STANDARD OPERATING PROCEDURE	
Department: Microbiology	**SOP No.:**
Title: Handling of Microbial Excursion in Water and Environment	**Effective Date:**
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1.0 OBJECTIVE:

To lay down the Procedure for Handling of Microbial Excursion in Water and Environment.

2.0 SCOPE:

This SOP is applicable for excursions from alert/action/specified limits as defined in the environmental monitoring program for all dosage from (sterile and non sterile) and aseptic manufacturing areas and microbial excursions from alert/action/specified limits of purified water, WFI and Pure steam condensate in Microbiology Section of Quality Control Laboratory.

3.0 RESPONSIBILITY:

Officer / Executive – Microbiology

4.0 ACCOUNTABILITY:

Head – QC

5.0 ABBREVIATIONS:

BET	: Bacterial Endotoxin Test
CAPA	: Corrective and Preventive Action
Cfu	: Colony Forming Unit
GPT	: Growth Promotion Test
HVAC	: Heating Ventilation and Air Conditioning
HQC	: Head Quality Control
NA	: Not Applicable
No.	: Number
PSC	: Pure Steam Condensate
QA	: Quality Assurance
QC	: Quality Control
RH	: Related Humidity
SOP	: Standard Operating Procedure
TVAC	: Total Viable Aerobic Count
TMC	: Total Microbial Count
TFC	: Total Fungal Count
Temp.	: Temperature
WFI	: Water for Injection
ΔP	: Differential Pressure

6.0 PROCEDURE:

6.1 DEFINITION:

6.1.1 Standard Operating Procedure (SOP): A written authorized procedure, which gives instructions for performing operations.

6.1.2 **Microbiological Identification:** Biochemical characterization of isolated colonies to determine the isolate genus and where feasible and appropriate the species.

6.1.3 **CAPA:** Corrective and Preventive action, a systematic approach that includes actions needed to correct (correction), prevent recurrence ("Corrective Action"), and eliminate the cause of potential non conforming product and other quality problems (preventive action).

6.1.4 **Alert Limit:** An established microbial or airborne particle limit giving early warning of potential drift from normal operating conditions and triggers appropriate scrutiny and follow-up to address the potential problem. Alert limit are always lower than action limit.

6.1.5 **Action Limit:** An established microbial or airborne particle limit that, when exceeded, should trigger appropriate investigation and corrective preventive action based on the investigation.

6.1.6 **Specified Limit:** An specified microbial or airborne particle limit that, when exceeded, should trigger appropriate investigation and corrective action and preventive action based on the investigation.

6.1.7 **Immediate action:** A response taken to an excursion.

6.1.8 **Corrective Action:** Action to eliminate the cause of a detected nonconformity or other undesirable situation.

6.1.9 **Preventive Action:** Action to eliminate the cause of a potential nonconformity or other undesirable situation.

6.1.10 **Critical Area:** An area designed to maintain sterility of sterile materials. Sterilized product, containers, closures and equipment may be exposed in critical areas.

6.1.11 **Colony Forming Unit (cfu):** A microbiological term that describes the formation of a single macroscopic colony after the introduction of one or more microorganism to microbiological growth media. One colony forming unit is expressed as 1 cfu.

6.1.12 **Laboratory error:** An error associated with the performance of a test procedure or due to laboratory instrument failure.

6.1.13 **Hypothesis/Investigative Testing:** Testing is 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 /extraction; and potential equipment failures etc. Multiple hypotheses can be explored.

6.2 PROCEDURE:

6.2.1 If there is any excursion observed in environmental monitoring and water samples microbiologist shall initiate the intimation as per **Annexure-VI** (Notification of Excursion) to QA.

6.2.2 **Notification Criteria:** Intimate for alert/action/specified limit excursion when:

- Alert limit is exceeded

- Action limit is exceeded
- Specified limit is exceeded

6.2.3 If microbial result exceeds the alert limit, constitute a warning and do not necessary require a corrective action. However, sampling point shall be monitored for three consecutive days.

6.2.4 Water Sampling shall be done from the affected point(s), generation, storage and return loop sampling point.

6.2.5 If water system microbial result exceeds action limit, an immediate corrective action shall be taken to bring the process back to normal operating range.

6.2.6 In case alert limit excursions observed three times in succession from the same location, same shall be treated as action limit excursion.

6.2.7 In case of any excursion observed from the microbial alert/action/specified limits in Environment monitoring and water samples; inform concerned department Manager/Designee, Quality Control Head/Designee, Quality Assurance Head/Designee, and Production Head/Designee through **Annexure-VI** (Notification of Excursion).

6.2.8 Executive/Officer-QA shall enter the details of excursion in excursion logbook.

6.2.9 Result of excursion in Water/Environmental Monitoring shall be documented in **Annexure-V** and Notification Number shall be generated by Quality Assurance.

6.2.10 Assign the Notification Number as follows;
"XX/TOE /YY/NNN"

Where,

XX: Denotes Facility Code

TOE: Denotes type of Excursion (EME for Environment Monitoring Excursion and WME indicating Water Excursion)

YY: Denotes year, i.e. 21 for 2021.

NNN: Denote to serial Number of allotted notification.

6.2.11 The product manufactured on the day when action limit exceeds shall be kept under hold till the completion of investigation. Head- Quality Assurance (Head-QA) shall take appropriate decision regarding the release/rejection.

6.2.12 After creation of a **"Notification of Excursion"** a sequential detailed Phase I Investigation process shall be conducted to determine the root cause.

6.2.13 Each step of the investigation process shall be clearly defined, including the number of replicates and the outcome of each investigational step shall be evaluated.

6.3 IDENTIFICATION OF THE MICROORGANISMS AND ITS SOURCE:

6.3.1 Micro flora observed during environmental monitoring and water samples shall be isolated as per SOP.

6.3.2 Convey the information about identified microorganism to the head of the affected area through Annexure-VII "Identification of microorganism".

6.3.3 Operating Manager Micro/Designee with the concerned Microbiologist shall conduct laboratory Investigation.

6.4 PHASE-I INVESTIGATION: (INVESTIGATION OF MICROBIOLOGY LABORATORY)

6.4.1 Initiate investigation as per **Annexure-VIII** (in case of three times alert excursion in succession from the same location/action limits in the settle plate samples, active air samples, contact plate samples (wall/floor/surface), swab samples, personnel monitoring samples and water testing) for determine the root cause (But not limited to).

6.4.2 Operating Manager Micro shall investigate for potential laboratory errors which can occur while analysis.

6.4.3 Check if samples were incorrectly stored at inappropriate temperature or containers are not properly closed or possibly not sampled in the correct designated sampling container.

6.4.4 Investigation in the microbiology laboratory shall a review of relevant records as per the **Annexure-VIII.** Record observation in the given space in 'Observation' column. Wherever the observations are not complying, give details.

6.4.5 Check for the sampling error, ensure the sampling is done as SOP correctly.

6.4.6 Quality Assurance shall give the approval for Re sampling of water samples.

6.4.7 Retesting shall be performed by two microbiologists.

6.4.8 The microbiologist who performed the original testing shall be preferably selected to perform reanalysis as one of the analyst.

6.4.9 If found that the person made error in any of the particular microbiological testing or aspects, training shall be imparted to the responsible person and necessary evaluation shall be taken.

6.4.10 If laboratory error found or any mechanical failure is identified inform to Head-Quality Assurances (Head-QA) to Document the corrective action taken and perform the re-analysis (if required).

