PROCESS VALIDATION PROTOCOL

FOR

TRANEXAMIC ACID INJECTION BP

100 mg/ml (500 mg in 5 ml)

PROCESS VALIDATION PROTOCOL FOR TRANEXAMIC ACID INJECTION BP 100 mg/ml (500 mg in 5 ml)

PROTOCOL CONTENTS

1.0 PROTOCOL APPROVAL

PREPARED BY:

DESIGNATION	NAME	SIGNATURE	DATE
OFFICER/EXECUTIVE (QUALITY ASSURANCE)			

REVIEWED BY:

DESIGNATION	NAME	SIGNATURE	DATE
EXECUTIVE/MANAGER (QUALITY ASSURANCE)			
HEAD (QUALITY CONTROL)			
HEAD (MICROBIOLOGY)			
HEAD (PRODUCTION)			
HEAD (ENGINEERING)			

APPROVED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (QUALITY ASSURANCE)			

2.0 OBJECTIVE:

- The objective of this protocol is to validate the manufacturing process of Tranexamic Acid Injection BP 100 mg/ml (500 mg in 5 ml) using qualified facilities, equipment & utilities by evaluating the consecutive batches being manufactured at the Ampoule Line.
- This study shall be conducted for the generation of sufficient data to establish documentary evidence that the manufacturing process including dispensing, CIP/SIP, bulk preparing, filtration, filling, sealing, visual inspection and packing process is suitable and appropriate for its intended purpose and validated process shall consistently meet the predefined specifications and quality attributes of the finished product.

3.0 SCOPE:

- The scope of this protocol is to validate the manufacturing process of Tranexamic Acid Injection BP 100 mg/ml (500 mg in 5 ml) ampoules manufactured at Ampoule Line.
- **Type of validation:** Concurrent Validation

4.0 RESPONSIBILITY:

DEPARTMENT	RESPONSIBILITIES
Quality Assurance	1. Responsible to prepare, review and approve process validation protocol. 2. To co-ordinate with cross functional teams to support the process validation execution and also responsible to monitor the execution of process validation. 3. Ensure that the facility/equipment's/instruments and utilities conform to the validated/calibrated state prior to the execution of process validation. 4. To review the trends/statistical evaluation for Critical Process Parameters (CPP) / Critical Quality Attributes (CQA) for every product manufactured at the site.
IPQA	1. To perform Process validation sampling as per sampling plan and submit them to Quality Control Department. 2. To monitor, verify and record critical process attributes. 3. To record and report any deviation either planned or unplanned happened during batch manufacturing.
QC	1. Responsible to review process validation protocol.

DEPARTMENT	RESPONSIBILITIES
	2. To analyze the samples as per sampling plan during process validation and to maintain the records of the test results followed by the reporting of the results. 3. Review of analytical data & submission of analytical results to QA.
Microbiology	1. Responsible to review process validation protocol. 2. Responsible to collect sample as per process validation protocol. 3. To analyze the samples as per sampling plan during process validation and to maintain the records of the test results followed by the reporting of the results. 4. Review & submission of results to QA.
Production	1. Responsible to review process validation protocol. 2. Ensure that the current effective version of SOP's, Batch Records etc. are implemented and Concerned Personnel are trained. 3. Prior to execution of process validation batch to ensure that facility / equipment / instruments & utilities are in validated / calibrated state. 4. Execution of process validation and collection of routine in-process samples as defined in the batch manufacturing record.

5.0 VALIDATION APPROACH

Validation shall be carried out in three consecutive batches with prospective approach as new product is introduced to the facility. Study shall be carried out in two phases

- Review of documents.
- Manufacturing of batches.

Review of documents shall include

- Standard Operating and cleaning Procedures & Qualification and Validation status of equipment and system.
- Manufacturing Process & BMR.
- Standard Testing Procedure.
- Raw material, packing material, in-process, finished product specifications.

6.0 REASON FOR VALIDATION:

- New Product manufactured at Ampoule Line.

7.0 REASON FOR REVALIDATION:

- Any major change in the manufacturing process which may affect the quality of the product.
- Any change in the batch size.
- Any change in the batch formula.
- Change in manufacturing site.
- Any modification in any critical equipment.
- Any major modification in the related utility system.
- Any change in the specification and/or change in the source of active pharmaceutical ingredient (API).

