PROCESS VALIDATION REPORT

FOR

LEVOCETIRIZINE DIHYDROCHLORIDE SYRUP

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1.0 SUMMARY PLAN OF STUDY:

1.1 PRODUCT AND BATCH DETAILS:

Process Validation of **Levocetirizine Dihydrochloride Syrup** was carried out on three consecutive batches.

The details are as under:

Product Name			
Generic Name	Levocetirizine Dihydrochloride Syrup		
License No.			
Product code			
Description	Light orange to orange coloured syrup with pineapple flavor.		
Label Claim	Each 5 ml contains		
	Levocetirizine Dihydrochloride	2.5 mg	
	Flavored Syrupy base	q. s.	
	Colour: Sunset Yellow FCF		
Batch Size	600.00 liters /20,000 bottles		
Pack Size	30 ml		
Shelf life	24 Months		
Storage Condition	Sore at a temperature below 30ºC, protect from light.		
Market			
PV Batch Number			
Batch Size	600.00 Liters	600.00 Liters	600.00 Liters
	20,000 Bottles	20,000 Bottles	20,000 Bottles
Mfg. Date			
Exp. Date			
Date of commencement			
Date of completion			
Vendor details of active pharmaceutical ingredients			
API Manufacturer: Levocetirizine Dihydrochloride			

2.0 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	

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3.0 MANUFACTURING EQUIPMENT AND ACCESSORIES USED IN THE PROCESS:

The various equipment's used for the Process Validation of **Levocetirizine Dihydrochloride Syrup** are as follows:

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

All critical equipment's were verified for their Installation, Operational and Performance Qualification. Further all the equipment was cleaned and operated as per relevant SOP's as indicated in the Process Validation Protocol.

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The vessels and accessories used in the Process Validation of **Levocetirizine Dihydrochloride Syrup** are as follows:

EQUIPMENT NAME	**BATCH No.**	**BATCH No.**	**BATCH No.**
Dispensing Booth (Excipients)			
Dispensing Booth (API)			
Dispensing Booth (Solvents)			
Sugar preparation tank			
Bucket filter			
Manufacturing tank			
Storage Tank			
Filter press			
Bottle Washing Machine			
Filling Machine			
Sealing Machine			
Visualization Table (Filled Bottles)			
Labeling Machine			
Packing Conveyor Belt			
Leak Test Apparatus			

The vessels and Accessories were cleaned as per the relevant SOP before use for manufacturing.

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4.0 ANALYTICAL REPORT NUMBERS AND QUANTITY OF RAW AND PACKING MATERIALS:

MATERIAL	UOM	STD. QTY./ 600 liters							
			QTY USED	A.R NUMBER	QTY USED	A.R NUMBER	QTY USED	A.R NUMBER
RAW MATERIALS									
*Levocetirizine Dihydrochloride	Kg	0.300							
Sugar (Refined)	Kg	300.00							
Methyl Paraben	Kg	0.900							
Propyl Paraben	Kg	0.120							
Disodium EDTA	Kg	0.012							
Citric acid	Kg	0.198							
Tri-sodium citrate	Kg	0.180							
Sorbitol (70% Non-crystallizing)	Kg	90.00							
Pineapple Flavour	Kg	1.200							
Colour Sunset Yellow FCF	Kg	0.010							
Purified water	Kg	q.s.							
PACKING MATERIAL									
Amber colored PET bottles, 30 ml	Nos.	20,400							
ROPP caps 25 mm golden colored with logo EPE wads	Nos.	20,400							
Sticker Labels	Nos.	20,400							
Measuring caps	Nos.	20,400							
Cartons	Nos.	20,400							
Shipper	Nos.	204							

5.0 STAGE WISE ENVIRONMENTAL CONDITIONS (TEMPERATURE):

S.No.	STAGE			
		Temp. (°C)	Temp. (°C)	Temp. (°C)
1	Manufacturing	24.0 °C	23.0 °C	24.0 °C
2	Liquid Filling	24.0 °C	24.0°C	25.0 °C

6.0 EXPERIMENTAL PLAN, RESULTS AND DISCUSSION:

The following critical parameters were monitored in this study:

PROCESS PARAMETERS:

- Analysis of the solution at different time intervals (10, 15 and 20 minutes) for Assay.
- Analysis of the composite solution (top, middle and bottom layers) from manufacturing tank for Assay.
- In Process check parameters like Description, Average fill volume, Fill variation, Sealing & Threading quality & weight per ml at different stages.
- Analysis of pH, weight per ml and Assay at three different stages (initial, middle& near to end stage).
- Performing of leak test as per protocol.
- Analysis of finished product as per finish product specification.

