PROCESS VALIDATION PROTOCOL

FOR

LEVOCETIRIZINE DIHYDROCHLORIDE

SYRUP

PROCESS VALIDATION PROTOCOL FOR LEVOCETIRIZINE DIHYDROCHLORIDE SYRUP

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1.0 PROTOCOL APPROVAL

PREPARED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE

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2.0 OVERVIEW:

2.1 OBJECTIVE:

To validate the manufacturing process of **Levocetirizine Dihydrochloride Syrup** as per the Batch Manufacturing Record & Batch packing record to establish documentary evidence that the process will consistently produce the product, meeting its predetermined in-process and finished product specifications by examining three consecutive batches.

2.2 SCOPE:

This protocol is applicable to the three batches of **Levocetirizine Dihydrochloride Syrup** manufactured in liquid section to be taken for conducting validation study.

2.3 RESPONSIBILITY:

Following department shall be responsible for conducting validation study.

Production	:	Operating the production process as per process parameter
Engineering	:	Maintenance of facility, equipments and utilities as per the Batch requirement.
Quality Control	:	Testing of Raw Material, Packing Material, In-process Samples, and finished samples as per the specifications.
Quality Assurance	:	Monitoring the key quality parameters, sampling at various Processing stages as per protocol. Collection of reports from QC, processing data from production and compilation, Review and approval the protocol and report.

2.4 RE-VALIDATION CRITERIA:

Revalidation on three consecutive batches shall be carried out, if there are:

2.4.1 Changes in the Raw material(s), if there is change in vendor (API).

2.4.2 Change or replacement in any critical part of equipment or complete change in any equipment.

2.4.3 Changes in manufacturing process or other changes that could affect product quality.

2.4.4 Changes in the manufacturing area and support system.

2.4.5 Three sequential batches that fail to meet product & process specification.

2.4.6 Change in the process validation parameters.

2.4.7 Change in batch size, revalidation shall be Performed up to mixing stage.

3.0 PRODUCT INFORMATION:

Product Name		
Generic Name	Levocetirizine Dihydrochloride Syrup.	
License No.		
Product code		
Description	Light orange to orange coloured syrup with Pineapple flavour.	
Label Claim	**Each 5ml contains**	
	Levocetirizine Dihydrochloride I.P.	2.5 mg
	Flavored Syrupy base	q.s.
	Colour: Sunset Yellow FCF	
Batch Size	600.00 liters /20,000 bottles	
Pack Size	30 ml	
Storage Condition	Sore at a temperature below 30ºC, protect from light.	
Market		

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3.1 LIST OF RAW MATERIAL:

S.No.	ITEM CODE	INGREDIENTS	SPEC.	QTY./600 Liters (in kg)
1.		*Levocetirizine Dihydrochloride	IP	0.300
2.		Sugar (Refined)	IP	300.000
3.		Methyl Paraben	IP	0.900
4.		Propyl Paraben	IP	0.120
5.		Disodium EDTA	IP	0.012
6.		Citric acid	IP	0.198
7.		Tri-sodium citrate	IP	0.180
8.		Sorbitol (70% Non-crystallizing)	IP	90.000
9.		Pineapple Flavour	IHS	1.200
10.		Colour Sunset Yellow FCF	IHS	0.010
11.		Purified water	IP	q.s.

3.2 LIST OF PACKING MATERIAL:

S.No.	INGREDIENTS	UOM	STD. QTY./20,000 Bottles
1.	Amber Coloured 30 ml PET Bottles	Nos.	20,400
2.	ROPP Caps 25 mm golden colored with logo EPE Wads	Nos.	20,400
3.	Sticker Labels	Nos.	20,400
4.	Measuring Cups 10 ml	Nos.	20,400
5.	Cartons	Nos.	20,400
6.	Shipper 5 Ply	Nos.	204

4.0 LIST OF REFERENCE DOCUMENTS:

S.No.	DOCUMENT	REFERENCE
1	Master Formula Record	
2	Master packing record	
3	Batch manufacturing record	
4	Batch packing record	
5	Bulk Product Specification	
6	Finished Product Specification	

NOTE: Current revision / version of document to be referred.

