

SHILPA PHARMA LIFESCIENCES LIMITED, UNIT-2

**REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC
(PREDICTED NO EFFECT CONCENTRATION)**

Department: EHS

Report No.: RPT/EHS/001/26

Protocol Ref. No.: PC/EHS/001/26

Page 1 of 11

**REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC
(PREDICTED NO EFFECT CONCENTRATION)**

SHILPA PHARMA LIFESCIENCES LIMITED, UNIT-2	
REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC (PREDICTED NO EFFECT CONCENTRATION)	
Department: EHS	
Report No.: RPT/EHS/001/26	Page 2 of 11
Protocol Ref. No.: PC/EHS/001/26	

INDEX

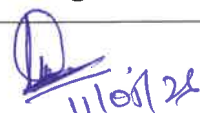
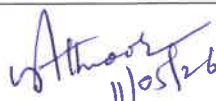
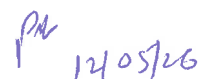
S. No.	Content	Page No.
--	Cover page	1
--	Index	2
--	Approval page	3
1	Objective	4
2	Scope	4
3	Responsibilities	4
4	Abbreviations / Definitions	4-5
5	Reason for the study	5
6	Procedure	5-6
7	Method of Analysis Pemetrexed disodium API Content (By HPLC)	6-8
8	PiE Risk Assessment and PEC/PNEC Evaluation	9
9	Conclusion	10
10	Distribution Record	11
11	Attachments	11

SHILPA PHARMA LIFESCIENCES LIMITED, UNIT-2	
REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC (PREDICTED NO EFFECT CONCENTRATION)	
Department: EHS	
Report No.: RPT/EHS/001/26	Page 3 of 11
Protocol Ref. No.: PC/EHS/001/26	

APPROVAL PAGE

Signing of this approval page of miscellaneous study report indicates agreement with the methodology and the various factors captured in this report.

	Name	Designation	Sign/Date
Prepared by	Mr. Suman	Executive-EHS	 11/05/26

	Name	Designation	Sign/Date
Reviewed by	Mr. Govindappa Galagali	DGM Production NON-ONCO	 11/05/26
	Mr. Veereshappa	AVP Production ONCO	 11/05/26
	Mr. B.K. Mangaraj	AVP –QC	 11/05/26
	Mr. Elangovan R.	DGM-EHS	 11/05/26
	Mr. N. Prasad Achanta	Sr. Manager-QA	 12/05/26

	Name	Designation	Sign/Date
Approved by	Mr. N. Saravanan	AGM-QA	 12/05/26

SHILPA PHARMA LIFESCIENCES LIMITED, UNIT-2	
REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC (PREDICTED NO EFFECT CONCENTRATION)	
Department: EHS	
Report No.: RPT/EHS/001/26	Page 4 of 11
Protocol Ref. No.: PC/EHS/001/26	

1.0 OBJECTIVE:

To define the procedure for monitoring, control, and reporting of wastewater quality at the ETP Polish RO permeate (outlet) in order to ensure that pharmaceutical residue levels are reduced to environmentally acceptable levels and support achievement of PNEC (Predicted No Effect Concentration).

1.1 To ensure treated wastewater at the ETP Polish RO outlet does not contain unacceptable levels of API residue.

1.2 To verify the efficiency of detoxification and downstream wastewater treatment.

1.3 To monitor treated effluent quality before discharge / reuse / onward management.

1.4 To generate documented evidence supporting achievement of PNEC at the ETP Polish RO outlet.

1.5 To ensure environmental protection and compliance with internal wastewater control requirements

2.0 SCOPE:

This protocol is applicable to:

2.1 Detoxified process effluent generated from API manufacturing blocks

2.2 Effluent transferred to ETP for treatment

2.3 RO system outlet stream after effluent treatment

2.4 Sampling, analysis, review, and reporting of API residue levels at ETP Polish RO outlet

This report is applicable for estimation of API concentration levels in ETP Polish RO permeate (outlet) for all APIs at M/s. Shilpa Pharma Lifesciences Limited, Unit-2.

3.0 RESPONSIBILITIES:

3.1 Production department personnel are responsible to prepare the report for determination of API concentration levels in ETP RO permeate (outlet).