ENVIRONMENTAL CONDITIONS:

- HVAC system as well as LAF units was conforming for Installation, Operational and Performance Qualification. Differential Pressure as well as Viable counts in HVAC system and LAF units were monitored on regular basis as per relevant protocols and the same were found to be conforming to specifications.
- Purified water plant, holding tanks and distribution loops were qualified as per the protocol and the same were found to be conforming to specifications.

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6.1 PROCESS PARAMETERS RESULTS:

6.1.1 FINAL MIXING RESULTS:

6.1.1.1 First Process Validation Batch Results of Mixing:

Process Validation Batch No.					
After 10 minutes Mixing					
Test	**Acceptance criteria**	**S_1**	**S_2**	**S_3**	.....
Description	Light orange to orange coloured syrup with pineapple flavor.	Complies	Complies	Complies	
pH	4.0 to 5.0				
Weight/ml	1.10 to 1.30 gm/ml				
Assay: Each 5 ml contains:					**RSD: NMT 2.0%**
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%				
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	85.0%-115.0%				
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	85.0%-115.0%				
After 15 Minutes Mixing					
Test	**Acceptance criteria**	**S_1**	**S_2**	**S_3**	.....
Description	Light orange to orange coloured syrup with pineapple flavor.	Complies	Complies	Complies	
pH	4.0 to 5.0				
Weight/ml	1.10 to 1.30 gm/ml				
Assay: Each 5 ml contains:					**RSD: NMT 2.0%**
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%				
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	85.0%-115.0%				
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	85.0%-115.0%				
After 20 Minutes Mixing					
Test	**Acceptance criteria**	**S_1**	**S_2**	**S_3**	.....

Description	Light orange to orange coloured syrup with pineapple flavor.				
pH	4.0 to 5.0				
Weight/ml	1.10 to 1.30 gm/ml				
Assay: Each 5 ml contains:					**RSD: NMT 2.0%**
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%				
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	85.0%-115.0%				
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	85.0%-115.0%				

6.1.1.2 Second Process Validation Batch Results of Mixing:

Process Validation Batch No.					
After 10 minutes Mixing					
Test	**Acceptance criteria**	**S_1**	**S_2**	**S_3**	
Description	Light orange to orange coloured syrup with pineapple flavor.				……
pH	4.0 to 5.0				
Weight/ml	1.10 to 1.30 gm/ml				
Assay: Each 5 ml contains:					**RSD: NMT 2.0%**
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%				
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	85.0%-115.0%				
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	85.0%-115.0%				
After 15 Minutes Mixing					
Test	**Acceptance criteria**	**S_1**	**S_2**	**S_3**	
Description	Light orange to orange coloured syrup with pineapple flavor.				……

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pH	4.0 to 5.0				
Weight/ml	1.10 to 1.30 gm/ml				
Assay: Each 5 ml contains:					**RSD: NMT 2.0%**
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%				
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	85.0%-115.0%				
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	85.0%-115.0%				
After 20 Minutes Mixing					
Test	**Acceptance criteria**	**S_1**	**S_2**	**S_3**	…….
Description	Light orange to orange coloured syrup with pineapple flavor.				
pH	4.0 to 5.0				
Weight/ml	1.10 to 1.30 gm/ml				
Assay: Each 5 ml contains:					**RSD: NMT 2.0%**
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%				
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	85.0%-115.0%				
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	85.0%-115.0%				

6.1.1.3 Third Process Validation Batch Results of Mixing:

Process Validation Batch No.					
After 10 minutes Mixing					
Test	**Acceptance criteria**	**S_1**	**S_2**	**S_3**	.....
Description	Light orange to orange coloured syrup with pineapple flavor.				
pH	4.0 to 5.0				
Weight/ml	1.10 to 1.30 gm/ml				
Assay: Each 5 ml contains:					**RSD: NMT 2.0%**
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%				
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	85.0%-115.0%				
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	85.0%-115.0%				
After 15 Minutes Mixing					
Test	**Acceptance criteria**	**S_1**	**S_2**	**S_3**	.....
Description	Light orange to orange coloured syrup with pineapple flavor.				
pH	4.0 to 5.0				
Weight/ml	1.10 to 1.30 gm/ml				
Assay: Each 5 ml contains:					**RSD: NMT 2.0%**
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%				
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	85.0%-115.0%				
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	85.0%-115.0%				
After 20 Minutes Mixing					

