STANDARD OPERATING PROCEDURE					
Department	**Quality Assurance**			**Copy No.**	
Title : SOP On Out Of Trend					
SOP No.	SOP/QA/GE/059	**Revision No.**	00	**Effective Date**	
Supersede No.	Nil	**Version No.**	Nil	**Next Review date**	

1. Purpose

To lay down a procedure for handling of out of trend

2. Scope

This SOP is applicable for all departments in Shri Bhavani Pharmaceuticals.

3. Role and Responsibility

Roles	Responsibility
Officer / Executive Quality Control	Responsible to evaluate the test results after complete analysis, inform to reporting authority for the out of trend results
Head Quality Control	Responsible to review the analytical data and identify any out of trend results by compare with the previous trends or pre-defined criteria for out of trend results & also ensure OOT results are evaluated and investigated as per the lay down procedure.
Head Quality Assurance	To participate in the out of trend results investigations, review the initial results & investigation.

4. Definitions

Terms	Definitions
Out of Trend	Those analytical results which are within specification /acceptance criteria but that

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(OOT)	does not follow the expected trend in comparison with previous results collected from past history or shown as unusual tendency

5. External References And Associated Documents

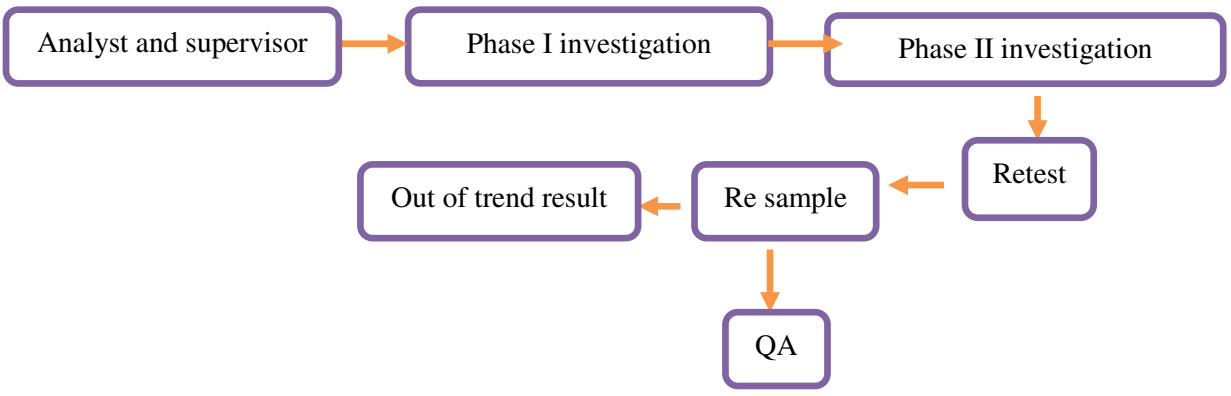
5.1 External References

External Document No.	Title
Not Applicable	**Not Applicable**

5.2 Associated Documents

Associated Document No.	Title
Not Applicable	**Not Applicable**

6. Process Overview



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7. Procedure

7.1 Phase I Investigation – Initial Investigation conducted by the analyst and supervisor using the laboratory investigation checklist. The investigation should be restricted to data/equipment/analysis review only and no re-testing

Examples of error

7.1.1 **Calculation Error**- analyst and supervisor to review, both initial and date correction

7.1.2 **Power outage**-analyst and supervisor document the event annotate "power failure analysis to be repeated" on all associated analytical documentation

7.1.3 **Equipment failure** – analyst and supervisor document the event annotate equipment failure, analysis to be repeated cross reference the maintenance record

7.1.4 **Testing error** – e.g. spilling of the sample solution incomplete transfer of a sample, the analyst must document immediately

7.1.5 **Incorrect Instrument Parameters-** e.g. 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

7.2 **Phase II Investigation -** Conducted when the phase I investigation did not reveal an assignable laboratory error. Phase II investigations are driven to determine whether there was a possible manufacturing root cause

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7.3 **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 retesting for the purpose of testing of product into compliance it's not acceptable

7.4 **Re-Sample-** 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. A resample must be discussed and agreed by QA

7.5 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

7.6 Out Of Trend (OOT) Result : Is generally a stability result that does not followed the expected trend either in compression with other stability batches or with respect to previous results collected during a stability study. However if the trends of starting materials and in process samples may be also yield out of trend data. The results are not necessarily OOS but do not look like a typical data point. OOT shall be determined on the basis of the data of previous batches or previous analytical data or aberrant data observed during the analysis. The result may be within the specification but not within the trends