8.0 PRE-REQUISITE

8.1 TRAINING DETAILS:

- The validation team shall be approved by Head-QA
- All the personnel involved in the manufacturing and Packing of Validation Batches, Sampling and Testing of Validation Samples should be appropriately trained both in their job related activities and on the process validation protocol by Head-QA.

8.2 PRODUCT INFORMATION:

GENERIC NAME	**:**	Tranexamic Acid Injection BP 100 mg/ml
LABEL CLAIM	**:**	**Each ml contains:** Tranexamic Acid BP……100 mg Water for Injections BP ……q.s
PACK SIZE	**:**	5 ml Clear Glass Ampoule USP Type-I with blue dot (OPC)
STANDARD BATCH SIZE	**:**	240 Liters / 47058 Nos.
MANUFACTURING LICENSE No. :		…….
SHELF LIFE	**:**	36 Months
MARKET	**:**	Export
DOSAGE FORM	**:**	Liquid injection
DESCRIPTION	**:**	A clear, colorless solution free from foreign particulate matter filled in 5 ml clear glass ampoules.
STORAGE CONDITION	**:**	Do not store above 25ºC. Store in the original packaging. Do not refrigerate or freeze.
MANFACTURING LOCATION	**:**	

8.3 ENVIRONMENT MONITORING:

All environment parameters of critical area as listed shall be verified during execution of the process validation study.

- Passive air sampling/Settle plate monitoring
- Active air sampling/Volumetric air sampling
- Surface monitoring
- Personnel monitoring
- Non-viable particle monitoring
- Pressure differential monitoring
- Temperature & Relative humidity monitoring

8.4 MANUFACTURING PROCESS INSTRUCTIONS:

- **Manufacturing process**: Sequential steps in manufacturing process shall be followed as per the approved current BMR. Process parameters during each unit operation shall be monitored to demonstrate that product meets the acceptance criteria.
- **Raw material**: Raw materials to be used in the manufacturing shall be procured from the approved vendor and shall meet all the specifications in the analysis prior to use. All the raw materials shall have valid certification from quality control lab before use for manufacturing. Containers used in the dispensing of raw materials should be clean and dry. After dispensing of API, it should be stored in air tight container.
- **Primary Packing Materials**: Primary packing materials being used in the manufacturing shall be procured from the approved vendor and shall meet the laid down specification in the analysis prior to use.
- **Secondary & Tertiary Packing Material:** Secondary and Tertiary packing materials being used in the packaging process shall be procured from the approved vendor and shall meet the laid down specification in the analysis prior to use.
- **Bulk Preparing:** Temperature of bulk solution is to be maintained during entire batch manufacturing process. Bulk solution hold in SS 316 L mixing vessel should not exceed 12 hours before filtration and filtered bulk solution hold in SS 316 L holding vessel should not exceed 24 hours before final filtration.

- **Filtration**: Pre-integrity test and post-integrity test of 0.2 µ filter shall be done with Bubble Point Test at 20°C to 25°C. Bulk solution filtration and filling should not exceed 24 hours.
- Visual inspection of Ampoule for any defect like glass particles, black particles, sealing defects, empty Ampoule, low fill, over fill etc.

8.5 MANUFACTURING FORMULA:

RAW MATERIALS:

S.No.	Material Code	Ingredients	Specifications	Manufacturer Name	Label Claim	Theoretical Quantity (For 240 L)	Unit
1.		Tranexamic Acid	BP		100 mg/ml	24.363*	Kg.
2.		Disodium Edetate	BP		--	0.120	Kg.
3.		Sodium Hydroxide	BP		--	0.120#	Kg.
4.		Water for Injection	BP		--	q.s.	Ltr.

Remark 1: *Material has been taken with considering the assay NLT 99.0% on dried basis and LOD: NMT 0.5%.
Remark 2: # This qty. use for pH adjustment only.

PRIMARY PACKING MATERIALS:

S.No.	Material Code	Name of Material	Manufacturer Name	Function	Theoretical Quantity (For 240 L / 47058 Nos.)	Unit
1.		Clear Glass Ampoules 5 ml USP Type – I with Blue dot (OPC)		Primary Packing Material	47999*	Nos.

Remark:* 2% excess quantity of material to compensate processing loss.