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5.0 RATIONALE FOR IDENTIFICATION OF CRITICAL STEPS TO BE VALIDATED:

5.1 Preparation of Sugar Syrup:

5.1.1 Take required quantity of purified water in 600.0 Liters of Sugar preparation Vessel. Heat it up to 90ºC. Add dispensed quantity of Methyl Paraben (0.900 Kg), Propyl Paraben (0.120 Kg), Disodium EDTA (0.012) and Sugar (300.000 Kg) in same sequence. Continuous stirring to dissolve Sugar Syrup.

5.1.2 After dissolution, allow cooling of sugar syrup to 40ºC and filter the sugar syrup through Bucket Filter (5 micron) in manufacturing Vessel.

Variables: Temperature of purified water & Cooled Syrup temperature.

5.2 Addition of Levocetirizine Dihydrochloride:

Take required quantity of Purified Water Add Levocetirizine Dihydrochloride in Purified Water. under continuous stirring to dissolve. Transfer the solution to main tank.

5.3 Addition of Excipients:

5.3.1 Add Sorbitol 70 % Non- Crystallizing (90.00 Kg) in to Mfg. tank under constant stirring.

5.4 Addition of colours & flavors:

5.4.1 Take. Purified water Add the Color Sunset Yellow FCF. When completely dissolve add it in to Mfg. tank.

5.4.2 Add the Pineapple Flavour in to Manufacturing vessel under constant stirring.

5.5 pH adjustment:

5.5.1 Take required Purified water add citric acid in it. After complete dissolution transfer it to manufacturing tank under constant stirring of 15 minutes at 50 RPM.

5.5.2 Take required Purified water add tri Sodium citrate in it. After complete dissolution transfer it to manufacturing tank under constant stirring of 10 minutes at 50 RPM for adjusting the pH.

5.5.3 Adjust the pH (Limit 4.0 to 5.0)

5.6 Volume makeup & final mixing:

5.6.1 Take purified water to make up the volume to 600.0 ltrs and stir continuously for 20 minutes.

Variables: mixing time

Test Parameter: Description, pH, Weight/ml & Assay.

5.7 Filtration:

5.7.1 Before starting the filtration process, Production person shall take line clearance of filtration from QA person.

5.7.2 QA person shall verify the cleaning of filter press; filter the syrup using filter press through the sparkler filter using 1 micron filter. Store the solution in storage Tank.

5.8 PACKING (Filling & Sealing):

During packing operation, the bottles will be filled & sealed, labeled, place the measuring cup and then packed in carton and after that pack in to the shipper.

Variables: Filling Speed.

Test Parameters: Leak Test.

6.0 PROCESS VALIDATION PRE-REQUISITE:

Following shall be the pre- requisite for process validation of **Levocetirizine Dihydrochloride Syrup**.

6.1 PROCESS QUALIFICATION:

6.1.1 All the key process variables are to be identified and their operating ranges to be established.

6.2 RAW MATERIAL ACCEPTANCE:

6.2.1 All the raw materials to be used in the manufacturing shall be procured from approved vendors.

6.2.2 All the raw materials shall be tested as per respective specifications and approved by QC prior to use.

6.3 PACKING MATERIAL ACCEPTANCE:

6.3.1 All the primary packing materials and printed packing materials to be used in the manufacturing shall be procured from approved vendors.

6.3.2 All the packing materials shall be tested as per respective specification and approved by QC prior to use.

6.4 EQUIPMENT/INSTRUMENT QUALIFICATION:

6.4.1 The manufacturing equipment and control instruments to be used for manufacturing and analysis of the product shall be qualified.

6.4.2 All the instruments used in the process shall be duly calibrated as per the calibration schedule.

6.5 SUPPORT SYSTEM QUALIFICATION:

6.5.1 The support system, i.e. HVAC & Water system shall be qualified. The environmental conditions should meet the pre defined acceptance criteria prior to conducting the process validation study.

6.6 QUALITY SYSTEM:

6.6.1 Relevant SOPs shall be in place and training shall be completed on equipment operation, manufacturing instructions and sampling.