6.4.11 If results of re-analysis are complying (within the appropriate limit individually), then the initial results shall be invalidated and substituted with the average of retest results, conclude the investigation with the probable root cause.

6.4.12 If cause of excursion is identified at laboratory limit, carry out corrective action and re-analyze (if required)

6.4.13 If cause of excursion is not identified at the laboratory limit, than forward the investigation report to Quality Assurance for investigation in the production or concerned area.

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6.5 PHASE-II INVESTIGATION: (INVESTIGATION OF MANUFACTURING FACILITY)

6.5.1 Phase-II investigation team shall be identified by Head QA from QA, QC, Microbiology, Production, Engineering, SME, etc. as appropriate.

6.5.2 On receipt of the Phase-I Laboratory Investigation report from microbiology lab, investigate the cause of excursion as per **Annexure-IX** "Investigation of Microbial Excursion in Water" (PW/WFI/PSG, and as per **Annexure-X** "Investigation of Microbial Excursion in Environment".

6.5.3 Phase-II Investigation will include review of following records (but not limited to):

- Cleaning and sanitization
- Changing of filters/ regeneration records
- Disinfectant qualification record
- Area cleaning sanitization record
- Personnel qualification record
- Area Qualification reports
- HVAC qualification
- Storage and distribution
- Pretreatment and purification system and document of production parameters
- Other checks on the generation and distribution system.

6.5.4 Identify the root cause or most probable cause.

6.5.4.1 Executive/Officer-Microbiology, Head QA and Head production will make complete review of trend data (Environment or Water) and other information & comments regarding the trend data.

6.5.4.2 Based on the location of excursion and the type of sample, following are the suggested additional investigational checks but not limited to:

- Review aseptic technique of personnel.
- Evaluate mechanical equipment in area as possible source of contamination.
- Evaluate integrity of the room (e.g. peeling paint, cracks in ceiling, walls and floor)
- Investigate for possible sources of contamination.

6.5.4.3 If the investigation reveals the source or probable source of contamination, identify the root cause and plan appropriate corrective & preventive action.

6.5.4.4 If cause for excursion cannot be identified and excursions are occurring repeatedly, check the integrity of filters of the HVAC system of the affected area. An aseptic process stimulation (media fill) may be required.

6.5.4.5 If production is discontinued under impact assessment, it shall be commenced once the environmental results of the aseptic processing area/personnel are within the alert/action limits.

6.5.5 Investigation report shall be closed within 30 working days of its initiation. In case the report is not closed, an interim report shall be prepared with the justification for extension and new proposed timelines. Fill Extension form as per **Annexure-XI**. If any extension required.

6.5.6 Corrective Action and its implementation for Microbial Excursion in Water:

6.5.6.1 Plan appropriate corrective action such as flushing of the storage tank and the distribution loop, sanitization of the storage tank and distribution loop, quarantining the product, Area cleaning and fumigation etc.

6.5.6.2 After implementation of corrective action, collect samples (if required) from the particular usage point, return and supply of the water storage and distribution system and send it for analysis.

6.5.6.3 Record the details in the respective sampling log/register.

6.5.6.4 Based on the QA approval water usage may be stopped in the production to identify the failure and any further risk to the product.

6.5.6.5 If the re-sample of water taken meets the requirements of the test within the limits appropriate for the parameters. Resume the usage of water/steam.

6.5.6.6 If the sample still fails, plan further corrective action which may include checks and sampling at the pre-treatment stages and the generation and purification stages.

6.5.6.7 After appropriate corrective action, again sample from the same user point, return and supply of the storage and distribution system.

6.5.6.8 Based on the impact assessment, the sampling location can be increased.

6.5.6.9 If the results of retesting is complying (Within the appropriate limits), usage of water can resumed.

6.5.6.10 Appropriate decision regarding the release/rejection of the product manufactured on the day of excursion shall be taken by Head- Quality Assurance (Head-QA).

6.5.6.11 Provide the details of the investigation in chronological order. Assess the impact of water used during the period of excursion.

6.5.6.12 Any discussion that review data and make recommendations should be documented.

6.5.7 Corrective Action and its implementation for Microbial Excursion in Personnel Monitoring:

6.5.7.1 When the results from personnel monitoring and finger dabs are found to exceed alert(three times) or action limit and objectionable organisms are recovered when identified as per identification of isolates SOP, record the detail with appropriate operator/ personnel name in specific format attached with environmental monitoring reports and inform to production department/concern department.

6.5.7.2 If a person exceeds action limit, he/she shall not be allowed to enter the critical area and shall be re-qualified as per respective SOP and shall be only allowed to enter after successful completion of qualification program.

6.5.8 Corrective Action and its implementation for Microbial Excursion in Environment Monitoring:

6.5.9 If the notification for Environmental Monitoring results exceeding alert for three consecutive days or action limit then based on sampling location (Critical/Non-critical) further decision for stopping of production can be taken by Head-Quality Assurance (Head-QA) and appropriate corrective action shall be taken as given below (but not limited to).

- Extensive cleaning and sanitization with disinfectant.
- Fogging of area if required
- Re-training/Qualification of the personnel if count are exceeding in personnel monitoring.

6.5.10 If production is stopped, production activity shall be resumed after getting satisfactory results for 3 consecutive days of the environmental monitoring.

6.5.11 If the objectionable organism is repeatedly identified, appropriate corrective action shall be taken as given below (but not limited to).

- Source of contamination to be studied.
- Possibility of impact on product in filling areas.
- Extensive mopping with disinfectants. If appropriate, disinfectants with specific activity such as sporocidal can be used.
- Fumigation of area.
- Re-training & Qualification of the personnel if recovered in personnel monitoring.

6.5.12 If the results of Environmental monitoring for 3 consecutive days found satisfactory production activity shall be resumed.

6.5.13 Appropriate decision regarding the release/rejection of the product manufactured on the day of excursion shall be taken by Head- Quality Assurance (Head-QA).

6.6 TRENDING OF EXCURSION RESULTS:

6.6.1 Prepare the trends of Excursion on yearly basis by QA with Bar / Pie chart for better understanding to identify contributory factor causing Excursion test results i.e. Analyst, Instrument, Product/Material, Inconclusive for review and recommendation as per format in “Trending of Excursion Data” as shown in **Annexure –XII**.

7.0 ANNEXURES:

ANNEXURE No.	TITLE OF ANNEXURE	FORMAT No.
Annexure-I	Flow chart for Microbiological Monitoring Excursions	
Annexure-II	Flow chart for Investigation of Environment Monitoring Excursion.	
Annexure- III	Flow Chart for investigation for Water Excursion (TVAC)	

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Annexure- IV	Flow chart for investigation for water excursion (Bacterial Endotoxin Test)	
Annexure-V	Result of Excursion in Water/Environment/Personnel Monitoring	
Annexure- VI	Notification for Excursion	
Annexure-VII	Identification of Microorganism	
Annexure- VIII	Investigation of Microbial Excursion in Water/ Environment	
Annexure- IX	Investigation of Microbial Excursion in water (PW/WFI/PSG/Raw). (Phase-II Investigation)	
Annexure- X	Investigation of Microbial Excursion in Environment. (Phase-II Investigation)	
Annexure- XI	Extension form for Investigation of Microbial Excursion in water / Environment.	
Annexure- XII	Trending of Excursion Data	

ENCLOSURE: SOP Training Record

8.0 DISTRIBUTION:

- Controlled Copy No. 01 — Quality Assurance
- Controlled Copy No. 02 — Microbiology
- Master Copy — Quality Assurance

