General information including OOS details
* Product/ Batch history
* Investigation with Root cause analysis
* Root cause/Conclusion
* Correction/ Impact assessment
* Corrective action
* Preventive action
* Report approval details
1. **ANNEXURES:**

|  |  |  |  |
| --- | --- | --- | --- |
| **S.No.** | **Annexure No.** | **Title** | **Format No.** |
|  | Annexure-I | Flow chart for OOS Investigation |  |
|  | Annexure-II | Investigation Of Out Of Specification Results  |  |
|  | Annexure-III | Out of Specification results log book |  |
|  | Annexure-V | Hypothesis study protocol |  |
|  | Annexure-VI | Notification of out of specification results |  |
|  | Annexure-VII | OOS Investigation for Packing Materials |  |
|  | Annexure-VIII | Manufacturing Investigation |  |
|  | Annexure-IX | Vendor nonconformance Log |  |
|  | Annexure-X | Vendor Acknowledgement Form for Non-conformance to Quality Standard |  |
|  | Annexure-XI | Phase-III Investigation |  |
|  | Annexure-XII | Resampling of Out of Specification batch |  |

1. **REFERENCE:**

|  |  |  |
| --- | --- | --- |
| **S. No.** | **Title** | **Reference No.** |
|  | USFDA guidance for industry investigating out-of-specification (OOS) test results for Pharmaceutical Production. | NA |
|  | MHRA guideline on out-of-specification (OOS) investigation. | NA  |
|  | SOP for Incident Reporting CQA/A/SOP005. |  |
|  | CAPA |  |
|  | Laboratory Incidents |  |

*Phase-III Investigation*

*Doesn’t Complies*

**Retesting by Second & First analyst**

***Complies***

No Assignable cause/ Most probable causes

**Extended Lab Investigation (Phase-IIA)**

**Hypothesis protocol Study**

Assignable cause identified

**CAPA/ Retesting by Second analyst**

**Reporting Results**

*Doesn’t Complies*

**Batch Disposition**

Complies

CAPA / Retesting

Obvious error

**Not Identified**

**Manufacturing Investigation\***

**Phase-IIB**

 Phase-IA Investigation

Preliminary Laboratory Investigation (Phase-I)

**OOS Result**

No Assignable cause

Assignable cause identified

Correction/ No further investigation

Phase-IB investigation (with Check list)

Re-measurement

Obvious error

**Identified**

**Manufacturing Investigation/**

**Phase-II (B)**

Phase-III Investigation

Batch Disposition

*Retesting of Original sample*

*Doesn’t Complies*

*Complies*

*No Assignable cause*

Notification to Manufacturing

*Assignable cause*

*CAPA / Assessment*

*Experimental Investigation #*

Investigation through Checklist

*# Extended Laboratory Investigation*

CAPA/ Assessment

CAPA/ Method Validation

*Batch Disposition*

*Assignable cause*

*No Assignable cause*

*No Assignable cause*

*Assignable cause*

*Communication to ADL*

*Communication to PDL*

Consolidated Report

**Phase-III Investigation**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Name of Product** |  | **OOS Category** |

|  |  |
| --- | --- |
| *Regular* | *Stability* |

 |
| **Stage** |  | **Stability Interval & Condition** |  |
| **Batch No. (s)** |  | **Inspection Lot/** **A.R. No.** |  |
| **Test Parameter** |  | **Specification No. & STP No.** |  |
| **Reported Result** |  | **TDS/ Raw-data reference** |  |
| **Specification limit** |  |
| **Reported Date** |  | **Time** |  |
| Analyst Name(Reported by) |  | Sign & Date |  |
| Supervisor’s Comments: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Supervisor’s Name |  | Sign & Date |  |
| ***OOS reference number (by QA)***: |
| *History of OOS for the similar failure (Review last 1 year for reported OOS)? If yes, mention OOS No.* |  |
| **OOS Reference No** |  | Delay justification to be filled on (before 30th day) |  |
| Remarks: OOS number can be assigned/ cannot be assigned.  |
| OOS number issued by (Name)  |  | OOS number issued by Sign & Date |  |