8.7 BATCH DETAILS:

Batch No.	Manufacturing Date	Expiry Date	Shelf Life	Standard Batch Size
			36 months$	
			36 months$	
			36 months$	

Batch details such as batch number, manufacturing date and expiry date shall be recorded during protocol execution.
$ Shelf life is provisional and shall be ascertained based on real time stability data.

8.8 EQUIPMENT QUALIFICATION VERIFICATION:

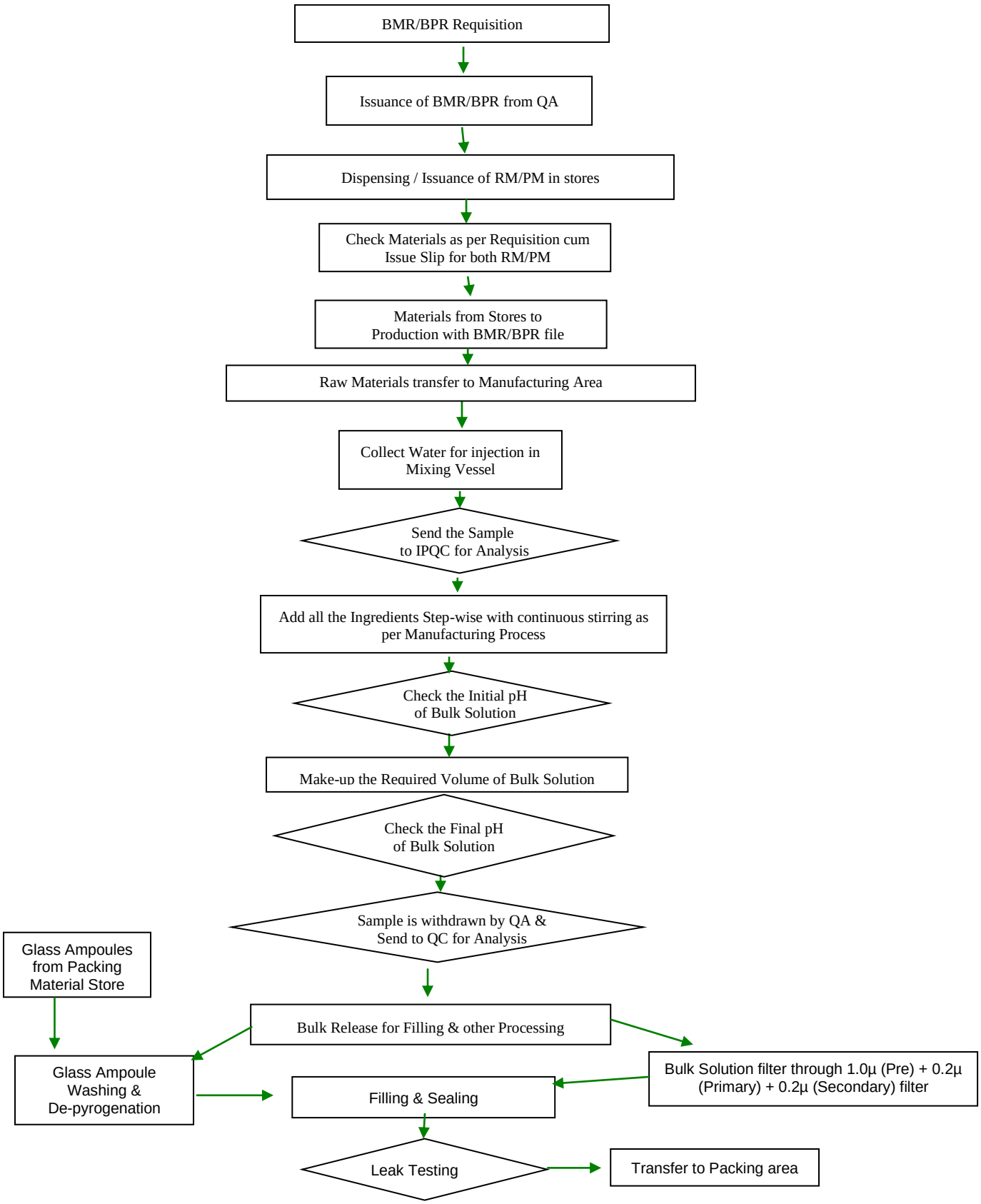
Ensure all equipment's to be used for the manufacturing must be qualified as per Qualification acceptance criteria. The reference Qualification Documents shall be verified and mentioned in the Process Validation Report. The list of major equipment's used for manufacturing of Tranexamic Acid Injection BP 100 mg/ml (500 mg in 5 ml) in Ampoule line mentioned below:

S.No.	Name of Equipment / Machine	Make	Identification No.
1.	Mixing Vessel		
2.	Holding Vessel		
3.	Ampoule washing machine		
4.	Ampoule Filling & Sealing Machine		
5.	Sterilization and Depyrogenating tunnel		
6.	Automatic Optical Inspection machine		
7.	Dynamic pass box		
8.	Dynamic pass box		
9.	LAF for Ampoule-2		
10.	Buffer Vessel		
11.	Visual inspection booth		
12.	Autoclave		
13.	Leak Test Apparatus		

PROCESS VALIDATION PROTOCOL FOR TRANEXAMIC ACID INJECTION BP 100 mg/ml (500 mg in 5 ml)

9.0	**MANUFACTURING PROCEDURE:**
	Dispensing, bulk preparation, filtration, filling & sealing and visual inspection shall be carried out as per the approved batch manufacturing record. All respective process parameters shall be evaluated as specified in this protocol.
	After each stage of process like bulk preparation, filtration, aseptic filling, the samples shall be tested.
	Test Results and data generated during the process validation study shall be compiled and reviewed at each stage of manufacturing.
	Warehouse shall issue the primary packing materials to production department based on the batch record.
	Ampoules are transferred to de-cartoning room for further processing.
	machine parts shall be sterilized in Autoclave Bung Processor as per the pre-validated loading pattern.
	After sterilization the machine parts shall be unloaded in sterile material unloading area and aseptically transferred to the filling room through mobile LAF and Assemble the accessories aseptically on filling machine as per respective SOP.
	Ampoules shall be decartoned & inspected in decartoning room and transferred to the ampoule washing machine through conveyor.
	The ampoules shall be washed using ampoule washing machine. The washed ampoule are depyrogenated through the Tunnel Sterilizer.
	The depyrogenated ampoules are obtained on the turn table of the ampoule-filling machine from tunnel sterilizer. The critical area Temperature, RH and differential pressure shall be checked & recorded.
	Perform the CIP, SIP, of mixing vessel and holding vessel along with product transfer line.
	Process validation batch of Tranexamic Acid Injection BP 100 mg/ml (500 mg in 5 ml) with a batch size of 240.00 L will be manufactured as per the approved BMR.
	After completion batch manufacturing activity, bulk solution is passed through the 0.2 µ filter from mixing vessel to holding vessel and record the filtration activity in BMR.
	Then bulk solution shall be filtered through 0.2 µ filter installed before the buffer vessel.
	Perform the filter integrity test for 0.2 µm filters before & after filtration.
	The filling machine shall fill the solution in to depyrogenated ampoules through the manifold, filling pump & filling nozzles.
	After completion of the batch sealing activity, reconcile all materials, yield are calculated and recorded in the batch record.
	Sealed ampoules are transferred to visual inspection and inspect the ampoules as per respective SOP.
	After visual inspection good ampoules shall be transferred to packing department.

10.0 PROCESS FLOW DIAGRAM:



11.0 DETERMINATON OF CRITICAL PROCESS PARAMETERS (but not limited):

Process Steps	Process Parameters	Rationale	Critical/ Non critical	Assessment Criteria
Dispensing	• Temperature • RH % • Balance Verification	Temperature, RH is critical and shall be maintained as per API and raw material requirement.	Critical	• Temperature: NMT 25°C • RH: NMT 55% • Should be Complies
Sterilization of Equipment's	• Sterilization time • Sterilization temperature	Sterilization time, Sterilization Temperature is critical and shall be maintained as per Sterility requirement.	Critical	• Sterilization time: NLT 30 Mins. • Sterilization temperature for m/c part: NLT 121.4° C • Sterilization temperature for mixing vessel & holding vessel: NLT 122° C
Preparation of bulk solution	• Load cell Verification • Temperature • pH • Stirrer speed • Volume makeup	Temperature and pH is critical for stability of formulation. Stirrer speed should be maintained to ensure complete dissolution of API and excipients.	Critical	• Should be Zero • Temperature: 40°C to 50°C • Stirring Speed: 250 RPM to 400 RPM • pH: 6.7 to 7.8 • 240 L
Filtration	• Filter type • Make • Filter pore size • Filter integrity • Filtration pressure • Filtration Time	Filtration is most critical step to maintain the sterility of the product	Critical	• Sartopore- 2 • Sartorius • 0.2 µ • ≥ 3172 mbar • ≤ 5000 mbar • NMT 2.5 kg • Total Filtration Time
Ampoule washing	• Pressure of Compressed Air • Pressure of Recycled WFI-1	During washing all respective parameters need to be checked for achievement of specified limit	Critical	• Pressure of Compressed Air 0.20 to 0.60 MPa • Pressure of Recycled WFI-1 0.20 to 0.50 Mpa