9.0 REFERENCES:

- USP Chapter No. 1116
  PDA TR#13

10.0 REVISION HISTORY:

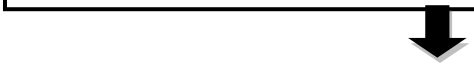
CHANGE HISTORY LOG

Revision No.	Change Control No.	Details of Changes	Reason for Changes	Effective Date	Updated By

ANNEXURE I

FLOW CHART FOR MICROBIOLOGICAL MONITORING EXCURSIONS

Observation and Reporting



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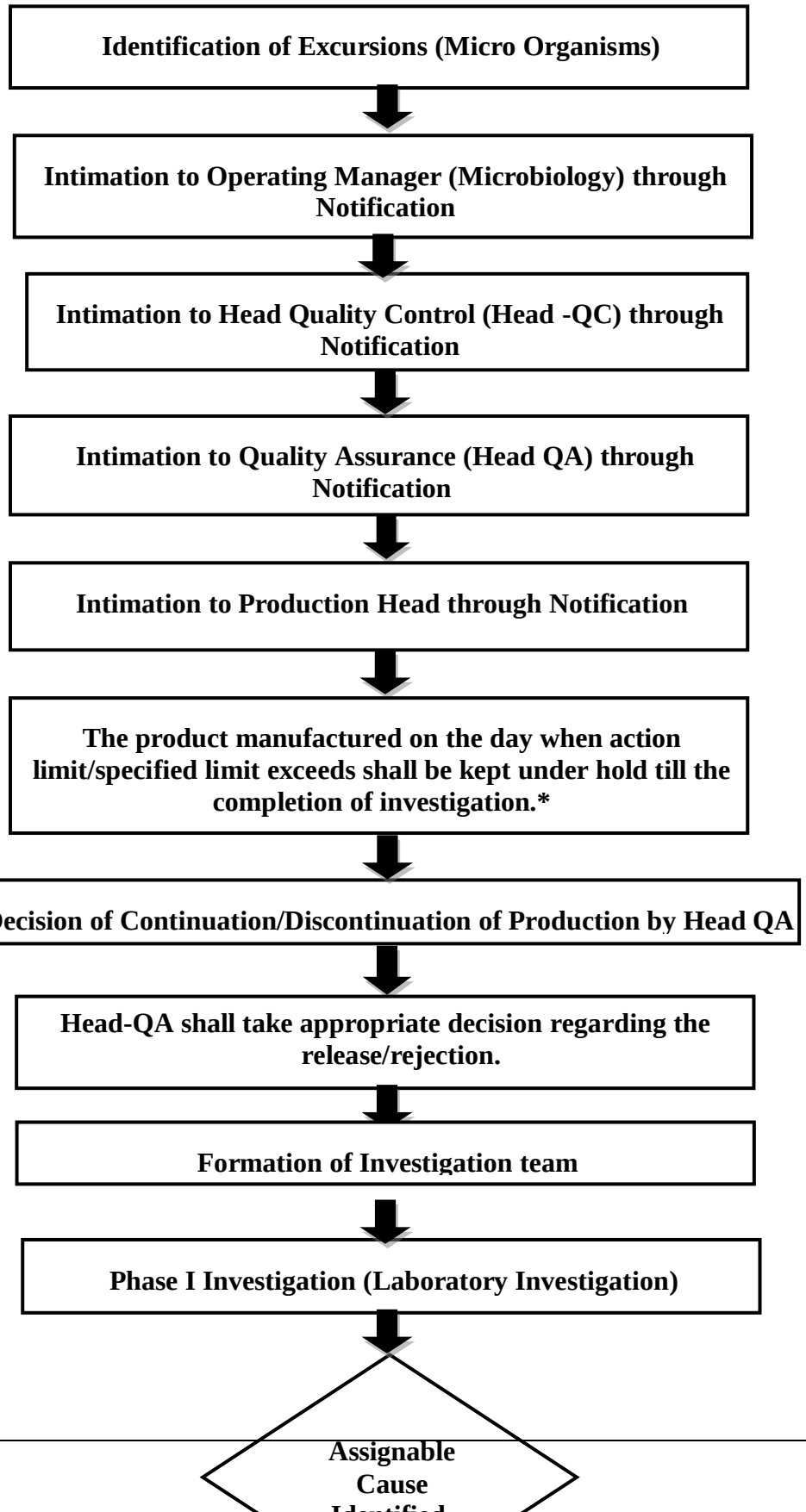

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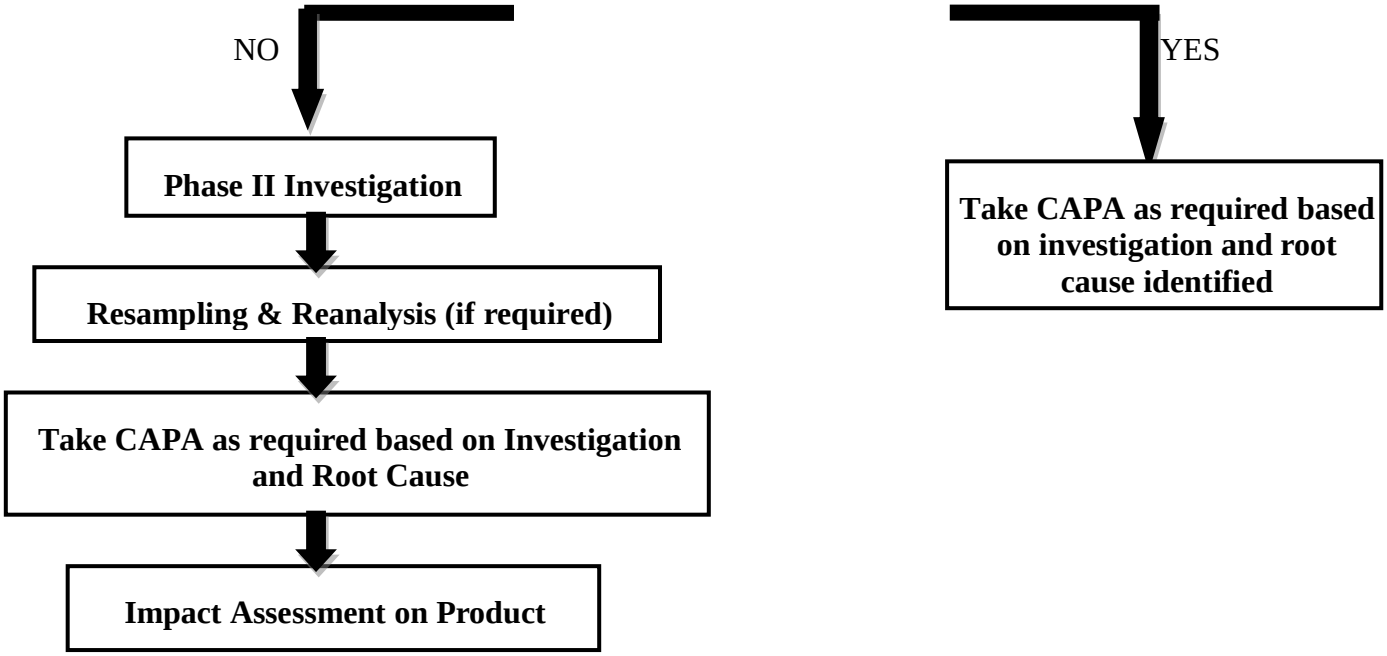