7.7 OOT shall be determined on the basis of the data of previous batches or previous analytical data or aberrant data observed during the analysis. The result may be within the specification but not within the trends

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7.8 While performing the analysis if any OOT or aberrant data is observed then the analyst shall inform to the group leader and group leader shall conduct the phase I investigation for the OOT observation due to any laboratory error and record the investigation in the Annexure I

7.9 During QA review if any OOT data noticed, the same shall be notified to QC head for further investigation of confirmation of OOT result

7.10 In case of stability study, trending shall be considered based on the historical data received from exhibit, validation batches or as compared to the previous time point / other packs of same batch, other batch results

7.11 In case of raw material of aberrant data observed during the analysis as compared to the report of manufacture/supplier COA, Previous batch result or previous analytical data of retest material then out of trend investigation shall be carried out

7.12 In case of process samples, if result obtained in any stage is not comparable with analytical observation of previous stage of subsequent stage then out of trend investigation shall be carried out

7.13 In case of finished product, if result obtained in any stage is not comparable with analytical observation of previous batches (If applicable) other packs of same batch then out of trend investigation shall be carried out

7.14 **Methodology To Identification Out Of Trend Result(OOT):**

Following method shall be used for identifying outlier and out of trend result

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7.14.1 **Control charts:** This criterion of using control chart to identify the out of trend result shall be used for the test like assay and water content for blend and finished product

7.14.2 **Standard Limits:** The criteria using standard limits shall be applicable to related substances, impurities and degradation product for stability

7.14.3 Studies, exhibits batches, validation batches, and commercial batches. These limits shall be applicable for related substances. In API and finished product for which trend is not established

7.14.4 **Use of Control Charts**

7.14.4.1 For establishing the trend of existing products, data of batches manufactured for past 3 years shall be collected and subjected to statistical analysis

7.14.4.2 For new product, data from new first new 10 or minimum 5 released batches shall be considered including validation batches.

7.14.4.3 Batches manufactured with same process and manufactured under similar conditions / controls are only required to be considered for trending of data.

7.14.4.4 The collected data shall be statistically reviewed by QA and subjected to statistical trending

7.14.4.5 Following statistical parameters shall be used to establish the acceptable limits of variation

7.14.4.6 For Assay & Water Content, OOT shall be considered as + 3% from the lower limit and -3% from the upper limit

7.14.5 **Use of standard Limits**

7.14.5.1 In this approach, the OOTs are identified based on certain fixed or standard rules as described below. This approach is useful for identifying OOTs for impurities without doing any statistical treatment or where there is no much data available (new product / process) and for easy online identification of OOTs

7.14.5.2 **For Drug substance**

Impurity	Impurity limit	OOT limit
Individual Impurity	Less than 0.05%	NIL
Unknown impurity	0.05% - 0.10%	NIL
Identified impurity	0.05% - 0.10%	NIL
Total impurity	0.1% and above	20% of impurity limit

7.14.6 **Phase I investigations: Related to analytical laboratory**

7.14.6.1 This investigation is to determine if there was an error in the laboratory during testing and has no impact on the specification of the product manufactured

7.14.6.2 The preliminary investigation shall be done as per the checklist during Phase I investigations

7.14.6.3 If the preliminary investigation does not reveal any error then the Supervisor/ Group leader shall conduct a full-fledged laboratory investigation as described under

7.14.6.4 The Supervisor / Group leader performing the laboratory investigation shall record his observations. This report shall be elevated & signed off by the Head QC or this Designee

7.14.7 Laboratory Investigation shall include but are not limited to the following

7.14.7.1 Analyst error

7.14.7.2 Calculation error

7.14.7.3 Weighing error

7.14.7.4 Dilution error

7.14.7.5 Instrument performance error

7.14.7.6 Non compliance to Critical steps during the analysis

7.14.8 **Evaluation of repeat analysis**

7.14.8.1 If anyone of the retesting shows an outlier result or out of trend result, then this confirms that there was no laboratory error during the performance of the analysis & no assignable laboratory error is confirmed. In such cases, Head QA or his designee shall recommend for the release of batch

7.14.8.2 The results for both analysis meet the specification and the results are well within the prescribed trend then OOT shall be invalidated and Head