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Test	**Acceptance criteria**	**S_1**	**S_2**	**S_3**	.....
Description	Light orange to orange coloured syrup with pineapple flavor.				
pH	4.0 to 5.0				
Weight/ml	1.10 to 1.30 gm/ml				
Assay: Each 5 ml contains:					**RSD: NMT 2.0%**
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%				
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	85.0%-115.0%				
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	85.0%-115.0%				

6.1.1.4 Results of Composite Bulk Sample (Final solution)

TEST	**ACCEPTANCE CRITERIA**	**BATCH No.**		
Description	Light orange to orange coloured syrup with pineapple flavor.			
pH	4.0 to 5.0			
Weight/ml	1.10 to 1.30 gm/ml			
Assay: Each 5 ml contains:				
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%			

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6.1.2 BOTTLE FILLING & SEALING :

6.1.2.1 SPEED CHALLENGE AT FILLING STAGE (LOW SPEED, OPTIMUM SPEED & HIGH SPEED):

6.1.2.1.1 Results of 1st batch:

PROCESS VALIDATION BATCH No.											
PARAMETER	**ACCEPTANCE CRITERIA**	**Set parameters**	**LOWER SPEED**		**OPTIMUM SPEED**		**HIGH SPEED**				
		Filling	**12 SPM**		**15 SPM**		**17 SPM**				
		Filling RPM Controller at	**2**		**4**		**5**				
		Sealing	**12 RPM**		**15 RPM**		**17 RPM**				
		Sealing RPM Controller at	**3**		**5**		**6**				
Description	Light orange to orange coloured syrup with pineapple flavor.	…….									
Average fill volume	NLT 30 ml										
Net volume variation	91.0% to 109.0%		Min.		Min.		Min.				
			Max.		Max.		Max.				
Sealing & Threading quality	Proper sealing should be done										
Leak test	Should Pass										
Set the machine at **optimum parameters** and fill the total batch.											

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6.1.2.1.2 Results of 2nd batch:

PROCESS VALIDATION BATCH NO.											
PARAMETER	**ACCEPTANCE CRITERIA**	**Set parameters**	**LOWER SPEED**			**OPTIMUM SPEED**			**HIGH SPEED**		
		Filling	**12 SPM**			**15 SPM**			**17 SPM**		
		Filling RPM Controller at	**2**			**4**			**5**		
		Sealing	**12 RPM**			**15 RPM**			**17 RPM**		
		Sealing RPM Controller at	**3**			**5**			**6**		
Description	Light orange to orange coloured syrup with pineapple flavor.	…….									
Average fill volume	NLT 30 ml										
Net volume variation	91.0% to 109.0%		Min.			Min.			Min.		
			Max.			Max.			Max.		
Sealing & Threading quality	Proper sealing should be done										
Leak test	Should Pass										
Set the machine at **optimum parameters** and fill the total batch.											

6.1.2.1.3 Results of 3rd batch:

PROCESS VALIDATION BATCH NO.									
PARAMETER	**ACCEPTANCE CRITERIA**	**Set parameters**	**LOWER SPEED**		**OPTIMUM SPEED**		**HIGH SPEED**		
		Filling	**12 SPM**		**15 SPM**		**17 SPM**		
		Filling RPM Controller at	**2**		**4**		**5**		
		Sealing	**12 RPM**		**15 RPM**		**17 RPM**		
		Sealing RPM Controller at	**3**		**5**		**6**		
Description	Light orange to orange coloured syrup with pineapple flavor.	…….							
Average fill volume	NLT 30 ml								
Net volume variation	91.0% to 109.0%		Min.		Min.		Min.		
			Max.		Max.		Max.		
Sealing & Threading quality	Proper sealing should be done								
Leak test	Should Pass								
Set the machine at **optimum parameters** and fill the total batch.									