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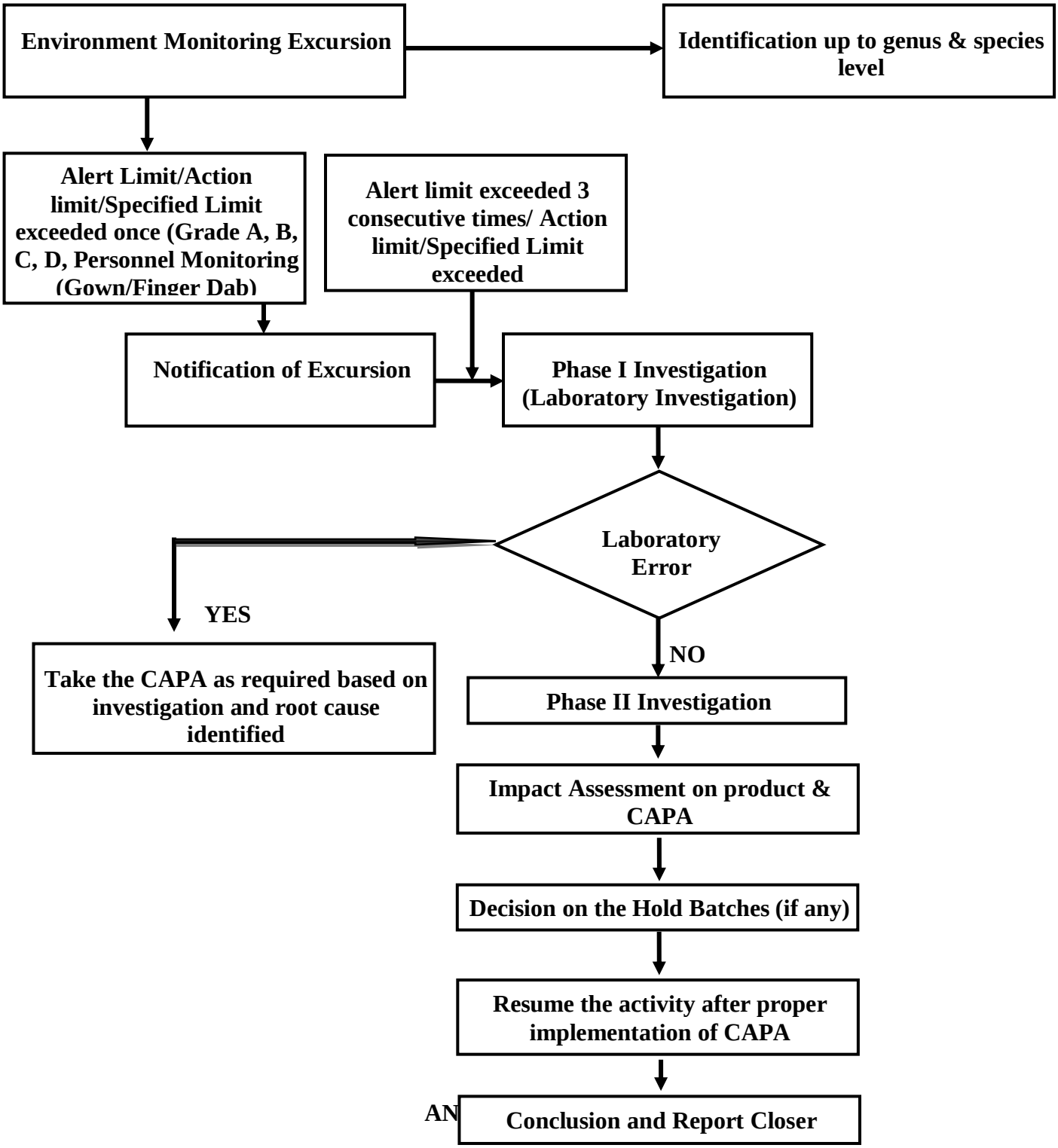
ANNEXURE II

FLOW CHART FOR INVESTIGATION OF ENVIRONMENT MONITORING EXCURSIONS



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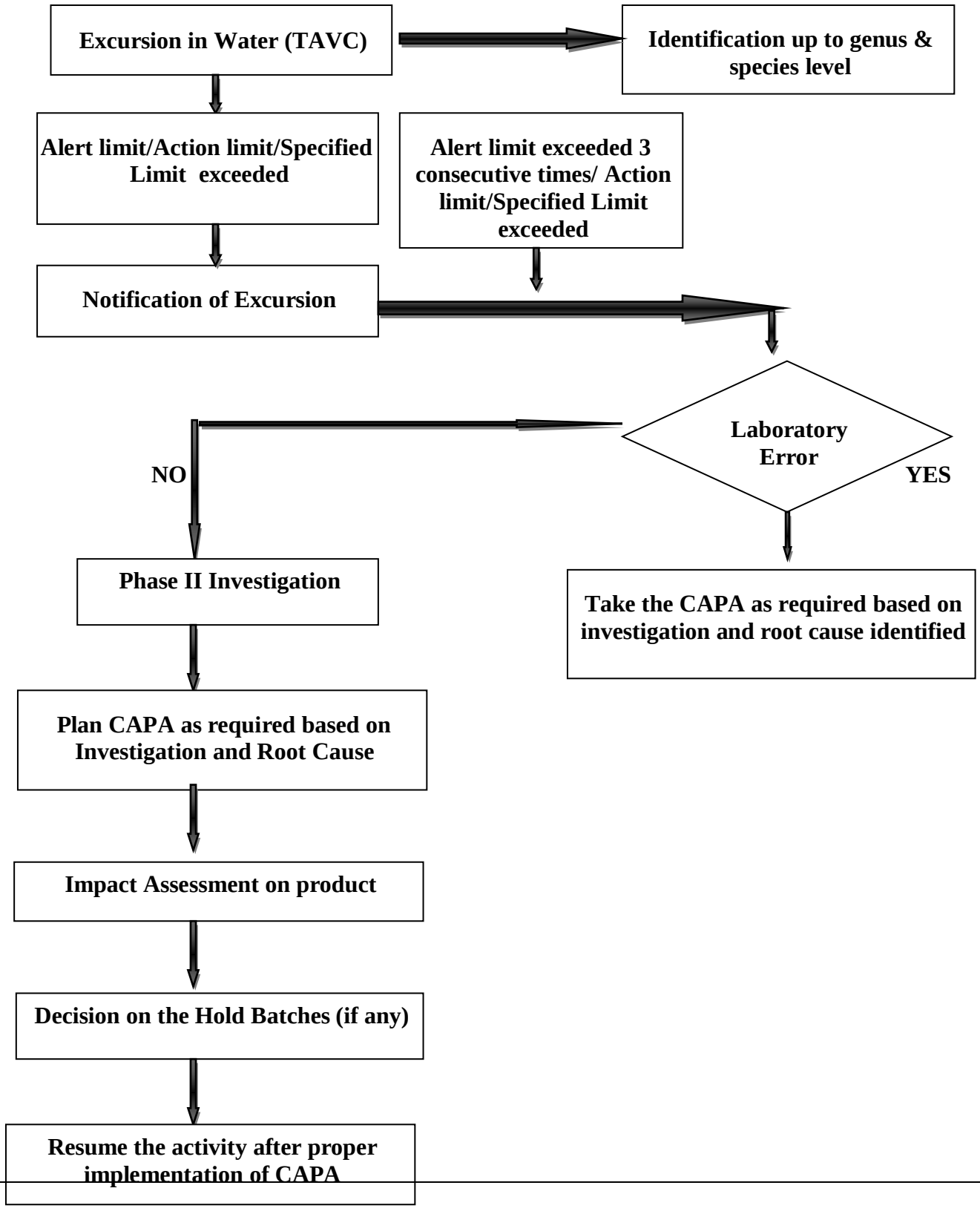
FLOW CHART FOR INVESTIGATION OF WATER EXCURSION (TAVC)