Process Steps	Process Parameters	Rationale	Critical/ Non critical	Assessment Criteria
	• Pressure of Recycled WFI-2 • Pressure of WFI • Speed of ampoule washing machine	mentioned in respective BMR/SOP for proper cleaning of each ampoule		• Pressure of Recycled WFI-2 0.12 to 0.50 Mpa • Pressure of WFI 0.07 to 0.30 Mpa • 210 to 420 ampoules/min
Depyrogenation of ampoules	• Temperature • DP of Drying, Heating and cool zone • Conveyor speed	During Depyrogenation all respective parameters need to be checked for achievement of specified limit mentioned in respective BMR/SOP for proper Depyrogenating of each ampoules.	Critical	• Preheating Zone • Heating Zone: More Than 320ºC • Cooling Zone: NMT 30ºC • Preheating Zone to room – 05-10 Pa • Heating Zone to room – 06-12 Pa • Cooling Zone to room – 05-10 Pa • NMT 110 mm/min
Aseptic filling and sealing of ampoules	• Filling Speed • Fill Volume verification • Sealing height • Sealing quality • Sealing integrity	Fill volume and filling speed is critical for content uniformity.	Critical	• 200 to 400 ampoules/min • 5.05 to 5.15 ml • 69 ± 2 mm • Free from sealing defect • Leak test shall be passed
Labelling Machine	• Machine Speed • Label printing quality	During Ampoule Labeling all respective parameters need to be checked for Quality Expects	Non Critical	• 200 to 300 ampoules/min • Label printing quality & text matter shall be readable
Blister/Tray packing	• Tray pack Forming temperature • Machine Speed	During Blister packing all respective parameters need to be checked for Quality Expects	Non Critical	• 135^0C to 155^0C • 20 to 40 CPM
Visual inspection	• Critical, major, minor defects	Removal of defective ampoules	Critical	• Visual inspection shall be done as per respective SOP

11.1 HOLD TIME OF COMPONENT:

- Cleaned & sterilized component/garments shall be used within the recommended hold time of respective components and shall be stored under LAF unit.
- Hold time shall be considered from the process end time i.e. cleaning & sterilization upto the uses of components.
- Recommended hold time of various component at different stages is mentioned below.

S.No.	Location	Stage	Component	Recommended Hold Time
1.	Ampoule Line	After Cleaning	Mixing Vessel	24 Hours
2.			Holding Vessel	24 Hours
3.			m/c Parts	24 Hours
4.		After Sterilization	Sterile Garments	48 Hours
5.			Mixing Vessel	24 Hours
6.			Holding Vessel	24 Hours
7.			m/c Parts	24 Hours