7.0 PROCESS EQUIPMENT:

S.No.	EQUIPMENT	EQUIPMENT NUMBER
1.	Dispensing Booth (Excipients)	
2.	Dispensing Booth (API)	

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S.No.	EQUIPMENT	EQUIPMENT NUMBER
3.	Dispensing Booth (Solvents)	
4.	Sugar preparation tank	
5.	Bucket filter	
6.	Manufacturing tank	
7.	Storage Tank	
8.	Filter press	
9.	Bottle Washing Machine	
10.	Filling Machine	
11.	Sealing Machine	
12.	Visualization Table (Filled Bottles)	
13.	Labeling Machine	
14.	Packing Conveyor Belt	
15.	Leak Test Apparatus	

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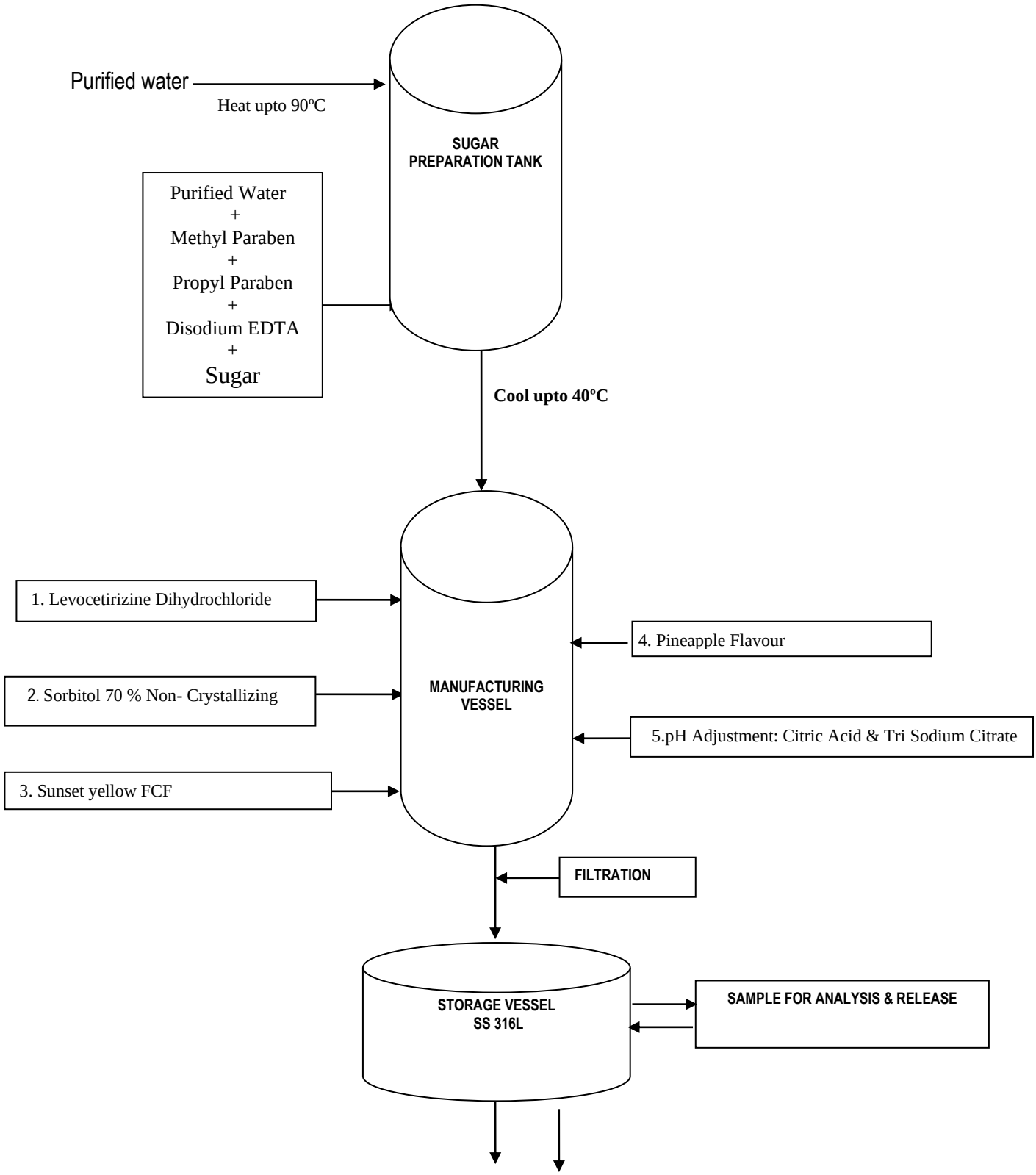
8.0 MANUFACTURING & PACKING PROCEDURE:

8.1 PROCESS FLOW CHART



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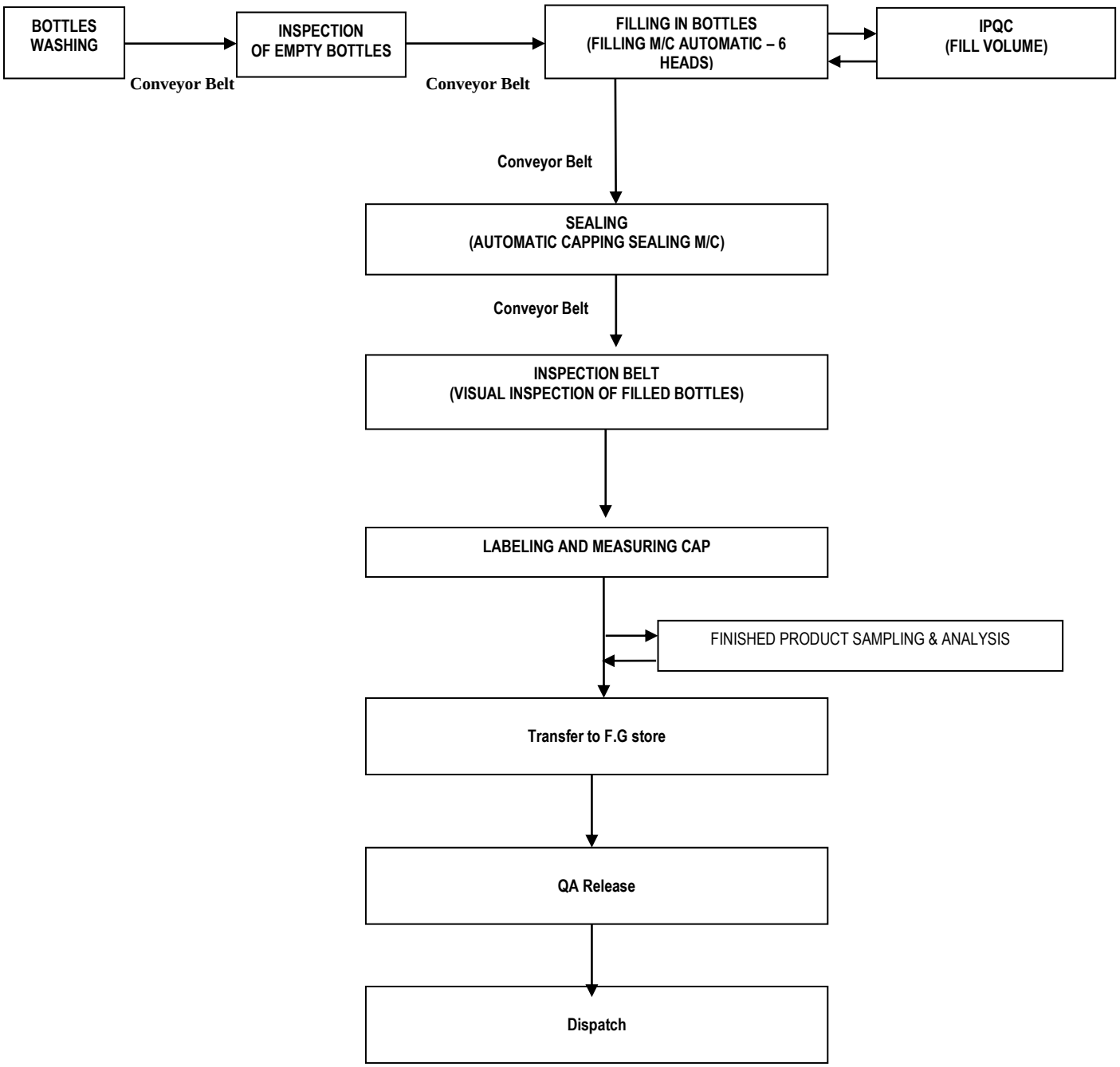