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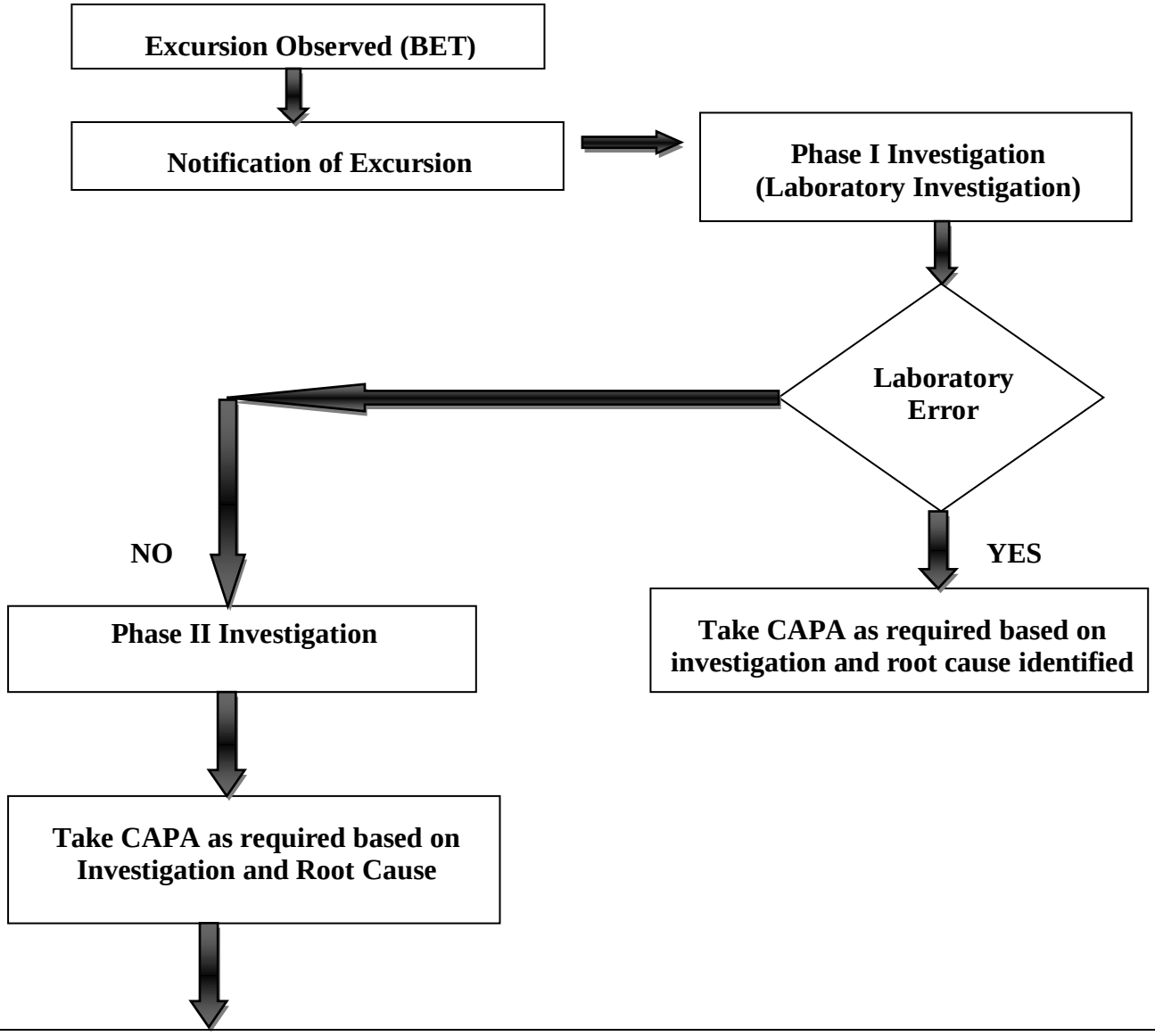
Conclusion and Report Closer

ANNEXURE IV

PURE & CURE HEALTHCARE PVT. LTD.
HARIDWAR
MICROBIOLOGY

FLOW CHART FOR INVESTIGATION WATER EXCURSION IN BET



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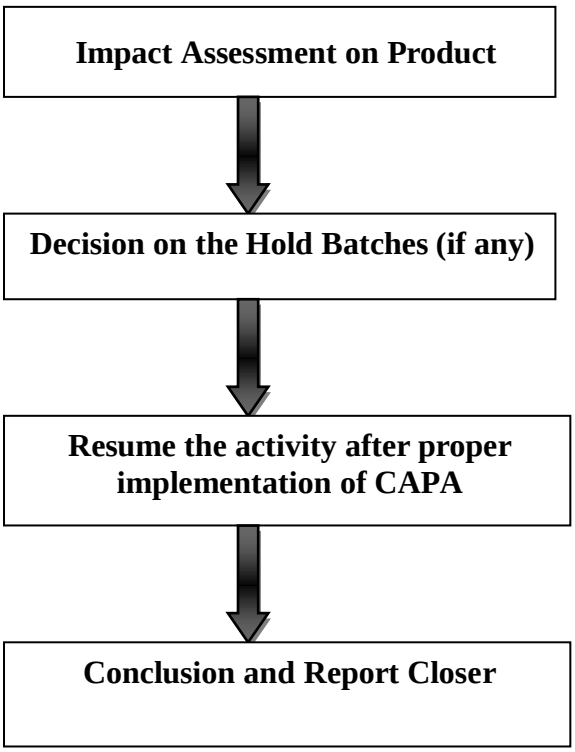

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ANNEXURE V
RESULT OF EXCURSION IN WATER/ENVIRONMENT/ PERSONNEL MONITORING

Date of Notification	Notification No.	Name of facility	Type of Sample(Water/ EM/ Personnel)	Sampling Point ID./ Location ID	A.R. No./ Lot No.	Limits			Result Observed			Investigation Completion date	CAPA Recommended (Y/N)	Initiate by (Sign/Date)	Reviewed By (Sign/Date)
						Alert	Action	Specified	TBC	TFC	TMC				

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ANNEXURE VI
NOTIFICATION FOR EXCURSION

From : QC-Microbiology							
Date of Analysis		Type of Excursion		Date of Water Sampling/ Monitoring			
Type of Analysis		Date of Observation		Sample Analysed By: / Monitoring done By: Name/Date		Result Observed By Name./Date	
Details of Excursion:							
(Excursion in Environment Monitoring/ Water Sample)							
S. N.	Area	Sampling Point ID./Location ID.	Lot. No./ A.R. No.	Observations	Alert limit	Action Limit	Specified Limit
(Personnel Monitoring)							
S. N.	Name of the Person	Location	Observations (cfu)	Alert limit	Action Limit	Specification Limit	
Operating Manager-Micro (Sign./Date)			Head Quality Control (Sign./Date)				
Head Quality Assurance (Sign./Date)			Head Production (Sign./Date)				

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Notification No.			