12.0 SAMPLING AND ANALYSIS PLAN:

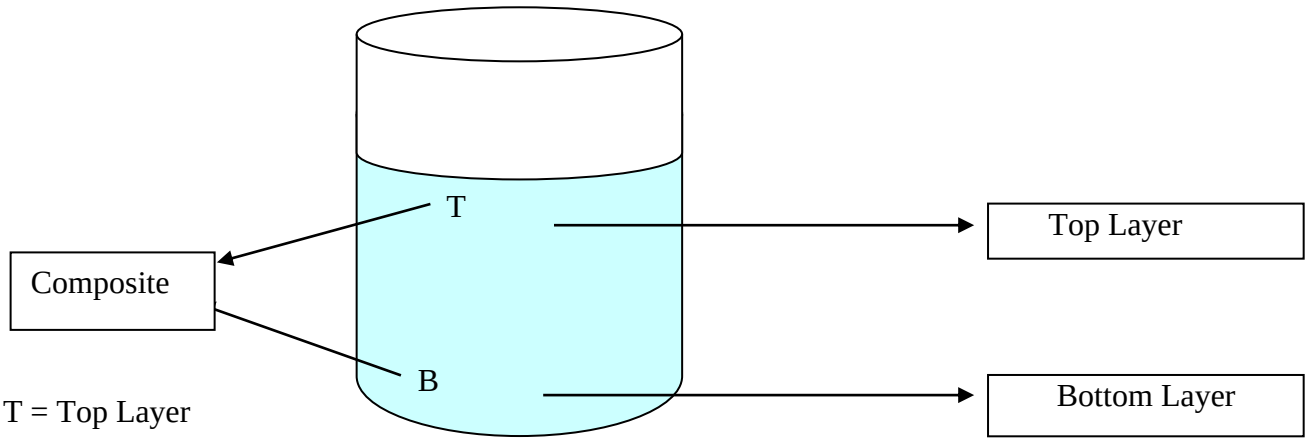
Collect the samples at various intervals at different operations as per the Sampling Plan mentioned below.

STAGE	Location of Collection	Test to be performed	Sample size	Responsibility
Cleaning of Equipment's	Mixing Vessel	Description Clarity pH Conductivity	100 ML	QA/QC & Production
	Holding Vessel	Description Clarity pH Conductivity	100 ML	
	m/c Parts	Description Clarity pH Conductivity	100 ML	
Water for Injection	Before batch mixing	Description pH Conductivity	100 ml	QA/QC & Production
		BET	10 ml	QA/Micro & Production
Preparation of Bulk Solution	Bulk Mixing after 15 min. (Top)	Description pH Assay	50 ML	QA/QC & Production
	Bulk Mixing after 15 min. (Bottom)	Description pH Assay	50 ML	
	Bulk Sample before Filtration	Description pH Weight per ml Colour Index Assay	100 ML	
		Bioburden	100 ML	QA/Micro & Production
Filtration of Bulk Solution	Bulk sample after filtration	Sterility	100 ML	QA/Micro & Production
Turn Table	Ampoule Before Washing	Bioburden	10 Nos.	QA/Micro & Production
Washing Ampoules	Washed Ampoule (For PV batches initial, Middle, End)	LBPC Visual Inspection	36 Ampoule from each stage	QA/QC & Production
	Ampoule After Washing	Bioburden	10 Nos.	QA/Micro & Production
Depyrogenated Ampoule	Initial of filling Middle of filling	Sterility	22 Ampoules from each	QA/Micro & Production

STAGE	Location of Collection	Test to be performed	Sample size	Responsibility
	End of filling	BET	stage.	
Nitrogen gas from user point	From ampoule Filling area (For PV batches Initial, Middle, End of filling)	Sterility	1000 Ltr.	QC Micro
Filling & Sealing	Initial of filling Middle of filling End of filling	Description	35 Nos. from each stage	QA & Production
		Extractable volume		
		Acidity or Alkalinity		
		Particulate Contamination		
		Assay		
		Sterility	22 Nos. from each stage	QA/Micro & Production
		BET		
Finished sample	Finish Stage	Description	35 Nos.	QA/QC & Production
		Identification		
		Extractable volume		
		Acidity or Alkalinity		
		Related Substances		
		Particulate Contamination		
		Assay		
		BET	22 Nos.	QA/Micro & Production
		Sterility		

13.0 SAMPLING LOCATIONS:

MIXING VESSEL:



T = Top Layer

B = Bottom Layer

T + B = Composite (Bulk sample before filtration)