8.2 CRITICAL PROCESS PARAMETERS TO BE MONITERED DURING PROCESSING & PACKING:

S.No.	PROCESS	PARAMETER	SPECIFICATION
1.	**Sugar Syrup Preparation**	Purified Water Temperature	90±5ºC
		Mixing Time	For information only
		Cooled Syrup Temperature (Sugar syrup)	NMT 40ºC
		Filter	5 micron
2.	**pH adjustment**	Stirring time and RPM in addition of Citric acid	15 minutes at 50 RPM.
		Stirring time and RPM in addition of Tri sodium citrate	10 minutes at 50 RPM.
3.	**Final Syrup**	Description	Light Orange to orange colour liquid with pineapple flavor.
		Mixing Time	20 minutes
		pH	4.0 to 5.0
		Wt/ml	1.10 to 1.30 gm/ml
		Assay (Each 5 ml contains) Levocetirizine Dihydrochloride I.P. 2.5 mg	90% to 110%
4.	**Filling & Sealing)**	Description	Light Orange to orange colour liquid with pineapple flavor.
		Average Fill Volume	NLT 30ml
		Fill variation	91% of 109%
		pH	4.0 to 6.0
		Wt/ml	1.10 to 1.30 gm/ml
		Sealing & Threading quality	Should be clean
		Leak test	None of the bottle should be failed in leak test
		Microbial limits	
		TAMC (Total Aerobic Microbial Count)	NMT 100 cfu /ml
		TYMC (Total Microbial Yeast & Mould Count)	NMT 10 cfu /ml
		Escherichia Coli	Should be absent /ml
		Salmonella species	Should be absent /10ml
		Pseudomonas	Should be absent /ml
		S. Aureus	Should be absent /ml

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S.No.	PROCESS	PARAMETER	SPECIFICATION
		Assay (Each 5 ml contains) Levocetirizine Dihydrochloride I.P. 2.5 mg	90% to 110%
5.	**Packing**	Labeling on Bottles	Should be labeled properly.
		Batch Coding on Bottles	Should be readable.
		Measuring caps	Should be place on each bottle.
		Sealing quality	Should be proper.

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9.0 VALIDATION SAMPLING PLAN

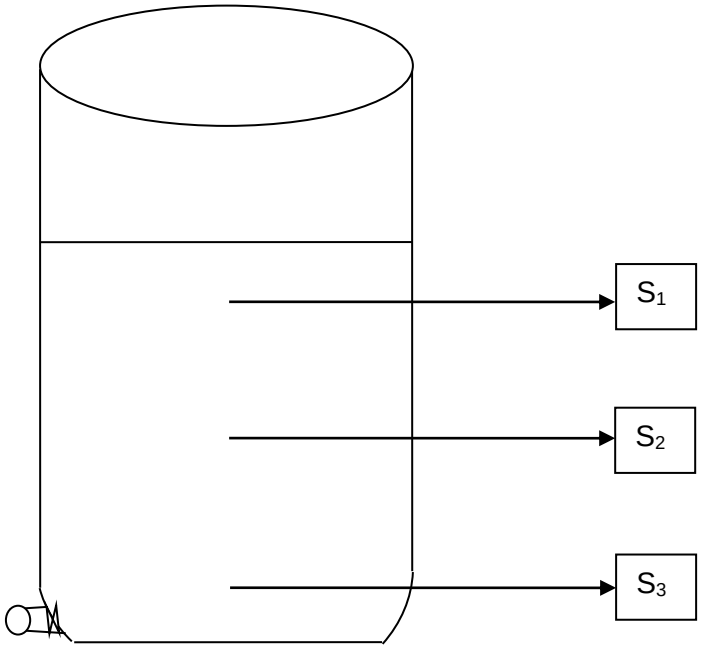
UNIT OPERATION	SAMPLING POINT	SAMPLE QUANTITY	SAMPLE CODE	CONTROLLED PARAMETER	MEASURED RESPONSE
Final Mixing Stage	Sample shall be drawn from 3 locations of the tank at intervals of 10 min, 15 min & 20 min	100 ml each from 3 sampling location (3 x 100ml x 3)	S_1, S_2, S_3.	• Mixing Time	• Description • Wt/ml • pH • **Assay** -Levocetirizine Dihydrochloride -Methyl Paraben -Propyl Paraben
Storage tank (Composite)	Sample shall be drawn from storage tank for bulk analysis.	100 ml	CS_1	--------	• As per bulk product specification.
Filling & Sealing	**#Three different speeds** Run the filling machine at 3 different speeds and collect the samples at each speed	10 Bottles at each sampling point. (10 x 3 Bottles)	SS_1 SS_2 SS_3	Filling Speed	• Description • Average fill volume • Individual Fill volume • pH • Bottle cleanliness • Sealing & Threading quality • Leak test
	Withdraw Samples at initial, middle & near to end of the filling operation.	12 Bottles for each sampling time. (12 X 3 bottles)	DS_1 DS_2 DS_3	• Fill volume • Sealing & Threading quality	• Description • pH • Weight per ml • **Assay** -Levocetirizine Dihydrochloride -Methyl Paraben -Propyl Paraben
Packing	Composite sample after completion of the filling (Collect the Bottles from Initial, middle & end of the process randomly)	12 Bottles	FS_1	--------	• As per finished product specification
	Collect the bottles after every 2 hours for visual inspection	……	…….	……	• Labeling on Bottles • Batch Coding on Bottles • Measuring caps • Sealing quality

Speeds of the filling machine will be decided at the time of filling.