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ANNEXURE VII
IDENTIFICATION OF MICROORGANISM

Notification No.		
Production Facility/Area		
Method of Identification		
Name of Organism Identified (Attach report):		
Probable Source of identified organism (Attach literature Reference, (if any):		
Prepared By: **Microbiologist**	**Verified By :** **Operating Manager-Micro**	**Approved By:** **Head-QC**

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ANNEXURE VIII
INVESTIGATION OF MICROBIAL EXCURSION IN WATER / ENVIRONMENT

PHASE I MICROBIOLOGY LABORATORY INVESTIGATION					
1. Investigation report for Excursion from Action Limit in PW/WFI/PSG/Raw Water					
Notification No.:					
Name of facility		Type of Water Sampling		Sampling Point/ Location	
Lot. No./ A.R. No.		Date of Sampling		Date of Testing	
Date of observation		Alert Limit		Action Limit	
Analysed By:		Count Observed By		Sampled By (Name)	

A. Investigation for water Excursion in TVAC/ Pathogen : □ Applicable/ □ Not Applicable

Dehydrated Media Lot. No. & Expiry		Media GPT	□ Complies □ Not Complies □ Not Applicable
Autoclave cycle no. of media used for testing eg. R2A/ SCDA		Autoclave cycle no. of liquid media used for testing eg. SCDM/Peptone Water	
Nature of prepared media, Physical appearance of solid/ liquid medium such as • Cracked containers or lids •	□ Complies □ Not Complies □ Not Applicable	Pre Incubation Condition (if applicable)	□ Complies □ Not Complies □ Not Applicable
Nature of contamination if any in pre incubated plates		Observation of any contaminations in the plates (same media lot) used for other samples of same day and/ or other days.	□ Complies □ Not Complies □ Not Applicable
Any unusual observation during preparation of media (in dehydrated, upon reconstitution & dissolution, pH) storage and usage.	□ Complies □ Not Complies □ Not Applicable	Negative Control of SCDM/R2A/SCDA/Dilutions	□ Complies □ Not Complies □ Not Applicable
Growth promotion test results of used media	□ Complies □ Not Complies □ Not Applicable	pH of Media	□ Complies □ Not Complies □ Not Applicable
0.45µ membrane negative control on agar media.	□ Complies □ Not Complies □ Not Applicable	Was there any crack, improper closures observed in the sampling containers?	□ Complies □ Not Complies □ Not Applicable

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Environment Monitoring of LAF (Used for analyzing the samples under investigation) settle plate results and active air sampling results (3 days)	□ Complies □ Not Complies □ Not Applicable	Environment Monitoring of associated and background environment (Used for analyzing the samples under investigation) - Settle plates and Active air sampling results (3 days)	□ Complies □ Not Complies □ Not Applicable
Trend analysis of environment monitoring of the LAF and background area	□ Complies □ Not Complies □ Not Applicable	Results of TVAC/Pathogen 3 days earlier	□ Complies □ Not Complies □ Not Applicable
Power failure during testing	□ Yes □ No	Preparation and sterilization of accessories	□ Complies □ Not Complies □ Not Applicable
Analyst Training (Microbiologist)	□ Complies □ Not Complies □ Not Applicable	Verification of Sterilization load	□ Complies □ Not Complies □ Not Applicable
Analyst Qualification	□ Complies □ Not Complies □ Not Applicable	Review of periodic cleaning of pre filter	□ Complies □ Not Complies □ Not Applicable
Any previous history of the sample under investigation, analyst involved in testing	□ Complies □ Not Complies □ Not Applicable	Ensure the samplings done as per SOP.	□ Complies □ Not Complies □ Not Applicable
Sampling bottles sterilization	□ Complies □ Not Complies □ Not Applicable	Qualification/Validation of sterilization process	□ Complies □ Not Complies □ Not Applicable
Qualification/Validation of LAF	□ Complies □ Not Complies □ Not Applicable	SOP and standard testing procedure adopted for the testing of samples under investigation	□ Complies □ Not Complies □ Not Applicable
Any unusual observation during sampling (to be verified by means of an interview with the analyst, who has done the sampling)	□ Complies □ Not Complies □ Not Applicable	Other observation(if any)	
Interview of person for potential cause (attach report if required)	□ Complies □ Not Complies □ Not Applicable		
Investigation Evaluation Summary:			

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B. Investigation for water Excursion in BET: □ Applicable/ □ Not Applicable

Heating Block/Plate temperature	□ Complies □ Not Complies □ Not Applicable	BET Incubator/ calibration done on	
BET Incubator/ next calibration due on		Analyst qualification record done as on date	□ Complies □ Not Complies □ Not Applicable
Verification sterilization parameter	□ Complies □ Not Complies □ Not Applicable	Interview of person for potential cause (attach report if required)	□ Complies □ Not Complies □ Not Applicable
Depyrogenation of the glassware used in the preparation of samples and reagents	□ Complies □ Not Complies □ Not Applicable	Evaluation of Product Positive Control and Product Negative Control etc.	□ Complies □ Not Complies □ Not Applicable
Evaluation of the validity of reagents	□ Complies □ Not Complies □ Not Applicable	Confirm whether Limulus Amoebocyte Lysate(LAL)/ Control Standard Endotoxin/LAL Reagent Water was stored at correct temperature	□ Complies □ Not Complies □ Not Applicable
Confirm whether dry heat sterilizer (DHS) has been Calibrated/ Qualified and its temperature monitoring on routine basis	□ Complies □ Not Complies □ Not Applicable	Confirm whether reconstitutated Limulus Amoebocyte Lysate(LAL)/ Control Standard Endotoxin/LAL Reagent Water was used with in their shelf life.	□ Complies □ Not Complies □ Not Applicable
Confirm whether test for confirmation of labeled lysate sensitivity of LAL reagent was within Acceptance criteria.	□ Complies □ Not Complies □ Not Applicable	□ Complies □ Not Complies □ Not Applicable	□ Complies □ Not Complies □ Not Applicable
Any other parameters (if any)			
Investigation Evaluation Summary			

2. Investigation for Environment Monitoring: □ Applicable/ □ Not Applicable

Steam Sterilizer (Instrument ID)		Steam Sterilizer Validation done on	
Result of steam sterilizer	□ Complies	Steam Sterilizer validation	

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validation	□ Not Complies	due on	
Deviation if any (To be compare with previous case	□ Yes □ No	Media name & Lot No. used for environment monitoring	
Validity period of sterilized media		Date of media sterilization	
Sterilization cycle no.		Media plate prepared by (Name)	
Status of Negative control	□ Complies □ Not Complies □ Not Applicable	Review the sterilization cycle parameters	□ Complies □ Not Complies □ Not Applicable
Review the result of media GPT	□ Complies □ Not Complies □ Not Applicable	Lot No./ used before of pre sterilized petriplates.	
Pre-incubation of media plates completed (Date)		Review of training records of concern person/Microbiologist	□ Complies □ Not Complies □ Not Applicable
Preincubation of media plates started (date)		Preincubation of plate status (any contamination found)	□ Complies □ Not Complies □ Not Applicable
Review of microbial monitoring result of media preparation room is within the alert limit on the day of media prepared.	□ Complies □ Not Complies □ Not Applicable	Name and concentration of sanitizing/cleaning agent used.	
Area cleaning & sanitization done as per SOP	□ Complies □ Not Complies □ Not Applicable	Review the area qualification record	□ Complies □ Not Complies □ Not Applicable
Interview of person for potential cause (attach report if required)	□ Complies □ Not Complies □ Not Applicable	Ensure the samplings done as per SOP.	□ Complies □ Not Complies □ Not Applicable
Review the Environment condition plate preparation room (Temp., RH & DP)	□ Complies □ Not Complies □ Not Applicable	disinfectants used	□ Complies □ Not Complies □ Not Applicable
Review the viable microbial monitoring trends of microbiology laboratory (Two Months).	□ Complies □ Not Complies □ Not Applicable	Review of Non viable count if required	□ Complies □ Not Complies □ Not Applicable
Verify the entry exit procedure for microbiology area weather the entry made correctly.	□ Complies □ Not Complies □ Not Applicable	Review the procedure adopted to perform the test was correct or not	□ Complies □ Not Complies □ Not Applicable