14.0 ACCEPTANCE CRITERIA:

S.No.	Stage	Test	Acceptance criteria
1.	Cleaning of equipment's	**Description**	Clear Colorless Liquid
		Clarity	Should be clear
		pH	5.0 to 7.0
		Conductivity	NMT 1.3 µs/cm
2.	Water for Injection	**Description**	Clear Colourless Liquid.
		pH	5.0 to 7.0
		Conductivity	NMT 1.3 µS/cm
		BET	NMT 0.25 EU/ml
3.	Ampoule before Washing	**Bio-burden**	For Informative
4.	Ampoule Washing	**Visual Inspection**	Should be visually clean
		Clarity Test by LBPC	
		Visible particles:	Should be free from any visible particulate matter
		For sub visible particles :	(i) ≥ 10µm - NMT 6000 / container (ii) ≥ 25µm - NMT 600 / container
		Bio-burden	NMT 10 CFU / 100 ml
5.	Depyrogenated Empty Ampoule	**Sterility**	Should be sterile after 14 days of incubation.
		BET	NMT 0.25 EU/ml
6.	Nitrogen Gas	**Sterility**	Should be sterile after 14 days of incubation.
7.	Bulk Mixing	**Description**	A Clear colorless solution.
		pH	6.7 to 7.8
		Weight per ml	0.995 to 1.05 g/ml
		Colour Index	NMT 0.200 AU
		Assay: **Each ml contains:** Tranexamic Acid BP 100 mg	97.00 mg to 105.00 mg (97.0 % to 105.0 % of label claim)

S.No.	Stage	Test	Acceptance criteria
8.	Filling and Sealing	**Description**	A clear colorless solution free from foreign particulate matter filled in 5 ml clear glass ampoules.
		Identification	
		By IR	The Infrared absorption spectrum of the crystals should be concordant with the reference spectrum of tranexamic acid.
		Extractable Volume	NLT 5 ml
		Acidity or Alkalinity	6.5 to 8.0
		Related Substance	
		Impurity A	NMT 1.00%
		Impurity B	NMT 0.50%
		Impurity C	NMT 0.10%
		Impurity D	NMT 0.10%
		Any Other Secondary Impurity	NMT 0.10%
		Total Impurity	NMT 2.00%
		Bacterial Endotoxins	Less than 35 IU per ml.
		Test for Sterility	Should comply test of sterility.
		Particulate Contamination	
		Visible particles:	Should be free from any visible particulate matter
		For sub visible particles :	(i) ≥ 10 micron - NMT 6000 / container (ii) ≥ 25 micron - NMT 600 / container
		Assay: **Each ml contains:** Tranexamic Acid BP 100 mg	95.00 mg to 105.00 mg (95.0 % to 105.0 % of label claim)

15.0 CONTINUOUS PROCESS VERIFICATION:

Continuous Process Verification will be carried out for continuous monitoring of manufacturing process both Critical Quality Attributes & Critical Process Parameter as per SOP.

16.0 DEVIATIONS:

All protocol deviation, non-conformances and out of specification results obtained shall be investigated in accordance with corresponding SOP's and documented in the validation report.

17.0 VALIDATION REPORT:

A Validation Report shall be prepared as per the sampling and analysis plan mentioned in this Protocol by Quality Assurance Department. This Report shall be pre-approved by all functional heads of all the concerned departments. Validation data shall be recorded by Quality Assurance Department in the controlled copy of the pre-approved Process Validation Report. This Process Validation Report shall be reviewed and then post-approved by all functional heads of all the concerned departments.

18.0 CONCLUSION:

Validation data shall be written on Process Validation Report, clearly stating the achievement or Non-compliance of the acceptance criteria, effect of the deviations made during the validation and in case of failure, investigation carried out and their findings.

19.0 REFERENCE DOCUMENTS:

19.1 Relevant Specifications and Standard Testing Procedures

19.2 Relevant Standard Operating Procedures

19.3 Relevant Qualification Documents

19.4 British Pharmacopoeia

19.5 Supplementary Guidelines on (GMP): Validation

20.0 LIST OF ATTACHMENTS:

The relevant following documents to be attached with the Validation Report:

1. Records for all critical parameters with graphical representation, where applicable.
2. Relevant Sterilization Charts
3. Raw Data of Validation Testing.

4. Certificate of Analysis of API.
5. Certificate of Analysis of Finished Product.

21.0 ABBREVIATIONS:

API	: Active Pharmaceutical Ingredient
BP	: British Pharmacopoeia
BMR	: Batch Manufacturing Record
BPR	: Batch Packing Record
GMP	: Good Manufacturing Practice
IPQA	: In-process Quality Assurance
NLT/NMT	: Not Less Than/ Not More Than
SOP	: Standard Operating Procedure
STP	: Standard Testing Procedure
w/v	: Weight by volume
BET	: Bacterial Endotoxins Test
CIP	: Clean in Place
SIP	: Sterilization in Place

22.0 REVISION HISTORY:

Revision No.	Change Control No.	Detail of Changes	Reason for Change	Effective Date	Updated By
00		NA	New Protocol		