9.1 SAMPLING LOCATIONS FOR MIXING TANK (Diagram):

After completion of mixing for the defined period of time, remove the external stirrer and the samples shall be collected from different locations as Shown in the diagram.

- Top (S_1)
- Middle (S_2)
- Bottom (S_3)



10.0 VALIDATION ACCEPTANCE CRITERIA:

The Process of **Levocetirizine Dihydrochloride Syrup** stands validated if various critical steps meet the following acceptance criteria:

STAGE	PARAMETER		ACCEPTANCE CRITERIA
Final Mixing	Description		Light Orange to orange colour syrupy liquid
	pH		Between 4.0 to 5.0
	Density (g per ml)		1.10 to 1.30 gm/ml
	Assay: Each 5 ml Contains		
	Levocetirizine Dihydrochloride 2.5 mg		90% - 110%
	Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg		85.0% - 115.0%
	Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg		85.0% - 115.0%
*****RSD for Assay at final mixing stage - NMT 2%			
Filling, Sealing & Packing	Description		Light Orange to orange colour syrupy liquid in Amber coloured 30ml pet bottle.
	Identification	Levocetirizine Dihydrochloride (By HPLC)	In the assay test, the chromatogram obtained with the test solution shows a peak with the same retention time as the peak due to Levocetirizine Dihydrochloride in the chromatogram obtained with the standard solution.
	pH		Between 4.0 and 6.0
	Density (gm/ml)		Between 1.10 and 1.30 gm
	Average net volume		Not less than 30 ml
	Fill variation		91.0% to 109 % of the label claim
	Microbial Limits		
	TAMC (Total Aerobic Microbial Count)		NMT 100 cfu /ml
	TYMC (Total Microbial Yeast & Mould Count)		NMT 10 cfu /ml
	Escherichia Coli		Should be absent /ml
	Salmonella species		Should be absent /10ml

STAGE	PARAMETER	ACCEPTANCE CRITERIA
	Pseudomonas	Should be absent /ml
	S. Aureus	Should be absent /ml
	Assay: Each 5 ml Contains	
	Levocetirizine Dihydrochloride 2.5 mg	90% - 110%
	Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	80.0% - 120.0%
	Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	80.0% - 120.0%

11.0 YIELD VERIFICATION:

S.No.	Stage	Yield % Acceptance Criteria
1.	Manufacturing stage	NLT 99.5%
2.	Packing	NLT 96.0%

12.0 CONCLUSION:

Statement made for in this protocol on acceptability of manufacturing process meeting the objective of protocol.

13.0 REPORT:

Process validation report shall cover the following:

- Summary Plan of Study, Acceptance Criteria
- Results, Discussion and Conclusion

The following attachment shall be referred to in the Process validation report:

- Validation Samples Report
- Analysis Reports
- Batch Manufacturing Record, Batch Packing Record
- Finished Product Analysis Report, Process Deviation report.

14.0 ABBREVIATIONS:

ABBREVIATED FORM	EXTENDED FORM	ABBREVIATED FORM	EXTENDED FORM
PVP	Process Validation Protocol	%	Percentage
Ltrs.	Liters	Spec.	Specification
BPR	Batch Packing Record	ROPP	Roll Over Pilfer proof
QC	Quality control	HVAC	Heating Ventilation and Air Conditioning.
API	Active Pharmaceutical Ingredient	Ph. Eur.	European Pharmacopeia
&	And	^{0} C	Degree Centigrade
No.	Number	Mins.	Minutes
Kg	Kilogram	#	Mesh
BP	British Pharmacopoeia	IHS	In House Specification
mg	Milligram	wt/ml	Weight per milliliter
MPR	Master Packing Record	CR	Child Resistant
MFR	Master Formula Record	RM	Raw material
HCL	Hydrochloride	ID	Identification
UOM	Unit of Measurement		