6.1.2.2 THREE DIFFERENT STAGE AT BOTTLE FILLING:

6.1.2.2.1 Results of 1st Batch:

Process Validation Batch No.				
Test	**Acceptance criteria**	**Initial**	**Middle**	**Near to end**
Description	Light orange to orange coloured syrup with pineapple flavor.			
pH	4.0 to 6.0			
Weight/ml (gm/ml)	1.10 to 1.30 gm/ml			
Assay				
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%			
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	80.0% to 120.0%			
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	80.0% to 120.0%			

6.1.2.2.2 Results of 2nd batch:

Process Validation Batch No.				
Test	**Acceptance criteria**	**Initial**	**Middle**	**Near to end**
Description	Light orange to orange coloured syrup with pineapple flavor.			
pH	4.0 to 6.0			
Weight/ml (gm/ml)	1.10 to 1.30 gm/ml			
Assay				
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%			
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	80.0% to 120.0%			
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	80.0% to 120.0%			

6.1.2.2.3 Results of 3rd batch:

Process Validation Batch No.				
Test	**Acceptance criteria**	**Initial**	**Middle**	**Near to end**
Description	Light orange to orange coloured syrup with pineapple flavor.			
pH	4.0 to 6.0			
Weight/ml (gm/ml)	1.10 to 1.30 gm/ml			
Assay				
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%			
Methylparahydroxybenzoate (Methyl Paraben) 7.5 mg	80.0% to 120.0%			
Propylparahydroxybenzoate (Propyl Paraben) 1.0 mg	80.0% to 120.0%			

6.1.3 PACKING OPERATION:

Perform packing operation as per recommended instructions. Over-coding of batch details on labels, coding on labels, measuring caps shall be verified.

6.1.3.1 IN PROCESS CHECKS (SECONDARY PACKING):

Note: Put Complies and Not Complies

1st Process Validation Batch No.					
Date	**Time**	**Labeling on Bottles**	**Batch Coding on labels**	**Measuring caps**	**Sealing quality**
2nd Process Validation Batch No.					
Date	**Time**	**Labeling on Bottles**	**Batch Coding on labels**	**Measuring caps**	**Sealing quality**
3rd Process Validation Batch No.					
Date	**Time**	**Labeling on Bottles**	**Batch Coding on labels**	**Measuring caps**	**Sealing quality**

6.1.3.2 RESULTS OF FINISHED PRODUCTS:

TESTS	ACCEPTANCE CRITERIA	BATCH NUMBER		
Description	Light orange to orange coloured syrup with pineapple flavor.			
Identification (By HPLC)	In the assay, 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 standard solution.			
pH	Between 4.0 to 6.0			
Weight/ml (gm/ml)	1.10 to 1.30 gm/ml			
Fill volume	NLT 30 ml			
Fill variation	91% of 109%			
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			
Assay: Each 5 ml contains				
Levocetirizine Dihydrochloride 2.5 mg	90.0% to 110.0%			

7.0 STAGE WISE YIELD VARIFICATION:

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

8.0 REASON OF VALIDATION:

To establishing documented evidence which provide a high degree of assurance that the process will consistently produce a product meeting its predetermined specifications and quality attributes.

9.0 CONCLUSION:

The formalized, final 3-batch validation sequence provides the necessary process validation document required to show product reproducibility and a manufacturing process in a state of control.

The test data and results show process reproducibility and consistency among validated batches of **Levocetirizine Dihydrochloride Syrup.** Description of the solution, pH, Weight per ml, Fill volume, Fill variation, Assay of API & Preservatives, package integrity and Microbial limits have been addressed both during in-process and final product testing. All the parameters fall well within acceptance criteria for **Levocetirizine Dihydrochloride Syrup.**

Testing has been sufficient to establish process reproducibility and demonstrate, with a high degree of certainty that the product, **Levocetirizine Dihydrochloride Syrup** and process is validated and under control.

10.0 RECOMMENDATIONS:

10.1 For Final mixing:

The manufacturing process of **Levocetirizine Dihydrochloride Syrup,** verified through process validation and results found satisfactory. Hence no additional recommendations required. Mix the final suspension for 20 minutes after volume makeup.

10.2 For filling and sealing machines:

Operate the filling and sealing machines as per defined operating ranges: -

- Operate the Filling Machine Between (12 SPM to 17 SPM)
- Operate the Sealing Machine Between (12 RPM to 17 RPM)

- Set the RPM controller of Sealing Machine at 3 for 12 RPM, 5 for 15 RPM, 6 for 17 RPM.
- Set the RPM controller of filling machine at 2 for 12 RPM, 4 for 15 RPM, 5 for 17 RPM.

Further recommendations: Set the machines at optimum filling speed (15 SPM) and optimum sealing speed (15 RPM) and fill the total batch.

11.0 REPORT APPROVAL:

PREPARED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE
1				

REVIEWED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE
2				
3				
4				
5				

APPROVED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE
6				

AUTHORIZED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE
7				