1. **PRELIMINARY LABORATORY INVESTIGATION (Phase-I):**
2. **Phase-I (a) investigation:** (Any evidence for obvious error)

|  |  |  |
| --- | --- | --- |
| **Obvious error** | **Identified (Yes / No)** | **Remarks (If identified)** |
| Calculation error |  |  |
| Power outage |  |  |
| Instrument failure |  |  |
| Incorrect instrument parameters |  |  |
| Others \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  |  |

**Name of the analyst (Sign & Date):** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.

**Conclusion:**

**Supervisor Name & Sign (Investigator’s):** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.

1. **Phase-I (b) investigation:**

**Supervisor Name (Investigator’s):** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *Date of Testing* | *Analysis initiated by (Instrument readiness)* | *Standard/ Sample prepared by* | *Results reported by* | *Review done by* |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

|  |
| --- |
| **Interview details (as and when available):** |
| ***Name of the Employee*** |  | ***Privileges*** ***(Analyst / Reviewer)***  |  |
| Interview Summary (Understanding of Method & Practices shall be discussed, but not limited to). |
| ***Sign & Date:*** |  | ***Head of QC/ Supervisor Sign & Date*** |  |
|  |
| ***Name of the Employee*** |  | ***Privileges*** ***(Analyst / Reviewer)***  |  |
| Interview Summary (Understanding of Method & Practices shall be discussed, but not limited to).  |
| ***Sign & Date:*** |  | ***Head of QC/ Supervisor Sign & Date*** |  |

Investigation shall be carried-out by conducting interview with the persons who done critical operations.

**Details of Instruments / Standards:**

|  |  |  |  |
| --- | --- | --- | --- |
| **Instrument Name** |  | **Instrument ID** |  |
| **Date of Calibration** |  | **Calibration due** |  |
|  |
| ***Name of the Balance*** | ***Balance ID (s)*** | ***Daily verification*** ***(Done/ Not done)*** | ***Monthly Calibration due*** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
| ***Name of the Standards*** | ***Batch Number*** | ***Validity*** | ***Condition during analysis*** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

| **LABORATORY INVESTIGATION CHECK LIST [Phase-I (b)]:** |
| --- |
| **S.No.** | **Investigation Questionnaire (Was…)** | **Observations** |
| No | Yes | Remarks (If No) |
| 1 | Analyst qualified for the Test parameter? Date: |  |  |  |
| 2 | Analyst trained for the Test/ Technique? |  |  |  |
| 3 | Right method (Spec/STP) used for the analysis? |  |  |  |
| 4 | Correct formula/ procedure used for calculations? |  |  |  |
| 5 | Instrument Calibrationdone as per the schedule?  |  |  |  |
| 6 | Balance calibration performed as per the schedule? |  |  |  |
| 7 | Sample Integrity is satisfactory? |  |  |  |
| 8 | Standard Integrity is satisfactory? |  |  |  |
| 9 | Sample stored at appropriate condition?Storage Condition: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  |  |  |
| 10 | Standards, Samples and reagents labelled properly? |  |  |  |
| 11 | Original Sample available?Approx. quantity available:\_\_\_\_\_\_\_\_\_\_ |  |  |  |
| 12 | Glassware available with Standard & Sample solutions? |  |  |  |
| 13 | Color of the Sample/ Standard solutions as per the trend? |  |  |  |
| 14 | Appropriate Glassware (Grade-A) used for the Analysis? |  |  |  |
| 15 | Glassware found in good/ acceptable condition? |  |  |  |
| 16 | Electrode used for the analysis was appropriate as per STP? |  |  |  |
| 17 | Condition of electrolyte and trend of the graph/ curve, appropriate? |  |  |  |
| 18 | Sample/ Standard solutions stored as per the respective STP/ MOA?  |  |  |  |
| 19 | Reagents/Chemicals/Solvents used for analysis were appropriate and recommended as per STP? |  |  |  |
| 20 | Valid Reagents/Chemicals/Solvents/Volumetric solutions used for the analysis?  |  |  |  |
| 21 | Instrument and all its components working properly? |  |  |  |
| 22 | If the instrument is HPLC/ GC, satisfactory w.r.t. the pressure, base-line? |  |  |  |
| 23 | Calibration performed in-case of break-down of the instrument?  |  |  |  |
| 24 | The area of Reference solutions and test sample within the historic trend?  |  |  |  |
| 25 | Column used as per the Method of Analysis/ STP? |  |  |  |
| 26 | Mobile phase prepared as per the Method of Analysis? |  |  |  |
| 27 | Mobile phase color unchanged as per the trend?(No Haziness) |  |  |  |
| 28 | Diluent Solutions prepared as per the Method of Analysis/ STP? |  |  |  |
| 29 | Method parameters are same as per the STP? |  |  |  |
| 30 | Dilutions of test and standard preparations were appropriate against STP? |  |  |  |
| 31 | System suitability parameters were met the criteria? |  |  |  |
| 32 | All the peaks were integrated properly? |  |  |  |
| 33 | Laboratory conditions appropriate?Temperature: \_\_\_\_\_\_\_°C & Humidity: \_\_\_\_\_\_\_\_%RH  |  |  |  |
| 34 | All calculations are appropriate? |  |  |  |
| 35 | Electronic data/ Audit trails are appropriate? |  |  |  |
| 36 | ***Stability Studies only*** |
| a | Stability packing condition was appropriate? |  |  |  |
| b | Respective Stability chamber condition and data was found without any major deviation? |  |  |  |
| c | History of similar OOS (Valid) by reviewing last One year data (mention if OOS history available). |  |
| d | Any data available by reviewing the Stability batches for the nature of the Product behavior w.r.t. time? |  |