QA or designee shall recommended for the release of batch. The results shall be recorded as described under "Reporting of the results"

7.14.8.3 If repeat analysis observed is not complying with specification then investigation shall be done as per SOP for out of specification investigation

7.14.9 **Reporting of the results:** Average of first two preparation of the first analysis shall be repeated with the highest total impurity result in two preparations

7.14.10 **Non Assignable Cause:** If a clear assignable cause is not established during laboratory investigation then phase II investigation be initiated

7.15 **Phase II investigation:**

7.15.1 Phase II investigation shall be carried by the Head Manufacturing or his Designee and Quality Assurance. They shall consult if required with Warehouse, QC, Engineering and R&D, for evaluating the probable root cause of the OOT results related to manufacturing

7.15.2 This investigation shall have complete review/ evaluation of potential causes during manufacturing process for OOT results. This evaluation shall include following but not limited to

7.15.3 Evaluation of Batch Production Records and related records for the subject batch

7.15.4 The manufacturing process as per the batch record instruction and process validation data.

7.15.5 Results of the In-process steps testing

7.15.6 Verification of the physical stock of material used in the batch

7.15.7 Verification of environmental conditions during storage of raw material, dispensing, manufacturing and packing of batch

7.15.8 Verification of dispensing procedure

7.15.9 Operating error

7.15.10 Equipment failure

7.15.11 Utility failure

Calibration error

Operator's interview

7.15.12 Cleaning, Sanitization, gowning procedure, personnel hygiene, environmental conditions shall be reviewed in case of OOT observation with respect to bio-burden/ microbiological analysis.

7.15.13 Head Manufacturing or his Designee shall prepare an investigation repot with his recommendation and conclusion after evaluating the deviations or errors during manufacturing process and he/ she shall provide the conclusion and this shall be evaluated and proceed by Head QA or his Designee.

7.15.14 Head QA or his Designee shall review and evaluate Phase I and Phase II manufacturing investigation findings.

7.15.15 If an assignable cause is related to manufacturing process. The CAPA shall be initiated in consultation with R&D and RA and the batch disposition shall be done.

7.15.16 **If non assignable cause is identified**: In case, during Phase II the investigation for the OOT does not reveal any assignable cause or where the results of the investigation inconclusive. Head QA or his designee shall release or reject the batch based on the evaluation as mentioned under batch description.

7.15.17 In Microbiology if OOT is observed with regards to water analysis, environmental monitoring and bio-burden on finished product sample or any other sample, Laboratory investigation shall be initiated which included but not limited to review of all the data related to sterilization of articles used in testing. Review of area monitoring record of testing area, review of testing procedure analyst. If laboratory error is established proceed as per instructions in the section "Assignable Cause in Laboratory". If no laboratory error is observed phase II investigation shall be initiated. Impact analysis to be done for any failure observed in microbiological failures with recommended CAPA.

7.15.18 No averaging of results for compliance to specification shall be done while reporting results of analytical set observations. In case of assay and related substance tests, one sample preparation shall be considered as single analysis.

7.15.19 Process records shall be evaluated.

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7.15.20 In case of OOT pertaining to stability samples, observation of previous stability test points shall be evaluated with reference to OOT observation. Wherever applicable forced degradation data of method validation shall be evaluated with reference to the subjected OOT. Any deviation, incident and execution of stability chamber and sample handling shall evaluated as a part of investigation and CAPA

7.15.21 Re-sampling shall be authorized by Head QA in the following cases

7.15.21.1 Where insufficient quantity of the original sample is taken from the batch for the analyst.

7.15.21.1.1 Where the sample was contaminated before the analysis.

7.15.21.1.2 Where the sample is degraded before analysis.

7.15.21.1.3 Sample intended for bio burden determination.

7.15.21.1.4 Sample for TOC (Total organic carbon) analysis.

7.16 **Batch Disposition**

7.16.1 If no laboratory or calculation errors are identified in the phase I and phase II there is no scientific basis for invalidating initial OOT results in favor of within trend retest results then the original out of trend shall be reported (in all QC documents and certificates of analysis) and all data shall to be considered in batch release decisions.

