DECODING PHARMA

QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
Title: Handling of Out of Specification Results	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

1.0 OBJECTIVE:

To lay down the procedure for handling of out of specification (OOS) laboratory test results in Quality Control Department to ensure that the OOS test results are properly investigated.

2.0 SCOPE:

2.1 This SOP is applicable to all the OOS results, which are obtained for Raw Material, Finished Products and Stability samples.

2.2 This SOP is not applicable for OOS to tests like Bulk density, Sieve analysis, Particle sizing and other physical parameters.

2.3 This SOP is not applicable for incomplete analysis (due to malfunction of equipments) where results are not derived.

3.0 RESPONSIBILITY:

Officer /Executive – Quality Control

Head - Quality Control

Head - Quality Assurance

4.0 DEFINITION(S):

4.1 **Evaluation samples:** Samples, which are of deviation batch, recovery batch, market complaint, pre-shipment sample, study and trial purpose.

4.2 **Questionable results:** A results, which is not confirm but out of limit at the first analysis considered as questionable and need to be investigated.

4.3 **Assignable cause:** A cause that has been identified as the reason to invalidate a questionable test result. The assignable cause is conclusion derived from direct or indirect evidence found during the investigation process, from the interpretation of analytical data or a combination of both.

NON assignable cause

4.4 **Investigation :** An investigation jointly conducted by an investigator and the analyst .The purpose of the analytical investigation is to verify that a valid result was obtained or discover what occurred to explain an invalid result .It must be thorough enough to discover any analyst or equipment error, if one occurred,

4.5 **OOS:** An unacceptable result that is out come of analysis .The result which does not meet the pre-established specification of test product shall be termed as OOS (out of Specification) result.

4.6 **Re-analysis:** Repeat the analysis by using one or more steps of test method. Preparation from the

original sample. A reanalysis may include the preparation of fresh standards and /or other test reagents as appropriate.

4.7 **Re-sampling:** A fresh sample is withdrawn by repeating the sampling procedure for product or material.

4.8 **Average Value:** Mean value of the results.

5.0 PROCEDURE:

5.1 In case of questionable result, analyst shall not destroy the sample preparation / solution till final disposition of analysis.

5.2 In case of sample preparation/ solution is not available due to solution stability purpose or less quantity, second time sample preparation can be allotted by head QC or designee for the analysis.

5.3 Refer Annexure-V (flow chart for OOS investigation) for proceeding the preliminary investigation and OOS identification.

5.4 In case, an out of specification result is generated for dissolution/ Drug release, uniformity of dosage units, weight variation, disintegration and friability test, preliminary investigation shall be carried out as per steps given under "Preliminary investigation and OOS identification" (refer point 5.5)

5.5 Preliminary Investigation and OOS Identification.

5.5.1 In case of observation of questionable results, analyst shall report to Head QC or designee.

5.5.2 Head QC or designee shall take following actions :

- Issue the photocopy of "Preliminary Investigation form"(Annexure II) to the analyst and make entry in the "Preliminary Investigation form issuance register" (Annexure I)
- Numbering system for "Preliminary investigation Form No" shall be PI/XXX/YYYY, where PI stands for preliminary investigation, XXX stands for serial number and YYYY stands for Current year.
    - Ex: First Preliminary Investigation form in year of 2007 shall be given form No. as PI/001/2007.)
    - Make entries in "Preliminary Investigation form issuance register" for

"Sr. No.", "product /Item" (Name of "product" in case of drug product and "item" in case of raw material) " Batch No./AR No." (Batch No. in case of drug product and AR Number in case of raw material), "Stage", "Test", "Form No", "Issued to" (Sign of analyst by whom questionable result generated) "Issued By / Date" (Sign of Head QC or designee), "received By/date" (Sign of Head QC or designee after the receiving the completed form) and

"Remark" (Any other information which needs to mentioned other than above).

- Make entry in issued "Preliminary Investigation form" for "Form No", "Issued By/ Date", "Issued to" (Name of analyst-1), "Product /Item", "Batch No./AR No.", "Stage", "Test", "Results", "Limit", "Analyzed By", "Date" and "Reference" (Reference of raw data document) based on the raw data and preliminary investigation form issuance register
- Carry out the investigation as per the checklist but not limited to check list provided in the form.
- Discuss following with the analyst as first investigation for the following but not limited to :
- Sample preparation
- Sample dissolution/temperature/sonication
- Sample weighing/dilution techniques
- Sample storage
- Glass ware condition
- Instrument operation and malfunction (if any during analysis)
- Enter the findings based on investigation and discussion with analyst-1 in "Observation" column of "Preliminary Investigation form" and outcome of discussion with analyst.
- Enter the comments into summary of investigation based on previous experience, raw data checking and discussion with analyst.