|  |  |
| --- | --- |
| 37 | *Status of Other batches analyzed in same set of Analysis (Mention batch details & status):* |
| 38 | *Status of the other test parameters of the batch (for any impacted):*  |
| ***Summary of Check list:***(If any observations found, details shall be mentioned below (but not limited to). |
| 39 |  |
| ***Supervisor*** ***Sign & Date*** |  | ***Head of QC/ Designee Sign & Date*** |  |

|  |
| --- |
| ***Re-measurement/ Re-verification:***(Re-measurement shall be carried-out to find-out the root-cause in presence of Lab supervisor) |
|  | Name of the analyst: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Name of the Supervisor: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_***Plan of Re-measurement***: (Re-injection / Re-vial / Re-dilution)\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Results of re-measurement:Re-Injection: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Re-Vial: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Re-dilution: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Specification: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Assignable cause: Identified/Not identifiedComments: Justification for not performing Remeasurement: |
| ***Supervisor (QC)******Name, Sign & Date*** |  |
| **Evaluation by QA:** |
|  | *Comments by QA:*(If assignable cause identified, proceed for retesting of the original sample.)*Proposal for Retesting/ Phase-II Investigation (IIA - Hypothesis study / IIB investigation)*. |
| ***Head of QA/*** ***Designee Sign & Date*** |  |
| 1. ***Phase-IIA investigation***
 |
| ***Hypothesis investigation Study:***(To investigate the exact error associated with the Laboratory) |
|  | Results/ Observations of Hypothesis Study:Assignable cause: Identified/Not identified.Root-cause:CAPA: |
| *Conclusion/ Proposal for further* investigation (Plan of Study): |
| ***Supervisor*** ***Sign & Date*** |  | ***Head of QC/ Designee Sign & Date*** |  |
|  | **Evaluation by QA:** |
|  | *Comments by QA:*(In-case of assignable cause identified, proceed for retesting of the sample etc.)*Proposal for Re-sampling/ Re-testing/ Further investigation.* |
| ***Head of QA/*** ***Designee Sign & Date*** |  |