3.2 Production Head or his authorized designee is responsible to review the report.

3.3 QA, QC & EHS department personnel are responsible to review the report.

3.4 QA Head or his authorized designee is responsible for approval of the report.

4.0 ABBREVIATIONS/DEFINITIONS:

4.1 ABBREVIATIONS:

SHILPA PHARMA LIFESCIENCES LIMITED, UNIT-2	
REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC (PREDICTED NO EFFECT CONCENTRATION)	
Department: EHS	
Report No.: RPT/EHS/001/26	Page 5 of 11
Protocol Ref. No.: PC/EHS/001/26	

QA	:	Quality Assurance	U-2	:	Unit-2
ETP	:	Effluent Treatment Plant	RPT	:	Report
ADI	:	Acceptable Daily Intake	PC	:	Protocol
EHS	:	Environment, Health & Safety	GEN	:	General
API	:	Active Pharmaceutical Ingredients	PD	:	Production
CR&D	:	Chemical Research and Development	QC	:	Quality Control
HPLC	:	High Pressure Liquid Chromatography			
CAS	:	Chemical Abstracts Service Registry Number			
IUPAC	:	International Union of Pure and Applied Chemistry			
SAP	:	Systems, Applications and Products in Data Processing			

4.2 DEFINITIONS:

- 4.2.1 **Detoxification:** Detoxification is a process to remove the toxicity of substance or neutralize the toxicity of the substance.
- 4.2.2 **API:** Active Pharmaceutical Ingredient (API) (or drug substance): Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.
- 4.2.3 **Cytotoxic API:** Cytotoxic drugs (sometimes known as antineoplastic) describe a group of medicines that contain chemicals which are toxic to cells, preventing their replication or growth, and so are used to treat cancer.
- 4.2.4 **PEC:** Predicted environmental concentration (PEC) is a calculated value of a chemical in the environment based on exposure models.
- 4.2.5 **PNEC:** The predicted no-effect concentration (PNEC) is the concentration of a chemical which marks the limit at which below no adverse effects of exposure in an ecosystem are measured.
- 4.2.6 **PEC/PNEC:** PEC is the predicted environmental concentration and PNEC is the predicted no effect concentration. They are used in the assessment of the environmental risk from residual APIs discharge in environment, as applicable.

SHILPA PHARMA LIFESCIENCES LIMITED, UNIT-2	
REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC (PREDICTED NO EFFECT CONCENTRATION)	
Department: EHS	
Report No.: RPT/EHS/001/26	Page 6 of 11
Protocol Ref. No.: PC/EHS/001/26	

5.0 REASON FOR STUDY:

API manufacturing processes may generate process effluent containing traces of active pharmaceutical ingredients through process washings, equipment cleaning, detoxification streams, and associated wastewater. Such residues, if not properly controlled, may pose environmental risk.

As part of environmental protection and continual improvement, this study / protocol is established to assess whether the wastewater treatment system, including detoxification where applicable and ETP-RO treatment, is capable of reducing API residues to acceptable levels at the ETP RO outlet.

This report also incorporates the Pharmaceuticals in Environment (PiE) Risk Assessment Tool to evaluate environmental risk by comparing Predicted Environmental Concentration (PEC) with Predicted No Effect Concentration (PNEC) for the relevant API.

6.0 PROCEDURE:

6.1 General Information

A list of all APIs manufactured at the site shall be maintained. APIs having potential to enter the wastewater stream shall be identified based on process, cleaning, and detoxification activities.

6.2 Segregation of Effluent

Effluent streams containing or suspected to contain API residues shall be identified and segregated from general wastewater. Such streams shall not be directly discharged to the treatment system without appropriate control.

6.3 Detoxification

Where applicable, API-bearing effluent shall be detoxified using approved product-specific detoxification agents and operating conditions before being transferred to ETP. The detoxification procedure shall be based on product development / established site procedure.

6.4 Transfer to ETP

After detoxification, the effluent shall be sent to ETP for further treatment through the defined treatment system.