7.16.2 The batch release / rejection decision shall be taken considering following but not limited to:

7.16.2.1 Product history and APQR review

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7.16.2.2 Any previous OOS and OOT observed

7.16.2.3 Impact assessment

7.16.2.4 Stability trend

7.16.2.5 Monitoring stability of the batch investigated for a stipulated period and condition as applicable

7.16.3 The entire document related to OOT investigation shall be complied by QA and reports of all the investigation shall be maintained by QA department after closer of OOT

7.16.4 After conclusion and QA sign off, if the batch is rejected then its disposition shall be initiated as per SOP of handling rejected material.

7.16.5 Disposition of the material shall be determined by the Head QA or his designee.

7.17 **Numbering and Filling of OOT:** Each OOT report shall be allotted as sequence number of eight character i.e. OOTYYXXX

Where

OOT – Out of Trend,

YY – Last two digits for year

XXX – Serial No. 01, 02, 03… so on.

8. Abbreviation

GE : General

QA : Quality Assurance

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SOP : Standard Operating Procedure

OOT : Out of Trend

APQR : Annual Product Quality Review

9. Training Requirements

Trainer : Quality Assurance Department

Trainees : Employee of Quality Assurance Department

Period : 30 Minutes

10. Distribution

Head QA : 01 Master Copy

Quality Assurance Department : 01 Copy

QC Department : 01 Copy

11. Attachments

Annexure - I : OOT Investigation Form. Format No. SOP/QC/GE/059-00-F1

Annexure - II : OOT Register. Format No. SOP/QC/GE/059-00-F2

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12. Revision History

S. No.	SOP No	Revision No.	Reason for revision	Change Control No.	Effective date
1	SOP/QA/GE/059	00	New SOP		

13. Space for Review, No Change Stamp

If no Change in the periodic review of SOP, this stamp shall be used

Reviewed, No Change	
Date	
Next review Date	
Reviewed by	
Approved by (QA Head)	

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Reviewed, No Change	
Date	
Next review Date	
Reviewed by	
Approved by (QA Head)	

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Annexure I :OOT Investigation Form

Date : OOT No.:

Name of the sample/product under investigation:

Batch No.: GRN No : Analytical No :

Stage of Mfg.: Mfg. Date: Exp. Date:

1.0 Details of Laboratory results :

Test/Parameter	Result	Specification/Limit	OOT (tick '✓' as applicable)	
			Inter-batch	Intra-batch

Intra-batch trend (if applicable) :

Sign/Date: _____ _____

Chemist HEAD QC

2.0 Laboratory Investigation (by Head QC)

Analysis verification done:

Comment:

HEAD QC

3.0 Review of Batch Documents:

Head Production

Annexure I :OOT Investigation Form

4.0 Investigation with Respect to GMP/Equipment and Calibrations:

Head Production

Head QA

Annexure I :OOT Investigation Form

5.0 Identification of cause : Cause identified : **Yes** ☐ **No** ☐

Head QA

Annexure I :OOT Investigation Form

6.0 Cause identified :

6.1 Details of cause :

Sign / Date of Head QC : _____

6.2 Confirmation plan :

Same sample ☐ New sample ☐

Reason for new sample :

Sign / Date : _____ _____

Head QC Head QA

6.3 Confirmation of Result for Analysis :

Sample passes the test : Yes ☐ **No** ☐

Sign / Date : _____ _____

Head QC Head QA

Annexure I :OOT Investigation Form

7.0 In-depth investigation :

7.1 Further investigation :

Review of Batch record ☐ QC record ☐

Material source ☐ Trend of previous batches ☐

Results of Investigation :

Sign / Date : _____ _____

Head QA Head QC

7.2 Confirmation for analysis plan: (resampling, re –analysis in duplicate by different chemist, parallel analysis using approved batch, etc.)

Sign / Date of Head QC : _____

7.3 Approval for re-sampling :

Sign / Date : _____ _____

Head QC Head QA

7.4 Results of re-analysis :

Sign / Date of Head QC : _____

Investigation summary :

OOT is confirmed : **Yes** ☐ **No** ☐

Sign/Date: _____ _____

Head QC Head QA

Annexure I :OOT Investigation Form

8.0 Corrective action / Preventive action plan :

Corrective action required : Yes ☐ No ☐

Preventive action required : Yes ☐ No ☐

Sign / Date : _____ _____

Head QC Head QA

Annexure II:OOT Register

Sr. No.	Date	OOT No.	Name of product	Batch No.	Stage of Mfg.	Mfg. date	Exp. date	OOT results	CAPA No	Closing Date/ Sign QA