***Note:*** Further investigative study shall be attached as an Annexure along with protocol.

|  |
| --- |
| ***Status/ Conclusion of Phase-II (Phase-IIB & Phase-IIA)*** |
| *(If assignable cause not identified/Probable cause identified during Phase-II, Retesting with different analysts – Second &most preferable First with Original sample)*  |
| ***Head of QA/ Designee Sign & Date*** |  |

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| --- |
| 1. ***Re-testing (If assignable cause identified):***
 |
|  |

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| Name of the Analyst (Second analyst\*):(\*In-case of exact root-cause w.r.t. Instrument/ Method, initial analyst can be performed) |
| ***Measurements*** | ***Result*** | ***Conclusion******(Complies/ Does not comply)*** | ***Specification*** |
| I |  |  |  |
| II |  |  |
| III |  |  |
| Average |  |  |
| ***Observation:*** *Complies/Does not Comply* |

Final Reporting Result: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (Batch Status: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_). |
| ***Supervisor*** ***Sign & Date*** |  | ***Head of QC/ Designee Sign & Date*** |  |

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| 1. ***Re-testing (If assignable cause not identified/ Most probable causes identified):***
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| Name of the Analyst (Second analyst): |
| ***Measurements*** | ***Result*** | ***Conclusion******(Complies/ Does not comply)*** | ***Specification*** |
| I |  |  |  |
| II |  |  |  |
| III |  |  |  |
| Average |  |  |  |
| ***Observation***:*Complies/Does not Comply* |

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| --- |
| Name of the Analyst (First analyst/Third analyst): |
| ***Measurements*** | ***Result*** | ***Conclusion******(Complies/ Does not comply)*** | ***Specification*** |
| I |  |  |  |
| II |  |  |  |
| III |  |  |  |
| Average |  |  |  |
| ***Observation***:*Complies/Does not Comply* |

Average result of 6 measurements: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.Final Reporting Result: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (Batch Status: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_).***Note:*** Multiple batches re-testing results can be attached as an Annexure. |
| ***Supervisor*** ***Sign & Date*** |  | ***Head of QC/ Designee Sign & Date*** |  |

|  |
| --- |
| 1. ***Status of the OOS:***
 |
|  | Conclusion/Root cause:  |
| Proposed CAPA: |
| OOS Status:  | Confirmed (Valid)/ Not confirmed (Invalid) |
| **QC designee (Name/Sign &Date):** |  |
| 1. ***Conclusion by QA:***
 |
|  |  |
| **Name:** | **Sign & Date:** |
| 1. ***Disposition of the Batch:***
 |
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 | Batch can be **released** as the reported OOS shall be considered to be Invalid. |
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 | Batch shall be **reprocessed**. |
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 | Batch can be **diverted** to \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Market, as per the Specification \_\_\_\_\_\_\_\_\_\_\_\_. |
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 | Batch shall be **destroyed**. |
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 | **Customer** shall be notified. |
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 | **Stability study** can be Continued/ Discontinued. |
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 | Product **retest** shall be assessed. |
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 | **Phase-III investigation** is required. |
| **QA Head/Designee****(Name/Sign & Date)** |  |
| 1. ***Justification for extension of time-lines:*** *(To be filled on or before 30th days)*
 |
|  | **Justification:**  |
| Proposed Time-lines: |
| **QC Designee Name:** |  | **Sign & Date:** |  |
| ***Comments by QA Designee:*** |
| **QA Designee Name:** |  | **Sign & Date:** |  |
|  | **Follow-up by QA:** |
|  | **Date** | **Status of work completion** | **Sign (department)** | **Sign (QA)** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
| 1. ***OOS Closure:***
 |
|  | ***Comments:*****Further reference documents (CAPA):**  |
| **Head QA/ Name:** | **Sign & Date:** |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **S.No.** | **Date** | **OOS No.** | **Name of Product/** **Material** | **Category****(FP/ST/ RM/ KSM/ INT)** | **Batch No.** | **Test parameter** | **Specification limit** | **Result** | **Logged by** | **Extension (Yes/No)** | **OOS Status****(Valid/ Invalid)**  | **OOS Closed on** | **CAPA if any** | **Closed by** | **Reviewed By** | **Remarks** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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| --- | --- | --- |
| API UNIT \_ | **HYPOTHESIS STUDY PROTOCOL** |  |
| Title: |  |
| OOS No |  | **Annexure No.** |  |