6.5 Treatment Through ETP, RO and Final Monitoring

The effluent generated from manufacturing activities shall be routed through the complete wastewater treatment system in a controlled manner. The treatment sequence shall include:

- Equalization

SHILPA PHARMA LIFESCIENCES LIMITED, UNIT-2	
REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC (PREDICTED NO EFFECT CONCENTRATION)	
Department: EHS	
Report No.: RPT/EHS/001/26	Page 7 of 11
Protocol Ref. No.: PC/EHS/001/26	

- Pretreatment
- Biological Treatment
- Advanced Treatment
- MEE
- ATFD
- UF
- RO
- Polish RO

as applicable based on the nature of the effluent stream.

Initially, the effluent shall be collected in the equalization system to achieve homogenization of wastewater characteristics. After equalization, the effluent shall undergo pretreatment for adjustment and removal of load as required. Thereafter, the effluent shall be subjected to biological treatment and advanced treatment systems for reduction of organic load and improvement in water quality.

High TDS or concentrated streams shall be handled through MEE followed by ATFD for concentration and salt/residue management, wherever applicable. Streams suitable for membrane treatment shall further pass through UF and RO systems. The treated permeate shall then pass through Polish RO for final polishing.

The final outlet after Polish RO shall be considered as the critical monitoring point for evaluation of residual API concentration and verification of wastewater quality with respect to environmental safety and PNEC requirements.

6.6 Sample Collection

Representative samples shall be collected from the ETP polish RO outlet as per defined sampling plan. Samples shall be labeled with:

- 6.6.1 Date
- 6.6.2 Time
- 6.6.3 Sampling point
- 6.6.4 Name of sampler

Composite sampling shall be adopted as applicable. Samples shall be stored and handled under defined conditions to avoid degradation before analysis.

6.7 Analysis Results Recording

Samples collected from ETP Polish RO outlet shall be analyzed by QC using an approved product-specific analytical method. Results shall be recorded and reviewed against the defined acceptance criteria.

6.8 Acceptance Criteria

SHILPA PHARMA LIFESCIENCES LIMITED, UNIT-2	
REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC (PREDICTED NO EFFECT CONCENTRATION)	
Department: EHS	
Report No.: RPT/EHS/001/26	Page 8 of 11
Protocol Ref. No.: PC/EHS/001/26	

For each relevant API, the calculated Peak PEC and Annual Average PEC shall be compared against the corresponding PNEC value. The Risk Quotient (RQ) shall be calculated as follows:

$$RQ = PEC / PNEC$$

Interpretation shall be as follows:

RQ < 1 : Environmental risk is considered acceptable

RQ > 1 : Additional control, mitigation, or reassessment is required

Where the RQ exceeds acceptable limits, the following shall be considered:

- Improvement in source control
- Reduction in API loss to wastewater
- Improvement in detoxification practice
- Optimization of onsite treatment
- Additional treatment or containment measures
- Review of discharge route and dilution assumptions

API concentration at ETP Polish RO outlet shall meet one of the following:

Not Detected, or

Below the product-specific acceptable limit / PNEC-linked target value, where established

6.9 Review of Results

Analytical results shall be reviewed by QC, EHS, and QA. If results meet the acceptance criteria, the wastewater treatment performance shall be considered adequate for the monitored API.

6.10 Deviation Handling

If the API concentration is detected above the acceptable limit, the deviation shall be investigated. Corrective action shall include review of detoxification effectiveness, ETP / RO performance, repeat sampling, and implementation of CAPA.

7.0 METHOD OF ANALYSIS

The effluent samples from ETP RO outlet shall be analyzed for API concentration levels by approved product-specific analytical methods, such as:

- HPLC
- UPLC
- LC-MS

Any other validated analytical method, as applicable

SHILPA PHARMA LIFESCIENCES LIMITED, UNIT-2	
REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC (PREDICTED NO EFFECT CONCENTRATION)	
Department: EHS	
Report No.: RPT/EHS/001/26	Page 9 of 11
Protocol Ref. No.: PC/EHS/001/26	

The analytical method shall be capable of detecting the target API at environmentally relevant concentrations. The method shall define:

- Instrument details
- Column / detector details
- Flow rate
- Wavelength or detection mode
- Mobile phase
- Standard preparation
- Test solution preparation
- System suitability criteria
- Calculation method
- Reporting format

The uploaded report uses HPLC with UV detector and reports the analytical results for detoxified samples as Not Detected, which supports the same type of analytical control framework

8.0 PiE RISK ASSESSMENT AND PEC/PNEC EVALUATION

The Pharmaceuticals in Environment (PiE) Risk Assessment Tool shall be used for evaluation of environmental risk associated with API residues in wastewater.