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Review the isolate and their source and there occurrence with other type of tests such as bio-burden, microbial limit test, sterility test and water analysis.	□ Complies □ Not Complies □ Not Applicable	Check the any similar observation occurred previously, their investigation and corrective action taken.	□ Yes □ No
Review the cleaning & sanitization status of transportation containers.	□ Complies □ Not Complies □ Not Applicable	Sterilization date of peptone water bottle	
Container sterilization cycle no./ sterilization done		Sterilization date of air sampler sieve	
air sampler sieve sterilization cycle no.		Sterilization cycle parameter (Container/Air sampler sieve)	□ Complies □ Not Complies □ Not Applicable
Microbiology department HVAC validation due on		Result of HVAC validation	□ Complies □ Not Complies □ Not Applicable
Deviation in HVAC Validation (if any)	□ Yes □ No	To check microbiologist qualification record	□ Complies □ Not Complies □ Not Applicable
To check environmental reports other than the failure report for previous excursion (if any).	□ Complies □ Not Complies □ Not Applicable	Check the sterilization status of the materials used for test was correct eg. Media, filter paper, water, swab, saline etc.	□ Complies □ Not Complies □ Not Applicable
Check the history of data	□ Complies □ Not Complies □ Not Applicable	Review of isolated organism Obtained with previous history	
Review report of the laminar flow lab and the other testing reports of microbiology lab.	□ Complies □ Not Complies □ Not Applicable	Review for occurrence of any particular intervention in microbiology lab	□ Complies □ Not Complies □ Not Applicable
Investigate whether performance of any equipment or training of personnel or use of apparatus have not affected the results of the tests performed at that time.	□ Complies □ Not Complies □ Not Applicable	Any other cause/points for excursion	
Corrective action and preventive action (Mentioned CAPA taken,			

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in brief also mention CAPA reference No.	
Assignable cause found/ not found initiate the second phase investigation.	
Investigation Evaluation Summary:	
Conclusion:	

Microbiologist (Sign./Date)	Operating Manager-Micro (Sign./Date)	Head-QC (Sign./Date)	Head-QA (Sign./Date)

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ANNEXURE IX

INVESTIGATION OF MICROBIAL EXCURSION IN WATER (PW/WFI/PSG/RAW) (PHASE-II INVESTIGATION)

PHASE- II PRODUCTION AREA INVESTIGATION			
Notification No.:			
1. Potable Water Treatment : □ Applicable/ □ Not Applicable			
Check the chlorination/ disinfection treatment	□ Complies □ Not Complies □ Not Applicable	Check the SMBS dosing	□ Complies □ Not Complies □ Not Applicable
Check the Hardness of water	□ Complies □ Not Complies □ Not Applicable	Verify the Ion exchange parameters	□ Complies □ Not Complies □ Not Applicable
Check the effectiveness of filtration	□ Complies □ Not Complies □ Not Applicable	Cleaning frequency of raw water storage tank	□ Complies □ Not Complies □ Not Applicable
Any other parameters if required (As per water treatment system)	□ Complies □ Not Complies □ Not Applicable	Any unusual observation incidence occurs	□ Yes □ No
Training record of Concern person	□ Complies □ Not Complies □ Not Applicable		
2. Purified water Generation, Storage and Distribution System: □ Applicable/ □ Not Applicable			
Last sanitization done on		Check the online conductivity for any abnormal trend in purified water/WFI.	□ Complies □ Not Complies □ Not Applicable
Check for any leakage in Purified water/WFI Generation system.	□ Complies □ Not Complies □ Not Applicable	Check for calibration status of temperature, conductivity from the set limit for last 7 days of storage tank.	□ Complies □ Not Complies □ Not Applicable
Check the trend of TVAC return loop water	□ Complies □ Not Complies □ Not Applicable	Check the change in conductivity from the set limit for last 7 days of storage tank	□ Complies □ Not Complies □ Not Applicable
Check for the change in conductivity from the set limit for last 7 days of return loop	□ Complies □ Not Complies □ Not Applicable	Check for the change in velocity from the set limit for last 7 days	□ Complies □ Not Complies □ Not Applicable
Check for UV parameters as per limit	□ Complies □ Not Complies □ Not Applicable	Check for the decrease in water limit below the limit for last 7 days.	□ Complies □ Not Complies □ Not Applicable
Check for the last vent filter integrity done on	□ Complies □ Not Complies	Check for any maintenance work done/date	

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& test results	□ Not Applicable		
Check for any leakage in distribution system	□ Complies □ Not Complies □ Not Applicable	Values of critical parameters of RO system are as per the set limit	□ Complies □ Not Complies □ Not Applicable
Any other Parameters		Any unusual observation incidence Occurs	
Interview of operator for potential cause (Report attached if required)	□ Yes □ No	Training Record of Concern person	□ Complies □ Not Complies □ Not Applicable
3. WFI Generation, Storage and Distribution System: □ Applicable/ □ Not Applicable			
Check for any abnormal trend of distillate conductivity	□ Complies □ Not Complies □ Not Applicable	Check for any critical alarm	□ Complies □ Not Complies □ Not Applicable
Check for any maintenance work done	□ Complies □ Not Complies □ Not Applicable	Check for leakage if any	□ Complies □ Not Complies □ Not Applicable
Last sanitization done on		Check for the operation as per defined set parameter	□ Complies □ Not Complies □ Not Applicable
Check for any abnormal trend of distillate temperature	□ Complies □ Not Complies □ Not Applicable	Check for the change in temperature from the set limit for last 5 days of storage tank	□ Complies □ Not Complies □ Not Applicable
Check the decrease in water limit below the limit for last 7 days	□ Complies □ Not Complies □ Not Applicable	Check for the last vent filter integrity done on & test results	□ Complies □ Not Complies □ Not Applicable
Check for calibration status of temperature, conductivity & pressure sensors	□ Complies □ Not Complies □ Not Applicable	Check for the change in conductivity from the set limit for last 7 days of return loop.	□ Complies □ Not Complies □ Not Applicable
Check for the change in velocity from set limit for last 7 days.	□ Complies □ Not Complies □ Not Applicable	Check for any leakage in distribution system.	□ Complies □ Not Complies □ Not Applicable
Check for the change in conductivity from the set limit for last 7 days of storage tank	□ Complies □ Not Complies □ Not Applicable	Check for the change in temperature from the set limit for last 5 days of return loop	□ Complies □ Not Complies □ Not Applicable
Any maintenance work done/date		Any Other Parameter	
Any unusual observation incidence occurs	□ Yes □ No	Interview of operator for potential cause (Report attached if required)	□ Yes □ No
Training record of	□ Complies		