TABLE OF CONTENTS

|  |  |  |
| --- | --- | --- |
| ***S.No.*** | ***Title*** | ***Page No.*** |
| 1.0 | Background of OOS |  |
| 2.0 | * HYPOTHESIS PROCEDURE
 |  |
| 3.0 | CONCLUSION |  |
| 4.0 | PROTOCOL APPROVAL DETAILS |  |

* 1. Background of OOS:
1. HYPOTHESIS PROCEDURE:
2. CONCLUSION:
3. PROTOCOL APPROVAL DETAILS:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Report (by)** | **Name of the Employee** | **Department** | **Designation** | **Signature & Date** |
| **Prepared** |  | Quality Control |  |  |
| **Reviewed** |  | Quality Control |  |  |
| **Approved** |  | Quality Assurance |  |  |

|  |  |
| --- | --- |
| **To. : Production Department** | **From : Quality Assurance Department** |
| **OOS NUMBER** |  |
| **Date of Reporting of OOS** |  |
| **Product / Material Name** |  |
| **Batch / Lot Number** |  | **AR. No.** |  |
| **Mfg Date** |  | **Exp. / Retest Date** |  |
| **Test Under OOS** |  | **Date of Analysis** |  |
| **Specification/STP No.** |  |
| Brief description of Out of Specification result: |
| Prepared By Quality Assurance designee |  |
| Evaluation and comments by QA :  |
|  |
|  |
|  |
|  |
| Reviewed by Head Quality Assurance / designee |  |

**Phase I - Laboratory Investigation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Name of Material** |  | **Date** |  |
| **Name of Supplier** |  | **Name of analyst** |  |
| **Batch No.** |  | **Inspection Lot No./ A.R. No.** |  |
| **Test** | **Specification** | **OOS result** |
|  |  |  |
| ***OOS reference number (by QA)***: |
| **OOS Reference No** |  | Delay justification to be filled on |  |
| OOS number issued by (Name)  |  | OOS number issued by Sign & Date |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **S.No** | **Detail of Investigation** | **Observations** | **OK / Not OK & NA** | **Remarks** |
| 1.0 | Previous History of the Material (if any). |  |  |  |
| 2.0 | Ensure that standard solution is retained. |  |  |  |
| 3.0 | Sampling. |  |  |  |
| 3.1 | Is sampling carried out as per approved procedure? |  |  |  |
| 3.2 | Has trained personal collected the sample |  |  |  |
| 4.0 | **Any Other Observation:** |
| **Investigation Summary by QC Analyst:**AnalystSign/ Date |
| **Comments By QC Head:**Head/ Designee- QCSign/ Date |
| **Evaluation of Phase I Investigation by Head Quality Assurance / designee:** |
| Head Quality Assurance / designee | Signature / Date |
| Conclusion of Phase I Investigation**Information given to the vendor on dated : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ [Attach communication]****Disposition of material under investigation:** **Phase I Investigation Close out date:** |
| Head Quality Assurance / designee | Signature / Date |

|  |  |  |  |
| --- | --- | --- | --- |
| **OOS Reference No** |  | OOS Date |  |
| Notification date |  | Date to be completed |  |
| **Name of the Product** |  |
| Stage |  | Batch No |  |
| Material Code |  | Plant No |  |
| **OOS Description** |
|  |
| ***Production Designee Name*** |  | ***Sign & Date*** |  |

