PROTOCOL FOR DETERMINATION OF BENDAMUSTINE HYDROCHLORIDE API CONCENTRATION LEVELS IN DETOXIFIED PROCESS EFFLUENT

Block : I Block
Product : Bendamustine Hydrochloride API

INDEX

APPROVAL PAGE

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

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1.0 OBJECTIVE:

To define procedure for determination of Bendamustine Hydrochloride API concentration levels in detoxified process effluent there by to evaluate the efficiency of detoxification process of Bendamustine Hydrochloride APIs and its compliance to good EHS practices.

2.0 SCOPE:

This protocol is applicable for estimation of Bendamustine Hydrochloride API concentration levels in detoxified process effluent / washings, which is manufactured in I Block at M/s. Shilpa Pharma Lifesciences Limited, Unit-2.

2.1 To determine the concentration of Bendamustine Hydrochloride API in detoxified process effluent / washings.

3.0 RESPONSIBILITIES:

3.1 It is the responsibility of production personnel to collect the detoxified process effluent / washings sample of Bendamustine Hydrochloride API in a clean sample bottle.

3.2 It is the responsibility of QC personnel to analyze the detoxified process effluent / washings sample for Bendamustine Hydrochloride API concentration levels as per regular Bendamustine Hydrochloride API method of analysis.

3.3 It is the responsibility of QC personnel to calculate the concentrations and to provide the results of Bendamustine Hydrochloride API residual levels.

3.4 It is the responsibility of Head EHS/designee to evaluate the results and to ensure the compliance to EHS requirements.

3.5 It is the responsibility of QA personnel to review and approval of the protocol.

4.0 ABBREVIATIONS/DEFINITIONS:

4.1 ABBREVIATIONS:

QC	:	Quality Control	U-2	:	Unit-2
QA	:	Quality Assurance	PC	:	Protocol
ADI	:	Acceptable Daily Intake	GEN	:	General
ETP	:	Effluent Treatment Plant	PD	:	Production
SOP	:	Standard Operating Procedure			
EHS	:	Environment, Health & Safety			
API	:	Active Pharmaceutical Ingredients			
CR&D	:	Chemical Research and Development			
HPLC	:	High Pressure Liquid Chromatography			
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.

5.0 REASON FOR THE STUDY:

Bendamustine Hydrochloride API manufacturing process is validated and is being produced commercially on regular basis. During product development CR&D has established the detoxification procedure and concluded that, 5 % Sodium Hydroxide solution detoxification is suitable for Bendamustine Hydrochloride API. Accordingly CR&D detoxification procedure has been adopted for commercial use and 5 % Sodium Hydroxide solution is being used for detoxification of Bendamustine Hydrochloride API prior to send the effluent for further treatment.

As part of continual improvement, challenging study is planned to re-assess the efficiency of 5 % Sodium Hydroxide solution for detoxification of Bendamustine Hydrochloride API.

5.1 To determine the concentration of Bendamustine Hydrochloride API in detoxified process effluent / washings.

6.0 DETOXIFICATION PROCEDURE FOR PROCESS EFFLUENT:

Detoxification procedure for process effluent / washings of Bendamustine Hydrochloride API mentioned in **'API General Information and Detoxification Procedure: Annexure-I'**.

7.0 API GENERAL INFORMATION'S:

API general information's like; Name of the API, Description, IUPAC Name, CAS number, Pharmacological Activity, Molecular formula, Molecular Weight, ADE/PDE/ADI, Solubility,

Pharmacological activity, Detoxification Agent and Handling Precaution has been attached in **'API General Information and Detoxification Procedure: Annexure-I'**.

8.0 SAMPLING PROCEDURE:

8.1 During API manufacturing, process effluent / washings shall be collected in respective decontamination tank from mother liquor tank / separation tank / dedicated container etc.

8.2 Detoxification procedure for process effluent / washings of respective API shall be performed as per **'API general information and detoxification procedure: Annexure-I'**.

8.3 After detoxification, production personnel shall collect the sample from decontamination tank to determine the concentration levels of API.

8.4 **Selection of Samples:** Three consecutive day's detoxified process effluent / washings samples shall be considered for analysis. Samples shall be identified as follows;

Effluent Samples Details	
Sample No.	**Sample from decontamination tank**
Sample-1 (Detoxified)	Day-1
Sample-2 (Detoxified)	Day-2
Sample-3 (Detoxified)	Day-3

8.5 Ensure before sending sample to QC, analysis master data to be uploaded in SAP.

8.6 Production authorized SAP user shall generate individual inspection lot for each sample in SAP by using T-Code: QA01 and material code (miscellaneous samples- 8600644).

8.7 Production personnel shall send sample to QC for analysis through **'Requisition Slip for Analysis of Process Effluent Samples: Annexure-II'**.

8.8 After completion of analysis and usage decision of miscellaneous inspection lot, SAP generated analytical report shall be collected from QC dept.

9.0 METHOD OF ANALYSIS API CONTENT (BY HPLC):

9.1 The effluent samples shall be analyzed for Bendamustine Hydrochloride API concentration levels as per regular Bendamustine Hydrochloride API method of analysis. For details of method of analysis is mentioned in **'Method for Analysis of API Content (by HPLC): Annexure-IV'.**

9.2 After completion of analysis, QC personnel shall review the analytical data and provide the results of Bendamustine Hydrochloride API concentration levels in effluent sample.

The results should be derived based on quantitative calculation (w/v) in **'QC Analytical work sheet Annexure-III'**.

9.3 After completion of analysis, QC team shall handover the leftover effluent samples to EHS representative for safe disposal.

10.0 ACCEPTANCE CRITERIA:

Bendamustine Hydrochloride API concentration levels in detoxified effluent samples should be Not Detected. The results shall be reviewed to know the concentration levels of Bendamustine Hydrochloride API in effluent thereby to conclude the efficiency of detoxification agent to kill the active compounds.

11.0 DATA COMPILATION AND EVALUATION:

Data shall be compiled in report and evaluation shall be carried out based on,

- Effluent samples results
- QC Analysis reports

12.0 CONCLUSION:

Based on the analytical results, conclusions shall be made on the efficiency of detoxification solution and its environmental impact in order to ensure compliance to good EHS practices.

13.0 DISTRIBUTION RECORD:

S.No.	Department / Block	No. of Copies	Remarks
1.	I	01	----
2.	QA	01	----
3.	QC	01	----
4.	EHS	01	----

14.0 ATTACHMENTS:

14.1 API general information and detoxification procedure : Annexure-I

14.2 Requisition Slip for Analysis of Process Effluent Samples : Annexure-II

14.3 QC Analytical work sheet : Annexure-III

14.4 Method for analysis of API content (by HPLC) : Annexure-IV