5.6 Stage I (assignable cause)

(A) In case of any assignable cause identified, mention in the form and allot the reanalysis with either final solution/stock solution/or with the same sample (which ever is used in initial analysis) preparation to the same analyst (Analyst-1) who has analyzed the initial sample.

- Enter the results into the form and conclude :
- If sample passes, complete the investigation of the invalidation of the discrete OOS results, and release the product/ item for further process
- If sample fails, then assign the OOS and proceed as described in step 5.7

(B) Stage II (non-assignable cause)

During preliminary investigation, if assignable cause is not identified then sample preparation needs to be investigated. Head QC or designee shall instruct to analyst-2 to analyze the solution

prepared by analyst –1 by diluting stock standard / sample solution to the final solution or analyze the final standard / sample solution aliquot.

Enter the results into the form and conclude :

- If sample passes, proceed as follows:
- Analyze the new portion of the original sample (which ever is used in initial analysis) in triplicate by analyst –1.
- If all three analyses on the sample taken above passes (within the specification limit), complete the investigation of the initial failure and invalidation of the discrete OOS results. Attach the investigation report with Primary investigation form.
- Take the mean of above four results (analysed in step 5.7 by analyst –2 & step 5.7.1.2 analysed by analyst-1) and report the results.
- If sample fails, then assign the OOS no. and proceed as per point 5.7
- If assignable cause is not identified for tests like dissolution/ Drug release, uniformity of dosage units, weight variation, disintegration and friability test, perform the cross function investigation as per step 5.8 first and then proceed as per applicable respective Pharmacopoeia guidelines or criteria.
- If sample passes, as per acceptance criteria defined in respective pharmacopoeia, then complete the investigation of the OOS results, and release the product/ item for further process.
- Sample does not comply, then complete the investigation of the OOS results/ product failure, and reject the product.

5.6.(C)

- **Cross functional investigation**

(a)

- In case of non-assignable cause during the preliminary investigation, Head QC or designee shall inform to QA for the cross-functional investigation and issue the OOS investigation form.
- QA shall review but not limited to the followings in consultation with
- Concerned department(s):
- Batch manufacturing record review
- Equipment review
- Manpower review (training)
- Material review
- Process trends

- Any abnormal observation

(b) In case error is identified which leads towards the questionable results, then complete the investigation (as per procedure for handling of non - conformances) for the confirmation of the OOS results/ product failure, and close the further investigation of OOS. Appropriate decision shall then be taken by head quality assurance for further process / rejection of product/material

(c) In case error is identified but not leads towards the product failure, then assign the OOS no. and proceed as per step 5.7

(d) In case of tests like dissolution/Drug release, uniformity of dosage units, weight variation, disintegration and friability test etc., then review the results as per applicable respective Pharmacopoeia guidelines or criteria. Appropriate decision shall then be taken by head quality assurance for further process /rejection of product.

(e) In case error is not identified then assign the OOS no. and proceed OOS investigation as per step 5.7

(f) In case of tests like dissolution/Drug release, uniformity of dosage units, weight variation, disintegration and friability test etc., then review the results as per applicable respective Pharmacopoeia guidelines or criteria. Appropriate decision shall then be taken by head quality assurance for further process/rejection of product.

(g) QA shall intimate to the QC head or designee about the findings of the above cross-functional investigation.

5.7 OOS Investigation

5.7.1 Head QC or designee shall take following actions :

5.7.2 Issue the photocopy of “Out of specification investigation form” (Annexure -4) to the analyst and make entry in the “Out of specification form issuance register” (Annexure- 3)

5.7.3 Numbering system for “Out of specification form” shall be OOS/xxx/yyyy, where OOS stands for out of specification, xxx stands for serial no. and yyyy stands for current year (e.g. First OOS form in year of 2022 shall be given form no. as OOS/001/2022.)