|  |
| --- |
| **Investigation Team** |
|  |

|  |  |
| --- | --- |
| 1.0 | **Investigation as per checklist.** |
| **Check Points** | **Yes** | **No** | **NA** | **Remarks** |
|  | Is correct Batch Production record used |  |  |  | BMR No.\_\_\_\_\_\_\_\_\_\_\_ |
|  | Correct quantities of correct ingredients were used in manufacturing (KSM/RM/Solvents). |  |  |  |  |
|  | Starting material used in manufacturing are from the approved vendors. |  |  |  |  |
|  | Intermediates used in manufacturing are approved by QC. |  |  |  |  |
|  | Starting materials used in manufacturing are approved by QC. |  |  |  |  |
|  | Cleaning of equipment’s have been done as per cleaning procedure mentioned in BMR/BCR |  |  |  |  |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Balance used in dispensing /verification were calibrated using valid standards weights. |  |  |  |  |
|  | Equipment’s were used as specified in batch manufacturing records during manufacturing. |  |  |  |  |
|  | The processing steps were followed in correct sequence as per the BMR. |  |  |  |  |
|  | All the processing parameters were within the range as specified in BMR. |  |  |  |  |
|  | The components, intermediates, in-process materials were stored as per conditions. |  |  |  |  |
|  | The storage Hold times of various stages were not exceeded.  |  |  |  |  |
|  | Validity of Raw material shall be ensured prior to charging. |  |  |  |  |
|  | Environmental conditions during manufacturing were as per the standard limits. |  |  |  |  |
|  | Was any Incident/Temporary Change control from the manufacturing Process. |  |  |  |  |
|  | The yields at different stages were within acceptable range as defined in BMR. |  |  |  |  |
|  | All the monitoring equipment’s/ instruments used in the processing were calibrated. |  |  |  |  |
|  | All the processing equipment used in the processing were calibrated and as per BMR. |  |  |  |  |
|  | Whether there were any malfunctioning of equipment or breakdowns during process. |  |  |  |  |
|  | Whether there were any failure of utilities (like power, Water, Compressed air, Steam etc.) associated with the process. |  |  |  |  |
|  | All the in-process checks were performed as per the defined frequency and the results were within acceptance criteria. |  |  |  |  |
|  | Was the operator trained or experienced / any new person was involved in the process |  |  |  |  |
|  | Was there any vendor change / Process change  |  |  |  |  |
|  | Was there any incident related to raw material.  |  |  |  |  |
|  | Measuring instrument, sensor were in working condition and calibrated. |  |  |  |  |
|  | Any other (To be specified)  |  |  |  |  |
|  | **Observations:** |
|  |  |
| ***Production Designee Name*** |  | ***Sign & Date*** |  |
|  | **Operator interview (If applicable):** |
|  |  |
| ***Operator (Name)*** |  | ***Sign & Date*** |  |
|  | **Investigation conclusion (Manufacturing Process):** |
|  |  (Attach separate report for Root cause, CAPA and Conclusion)Designee-Production:Sign / Date: |
|  | **Conclusion by QA:**  |
|  | Assignable root-cause/ most probable-cause Identified.Assignable root-cause not identified.(Status of Phase-II A Investigation: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_)Designee-QA:Sign / Date: |
|  | Impact assessment (If assignable root-cause identified): |
|  | Designee-QA:Sign / Date: |
|  |  Corrective Action & Preventive Action (If assignable root-cause identified) |
|  | CAPA Reference number: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Head/Designee-QA:  Sign & Date: |
| **Phase-II investigation closure** |
| Comments: |
| ***QA Designee Name*** |  | ***Sign & Date*** |  |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| S.No. | Date  | Nonconformance Number | Name of RM/ PM | Batch / Lot Number | Material Receipt Date | Reference OOS no.  | Communicated on | Vendor response date | Closed by (Sign & Date) |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |

|  |  |
| --- | --- |
| Vendor Acknowledgement No. : |  |
| Name of RM/PM : |  |
| Material Code : |  |
| Vendor Batch No. / Lot No. : |  |
| Date of Receipt of RM/PM : |  |
| Reference Document no.  |  |
| Details Of Non-conformance :(if required additional sheet can be attached) |  |
| Immediate action taken : |  |
| Comment by QA : | \_\_\_\_\_\_\_\_\_\_\_\_\_\_Sign & Date |
| Non-conformance sent to Purchase dept. on : | **\_\_\_\_\_\_**\_\_\_\_\_Sign & Date |
| Response Received on : |  |
| Reviewed by QA Executive/Designee : | \_\_\_\_\_\_\_\_\_\_\_\_\_\_Sign & Date |
| Closing Remarks\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Closed By QA /Designee(Sign and Date) |