The following parameters shall be considered for the assessment:

Loss / PEC Calculation Items	Unit
Name of API	--
Total API Loss per Batch	Kg
API Loss as Solid Waste per Batch	Kg
API Loss into Streams Other Than Water per Batch	Kg
Number of Batches per Year	Nos
Number of Manufacturing Days per Year	Days
Batches per Day	--
API Loss per Manufacturing Day	Kg/day
Average API Loss per Day	Kg/day
API Loss to Wastewater per Manufacturing Day (Peak Loss)	Kg/day

SHILPA PHARMA LIFESCIENCES LIMITED, UNIT-2	
REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC (PREDICTED NO EFFECT CONCENTRATION)	
Department: EHS	
Report No.: RPT/EHS/001/26	Page 10 of 11
Protocol Ref. No.: PC/EHS/001/26	

Average API Loss in Wastewater per Day	Kg/day
Wastewater Flow to Onsite WWTP	m3/day
API Removal Efficiency in Onsite WWTP	%
Mode of Treatment in WWTP	--
Exit Flow from CETP/POTW to Receiving Water Body	m3/day
API Removal Efficiency in CETP/POTW	%
CETP/POTW Dilution Factor	--
Flowrate of Receiving Water Body	m3/day
Receiving Water Body Dilution Factor	--
Peak PEC	µg/L or applicable unit
Annual Average PEC	µg/L or applicable unit
PNEC	µg/L or applicable unit
Risk Quotient (RQ = PEC / PNEC)	--

8.1 Evaluation Criteria

The environmental risk shall be considered acceptable when:

Peak PEC < PNEC, and/or

Annual Average PEC < PNEC, and RQ < 1

8.2 Interpretation

If the RQ is greater than 1, suitable control measures shall be implemented, such as:

Minimizing API loss at source

Improving detoxification efficiency

Enhancing WWTP treatment efficiency

Improving containment and segregation

Reassessing process losses and dilution assumptions

8.3 Reporting

The PiE Risk Assessment Tool output shall be attached as supporting evidence and reviewed along with analytical results to demonstrate environmental acceptability of the wastewater management system.

9.0 CONCLUSION:

Based on the analytical results of samples collected from the ETP Polish RO outlet, and based on the assessment carried out through the Pharmaceuticals in Environment (PiE) Risk

SHILPA PHARMA LIFESCIENCES LIMITED, UNIT-2	
REPORT ON WASTEWATER MANAGEMENT PROTOCOL FOR ACHIEVING PNEC (PREDICTED NO EFFECT CONCENTRATION)	
Department: EHS	
Report No.: RPT/EHS/001/26	Page 11 of 11
Protocol Ref. No.: PC/EHS/001/26	

Assessment Tool, it can be concluded that the wastewater treatment system, including detoxification where applicable and treatment through ETP, RO, and Polish RO, is capable of controlling API concentration levels to acceptable limits or not detected levels.

Where the calculated PEC values are below the corresponding PNEC values and the Risk Quotient (RQ) is < 1 , the environmental risk is considered acceptable.

Calculate RQ values for all APIs as per Attachment IV, which are being treated in the existing wastewater treatment facilities to ensure $RQ < 1$ for all APIs to minimize environmental impact from API residues when discharged in the environment.

10.0 DISTRIBUTION RECORD:

S.No.	Department / Block	No. of Copies	Remarks
1.	EHS	01	----
2.	Production (AI, C, D, H, AM, E, G, AJ, AO, AO7, & I)	11	----
3.	QA	01	----
4.	QC	01	----

11.0 ATTACHMENTS:

- 11.1 API General Information and Detoxification Procedure : Attachment I
- 11.2 Requisition Slip & Results for Analysis of Process Effluent Samples : Attachment II
- 11.3 QC Executed Analytical Work Sheets and Chromatograms : Attachment III
- 11.4 Pharmaceuticals in Environment (PiE) Risk Assessment Tool : Attachment IV