5.7.4 Make entries in the “Out of specification form issuance register” for “Sr. No.”, “product /Item” (Name of “product” in case of drug product and “item” in case of raw material) “ Batch No./AR No.” (Batch No. in case of drug product and AR Number in case of raw material), “Stage”, “Test”, “Form No”, “Issued to” (Sign of analyst by whom questionable result generated) “Issued By / Date” (Sign of Head QC or designee), “received By / date” (Sign of Head QC or designee after the receiving the completed form) “Preliminary investigation number” and “Remark” (Any other information which needs to mentioned other than above).

5.7.5 Make entry in issued "Out of specification form" for "Form No", "Issued By/Date", "Issued to" (Name of analyst), "Product/Item", "Batch No./AR No.", "Stage", "Test", "Results", "Limit", "Analyzed By", "Date" and "Reference" (Reference of raw data document), and "Reference Preliminary Investigation Form No." (based on the preliminary investigation form) and shall follow the OOS form.

5.7.6 **Stage A (Testing of same sample with analyst-2 in triplicate)**

In case of sample does not comply in stage I and II of preliminary investigation then head QC or designee shall instruct analyst-2 to retest the new portion of the original sample in triplicate.

5.7.7 Enter the results into the form and conclude

(a) If sample complies (within the specification limit), proceed for stage B

(b) If sample does not comply, Head QC or designee shall give scientific rationale/justification for re-sampling and consult with Head-QA for proceeding for re-sampling.

After evaluation of the justification, the instruction will be given for re-sampling and proceeding further as per Stage-C of the OOS investigation.

If the justification for re-sampling is not appropriate, then complete the investigation of the confirmation of the OOS results/ product failure. A decision shall then be taken by Head Quality Assurance for further process / rejection of product/ material

5.7.8 **Stage B (Re-analysis of same sample with analyst-3 in triplicate)**

In case of sample comply in stage A of OOS investigation, then head QC or designee shall instruct to analyst-3 to retest the same sample in triplicate.

5.7.9 Enter the results into the form and conclude:

If all samples comply (within the specification limit), complete the investigation of the initial failure and invalidation of the discrete OOS results. Attach the investigation report with OOS form, and release the product/ material for further process.

- For reporting the results, take the mean of six analysis (analyzed in step 5.10 by the analyst-2 in triplicate & 4.11 by the analyst-3 in triplicate) and report.
- If any of the sample does not comply, then follow the procedure given in step –5.10.3.

5.8 Stage C (Re-analysis of re-sample product/ material with analyst-1 and 2 or 3 in triplicate)

- In case of sample analysed by analyst-3 does not comply in stage B of the investigation or by analyst-2 in stage A of OOS investigation, then head QC or his designee shall instruct, analyst 1 and analyst 2 (or analyst 3) to analyze the re-sample product/material in triplicate.

5.8.1 Head QC or designee shall arrange for re-sampling of product/material after taking the prior approval of Head Quality Assurance (as per details given in step 4.10.3) in OOS from.

5.8.2 Sampling shall be carried out as per the relevant standard operating procedure.

5.8.3 Sampling quantity and sampling position shall depend upon the investigation and discretion of QC head.

5.8.4 Head QC or Designee shall fill the result in "Out of investigation form" in stage C after reviewing & checking the raw data, put the remark & initial/ Date, and conclude:

If all samples comply (within the specification limit), complete the investigation of the initial failure and invalidation of the discrete OOS results. Attach the investigation report with OOS form.

- For reporting the results, take the mean of six analysis (analyzed above by two analysts in triplicate).

A decision shall then be taken by Head Quality Assurance for release of the product / material for further process.

5.8.5 If any of the sample does not comply, then complete the investigation of the confirmation of the OOS results/ product failure, and reject the product/ material.

5.8.6 Head QC or designee shall attach all pertinent records and raw data with the OOS form. OOS form shall be given to Head Quality Assurance along with all the attachments / raw data for the review.

5.8.9 After review, Head Quality Assurance shall make conclusion in "Final conclusion" column for the final disposition of product/material.

NOTE: SOP is based upon draft USFDA guidelines

6.0 ABBREVIATION (S) :

Nil

7.0 REFERENCE(S)

NA

8.0 ANNEXURE (S) :

ANNEXURE –I – Preliminary Investigation form Issuance Register

ANNEXURE –II – Preliminary Investigation form

ANNEXURE –III – Out of Specification form Issuance Register

ANNEXURE –IV – Out of Specification Investigation form

ANNEXURE –V – Flow chart for OOS investigation

9.0 REVISION CARD

S.No.	REVISION No.	REVISION DATE	DETAILS OF REVISION	REASON (S) FOR REVISION
	00		-------	New SOP