|  |  |  |  |
| --- | --- | --- | --- |
| **OOS Reference No** |  | OOS Date |  |
| Initiated on |  | Due date |  |
| **Name of the Product** |  |
| Stage |  | Batch No |  |
| Material Code |  | Plant No |  |
| **OOS Description** |
|  |
| Conclusion of Phase-I & Phase-II |
|  |
| ***QA Head******Designee Name*** |  | ***Sign & Date*** |  |

|  |  |
| --- | --- |
|  | **Notification to Cross functional Teams** |
| 1.1 | **Department** | **Process Development** |
| Communicated on/ by |  |
| Remarks: |
| Name Sign & Date: |  |

|  |  |  |
| --- | --- | --- |
| 1.2 | ***Department*** | ***Analytical Development*** |
| Communicated on/ by |  |
| Remarks: |
| Name Sign & Date: |  |
| 1.3 | **Department** | **Others \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** |
| Communicated on/ by |  |
| Remarks: |
| Name Sign & Date: |  |
| * 1. ***Justification for extension of time-lines:***
 |
|  | **Justification:**  |
| Proposed Time-lines: |
| **QA Designee Name:** |  | **Sign & Date:** |  |
| ***Comments by QA Designee:*** |
| **QA Designee Name:** |  | **Sign & Date:** |  |
|  | **Follow-up by QA:** |
|  | **Date** | **Status of work completion** | **Sign (department)** | **Sign (QA)** |
|  |  |  |  |
|  |  |  |  |
| 2.0 | Conclusion by QA: Designee-QA:Sign / Date: |
| 3.0 | Corrective Action & Preventive Action (If assignable root-cause identified)CAPA Reference number: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Head/Designee-QA:  Sign & Date: |
| ***4.0 Disposition of the Batch:*** |
|  |

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 | Batch can be **released** as the reported OOS shall be considered to be Invalid. |
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 | Batch shall be **reprocessed**. |
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 | Batch can be **diverted** to \_\_\_\_\_\_ Market, as per the Specification \_\_\_\_\_\_\_\_\_\_\_\_\_. |
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 | **Customer** shall be notified. |
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 | **Stability study** can be Continued/ Discontinued. |
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 | Product **retest** shall be assessed. |
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 | Batch shall be **destroyed**. |
| **QA Head/Designee****(Name/Sign & Date)** |  |
| Closure Comments: |
| ***QA Designee Name*** |  | ***Sign & Date*** |  |

|  |
| --- |
| 1. ***Re-sampling (Phase-II):***
 |
|  | Proposed plan: |
| Justification for re-sampling: |
| ***Proposed by QA:*** |  | ***Approved by Head QA/Designee:*** |  |
| Results of re-sampled analysis:Observations:CAPA: |
| ***Supervisor*** ***Sign & Date*** |  | ***Head of QC/ Designee Sign & Date*** |  |
| *Comments by QA:* |
| ***Head of QA/ Designee*** ***Sign & Date*** |  |
| 1. ***Investigation Conclusion & Re-testing:***
 |
|  | **Re-testing :**

|  |
| --- |
| Name of the Analyst (Second analyst): |
| ***Measurements*** | ***Result*** | ***Conclusion******(Complies/Does not comply)*** | ***Specification*** |
| I |  |  |  |
| II |  |  |
| III |  |  |
| Average |  |  |
| Observation: |

Final Reporting Result: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (Status\_\_\_\_\_\_\_\_\_\_\_\_\_\_). |
| ***Supervisor*** ***Sign & Date*** |  | ***Head of QC/ Designee Sign & Date*** |  |
| *Conclusion by Head QA/Designee:****Sign & Date***  |