concern person	□ Not Complies □ Not Applicable		
Investigation Evaluation Summary:			
4. Pure Steam Generation System: □ Applicable/ □ Not Applicable			
Check for any abnormal trend of distillate conductivity	□ Complies □ Not Complies □ Not Applicable	Check for any abnormal trend of distillate temperature	□ Complies □ Not Complies □ Not Applicable
Check for any critical alarm	□ Complies □ Not Complies □ Not Applicable	Check for the operation as per defined set parameters	□ Complies □ Not Complies □ Not Applicable
Check for any Maintainace work done	□ Complies □ Not Complies □ Not Applicable	Check for leakage if any	□ Complies □ Not Complies □ Not Applicable
Check for the results of online TOC	□ Complies □ Not Complies □ Not Applicable	Check for calibration status of temperature, conductivity & pressure sensors	□ Complies □ Not Complies □ Not Applicable
Interview of operator for potential cause (Report attached if required)	□ Yes □ No		
Investigation Evaluation Summary:			
Findings of investigation and final conclusion			
Investigation details (provide details in chronology order. Attach all supporting documents and details of isolates identified, if applicable):			
Root cause/Probable root cause:			
Impact Assessment			
Corrective action and preventive action (Mentioned CAPA taken, in brief also mention CAPA reference No.			
Final conclusion			
Head- QC/Micro (Sign./Date)	Head- Engineering (Sign./Date)	Head- Production (Sign./Date)	Head- QA (Sign./Date)

PHARMA DEVILS

MICROBIOLOGY DEPARTMENT

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ANNEXURE X
INVESTIGATION OF MICROBIAL EXCURSION IN ENVIRONMENT (PHASE-II INVESTIGATION)

Notification No.		Name of Production Facility/Area	
Date of Sampling		Sampling Location	
Type of Sampling		Area Classification	
PHASE II Review & Investigation in Affected Area/Manufacturing Area			
Review microbiological environment monitoring results of adjacent location of affected area	□ Complies □ Not Complies □ Not Applicable	Review microbiological environment monitoring trend (Last 60 Days)	□ Complies □ Not Complies □ Not Applicable
Review the microbial personnel Monitoring results	□ Complies □ Not Complies □ Not Applicable	Review the microbial personnel monitoring trend (Last 60 days)	□ Complies □ Not Complies □ Not Applicable
Review the NVPC results	□ Complies □ Not Complies □ Not Applicable	Review the NVPC trend (Last 60 days)	□ Complies □ Not Complies □ Not Applicable
Review the temperature, RH & ΔP of area trend (Last 60 □ Complies □ Not Complies □ Not Applicable days)		Review the ΔP of UAF/HEPA trend (Last 60 days)	□ Complies □ Not Complies □ Not Applicable
Review the no. of persons worked in the aseptic processing area Date & No.	□ Complies □ Not Complies □ Not Applicable	Review the qualification status of personnel entered in aseptic area	□ Complies □ Not Complies □ Not Applicable
Review the nature of activity performed in the room.	□ Complies □ Not Complies □ Not Applicable	Review the maintenance activity performed in area if any	□ Complies □ Not Complies □ Not Applicable
Check the personnel health/hygiene	□ Complies □ Not Complies □ Not Applicable	Review the usage of sterilized garments within the hold time.	□ Complies □ Not Complies □ Not Applicable
Verify the condition of sterilized garments	□ Complies □ Not Complies □ Not Applicable	To review load pattern of sterilization cycles.	□ Complies □ Not Complies □ Not Applicable
Name and concentration of sanitizing agent used		Preparation and expiry dates of disinfectants used.	
Cleaning and sanitization performed by		Review of training records of the personnel.	□ Complies □ Not Complies □ Not Applicable
Items passing to the aseptic processing area done as per SOP.	□ Complies □ Not Complies □ Not Applicable	Power failure if any	□ Yes □ No
Abnormal observation if any	□ Yes	HVAC Validation done on	

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	□ No		
HVAC Validation due on		Deviation if any results of HVAC Validation	□ Complies □ Not Complies □ Not Applicable
Check entry/Exit records for critical area	□ Complies □ Not Complies □ Not Applicable	Personnel's entered the area on the day count exceeds alert/action limit, whether the entry/Exit procedure was followed as per SOP.	□ Complies □ Not Complies □ Not Applicable
Review the gowning qualification of the personnel's entered the critical area.	□ Complies □ Not Complies □ Not Applicable	Check cleaning and sanitization record and usage of qualification disinfectants and their preparation as applicable.	□ Complies □ Not Complies □ Not Applicable
Check the personnel qualification record to enter in critical area	□ Complies □ Not Complies □ Not Applicable	Check RH Temperature and Differential pressure	□ Complies □ Not Complies □ Not Applicable
Evaluate BMR and check the duration of the filling	□ Complies □ Not Complies □ Not Applicable	Check AHU Operation log	□ Complies □ Not Complies □ Not Applicable
Check sterilization details for equipment/garments/accessories used on that particular day	□ Complies □ Not Complies □ Not Applicable	Check water system regeneration/sanitization record i.e. when it was done for the last	□ Complies □ Not Complies □ Not Applicable
Verify the sanitization and disinfection record	□ Complies □ Not Complies □ Not Applicable	Check the personnel hygiene of the persons involved	□ Complies □ Not Complies □ Not Applicable
HVAC breakdowns occurred during the exposure.	□ Complies □ Not Complies □ Not Applicable	Evaluate filter integrity records of all filters including autoclave vent filter integrity record	□ Complies □ Not Complies □ Not Applicable
Check the validation of AHU, Autoclave, Tunnel, Filter and Sanitizer efficacy	□ Complies □ Not Complies □ Not Applicable		
Interview operators (s) for potential cause:			
Investigation Evaluation Summary:			
Probable Cause for Excursion (based on isolate)			
Impact assessment			

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Corrective action and preventive action (Mentioned CAPA taken, in brief also mention CAPA reference No.			
Final Conclusion:			
Head-QC/Micro (Sign./Date)	Head-Engineering (Sign./Date)	Head-Production (Sign./Date)	Head-QA (Sign./Date)

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ANNEXURE XI
EXTENSION FORM FOR INVESTIGATION OF MICROBIAL EXCURSION IN WATER/ ENVIRONMENT

Notification No.		Date of Intimation	
Due Date		New Completion Date	
Reason for Extension:			
Extension Taken By: (Sign./Date)		Head- QA: (Sign./Date)	

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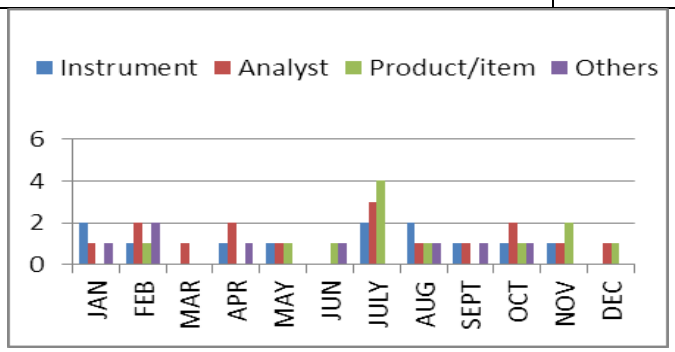
ANNEXURE-XII
TRENDING OF EXCURSION DATA

Month: **Year:**

Excursion Distribution							
S.No.	**Month**	**Total No. of Excursion**	**Month**	**Instrument**	**Microbiologist**	**Product/item**	**Others**
Total			**Total**				

Interview of person for potential cause (attach report if required)	□ Complies □ Not Complies □ Not Applicable



Review and Comments: ……

Operating Manager QA
(Sign &Date)

Head QA
(Sign &Date)