SHILPA PHARMA LIFESCIENCES LIMITED (UNIT-2)

ANNEXURE-I

API GENERAL INFORMATION AND DETOXIFICATION PROCEDURE

Document No.: PC/EHS/001/26

Effective Date

Page No.: 1 of 1

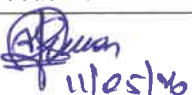
1. GENERAL INFORMATION OF API:

Name of the API	
Description	
IUPAC Name	
CAS Number	
Pharmacological Activity	
Molecular Formula	
Molecular Weight	
ADI Value ($\mu\text{g/kg/day}$)	
Solubility	
Detoxification Agent	
Handling Precaution	

2. DETOXIFICATION SOLUTION:

Name of the Product	Product Code	Detoxification Solution	Preparation of Detoxification Solution	Detoxification

3. DETOXIFICATION PROCEDURE:

	Prepared By	Reviewed By	Approved by
Name	Suman	R. Elangovan	N. Saravanan
Designation	Executive- EHS	DGM-EHS	AGM-QA
Sign & Date	 11/05/26	 11/05/26	 12/05/26

SHILPA PHARMA LIFESCIENCES LIMITED (UNIT-2)

ANNEXURE-II

REQUISITION SLIP FOR ANALYSIS OF PROCESS EFFLUENT SAMPLES

Document No.: PC/EHS/001/26	Effective Date:
	Page No.: 01 of 01

Location:	Date:		
Sampling Point:	Time:		
Sample Name:	Sample received time by QC:		
Sample No.:			
A.R. No.:	Analysis complete time :		
S.No.	Test	Result	Specification

Remarks: The sample complies / does not complies to above specifications.

Requested by:
Date :

Analyzed by :
Date :

	Prepared By	Reviewed By	Approved by
Name	Suman	R. Elangovan	N. Saravanan
Designation	Executive- EHS	DGM-EHS	AGM-QA
Sign & Date	 11/05/26	 11/05/26	 12/05/26

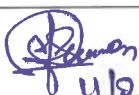
SHILPA PHARMA LIFESCIENCES LIMITED (UNIT-2)

ANNEXURE-III

QC ANALYTICAL WORK SHEET

Document No.: PC/EHS/001/26

Page __ of __

	Prepared By	Reviewed By	Approved by
Name	Suman	R. Elangovan	N. Saravanan
Designation	Executive- EHS	DGM-EHS	AGM-QA
Sign & Date	 11/05/26	 11/05/26	 12/05/26

SHILPA PHARMA LIFESCIENCES LIMITED (UNIT-2)

ANNEXURE-IV

PHARMACEUTICALS IN ENVIRONMENT (PiE) RISK ASSESSMENT TOOL

Document No.: PC/EHS/001/26

Page __ of __

Pharmaceuticals in Environment (PiE) Risk Assessment Tool

	Items	UOM	API-1
Loss	Name of API	Name	
	Total API loss Per Batch	Kg	
	API loss as solid waste/batch	Kg	
	API loss into streams other than water (per batch)	Kg	
	Number of batches per year	Nos	
	Number of manufacturing days/Year	Days	
	Batches/Day	-	
	API Loss per manufacturing day	Kg/d	
	Average API Loss per day	Kg/d	
	API Loss to wastewater/manufacturing day (peak Loss)	Kg/d	
	Average API Loss in waste water/day	Kg/d	
PEC calculation	Waste water flow to onsite WWTP.	m3/d	
	API removal Efficiency in onsite WWTP	%	
	Mode of treatment in WWTP	-	
	Exit flow from CETP/POTW to receiving water body	m3/d	
	API removal Efficiency in CETP/POTW	%	
	CETP/POTW dilution factor		
	Flowrate of receiving water body	m3/d	
	Receiving water body dilution Factor		
	Overall dilution factor	-	
	Peak PEC	µg/l	
	Annual Average PEC	µg/l	
Control	PNEC value	µg/l	
	(Risk quotient) RQ=PEC/PNEC	-	

	Prepared By	Reviewed By	Approved by
Name	Suman	R. Elangovan	N. Saravanan
Designation	Executive- EHS	DGM-EHS	AGM-QA
Sign & Date	 11/05/26	 11/05/26	 12/05/26