PROCESS VALIDATION PROTOCOL

FOR

PYRIDOXINE SUSTAINED RELEASE TABLETS

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1.0 APPROVAL

Prepared By	Signature	Date
(Quality Assurance)		

Checked By	Signature	Date
(Production)		
(Engineering)		
(Quality Control)		
(Quality Assurance)		

Approved By	Signature	Date
(Head Quality Assurance)		

2.0 OVERVIEW

2.1 Objective:

Validation of the manufacturing process of Pyridoxine Sustained Release tablets to be manufactured. The validation is being taken up for establishing documentary evidence that the product manufactured meets all quality and design specifications.

Three batches of increased batch size from 7.5 Lac tablet to 10.0 Lac tablet of **Pyridoxine Sustained Release tablets** shall be taken up for Concurrent process validation.

2.2 Scope:

This protocol covers three commercial batches of Pyridoxine Sustained Release tablets for process validation study.

2.3 Validation Approach:

Manufacturing process is expected to be validated to assure the product quality, which is derived from a number of factors including raw material, selection of quality parameters and materials, adequate product and process design, control of the process and in-process and end-process testing.

Manufacturing process shall indicate the critical inputs / critical steps and critical process parameters which directly or indirectly affect / alter the quality profile of the product. This protocol shall list these critical inputs / steps / parameters.

Finally this protocol shall provide the criteria to evaluate the results generated during study and to conclude the validation study.

2.4 Responsibility:

- **Production**

  Shall be responsible for the checking the protocol, executing the batches as per the designed Manufacturing Process and monitoring the process as per the process parameters and co-ordinate with Quality Assurance for withdrawal of validation samples, compilation, evaluation and review of the results.

- **Quality Assurance**

  Quality assurance shall be responsible for preparation of protocol, In-process monitoring of the process so as to assure the product of desired quality, withdrawal of validation samples as per the Sampling Criteria mentioned in the Protocol. Compilation of the data and evaluation of the results. QA shall be responsible for compliance of the protocol, review and evaluation of the reports.

- **Quality Control**

  Shall be responsible for checking the protocol, Analysis of validation samples as per Approved In-process and Finished product specifications.

- **Engineering**

  Shall be responsible for prequalification and calibration of all the processing equipment and maintain in state of proper functioning during the process validation batches. Engineering dept. shall ensure the calibration of all measuring devices and preventive maintenance as per schedules.

3.0 PROCESS VALIDATION METHODOLOGY

3.1 Validation study consists:

- Review of documents
- Master Formula / Documents Reference
- Raw Material Specifications
- Batch Manufacturing Record
- Batch Packaging Record
- Packaging Material Specification
- Finished Product Specification
- Equipment Qualification Documents

3.2 The product shall be tested as per In-process and Finished product specifications.

3.3 Following data to be collected during the validation study:

- Uniformity of mixing at Dry mixing stage.
- Drying homogeneity in FBD drying.
- Blend Uniformity Analysis of Final blend as per the protocol.
- In-process test data of Tablets as per In-process Specifications.
- Assay and Dissolution test of Tablets.
- All critical process control parameter as recorded.

Acceptance Criteria for each data is mentioned in the section 4.9.

3.4 Critical Process parameters and Critical Control points matrix at different manufacturing stages:

S.No.	STAGE	CRITICAL PROCESS PARAMETERS	CRITICAL CONTROL POINTS
1.	Sifting	% RH	Temperature of Heating Coils of AHU. Temperature of Cooling Coils of AHU. Flow Rate and Temperature of Chilled water.
		No Foreign particles	Sieve size
2.	Granulation	Mixing time	Timer
		Granulation time	Timer
		Speed	RPM of Impeller and Chopper
3.	Drying	Inlet temperature	Heater temperature
		Exhaust temperature	Heater temperature
		% LOD	Heater Temperature and Time
4.	Milling	%RH	Temperature of Heating Coils and Cooling Coils. Flow of Chilled water.
		Granule size uniformity	Mesh size

S.No.	STAGE	CRITICAL PROCESS PARAMETERS	CRITICAL CONTROL POINTS
5.	Lubrication	RPM of Conta Blender	RPM Regulator
		Mixing Time	Timer
6.	Compression	% RH	Temperature of Heating Coils. Temperature of Cooling Coils. Flow of Chilled water.
		Machine Speed	RPM of Turret.
		Compaction force	Thickness and Hardness of Tablet.
		Weight of Tablet	Distance of Lower Punch
8.	Primary Packaging	Sealing Temperature	Temperature of Heaters
		Machine Speed	RPM
		Forming Temperature	Temperature of Heaters

4.0 PRODUCT DETAILS

4.1 Product Name: …….

4.2 Generic Name: Pyridoxine Sustained Release Tablets

4.3 Product Design:

Label Claim	**Each Sustained Release tablet contains:** Pyridoxine Hydrochloride IP/BP- 100mg Appropriate overages of Vitamin added to compensate for loss on storage.
Overages % (w/w)	5.0 %
Average Weight / Tablet	253.4 mg
Shelf life	36 months
Active Pharmaceutical Ingredient percentage	41.43 %

4.4 Detail of Raw Materials:

RM Code	Ingredient	Specification	Std. Qty	% Content (w/w)	Function	Manufacturer	Country
	Pyridoxine Hydrochloride	IP/BP	105.0	41.43	Active		
	Talc	IP/BP	132.0	52.09	Diluent		
	Ethyl Cellulose (50 Cps)	IP/USP	15.0	5.91	Binder		
	Isopropyl Alcohol	IP/BP	96.0	NA	Solvent		
	Magnesium Stearate	IP/BP	1.4	0.55	Lubricant		

4.5 Primary Packaging Components:

PM Code	Ingredient	Specification No.	Function	Manufacturer	Country
	Ptd. Alu. Blister Foil Foil Width: 206 mm Foil Gauge: 0.025mm	PMS/B014/05-02	Lidding Foil		
	PVC foil with Metallic Lusture (Bilcare – Patina) Foil Width: 210 mm Foil Gauge: 0.25mm Colour : Peach		Base Foil		

4.6 Batch Details:

S.No.	BATCH No.	STRENGTH	SHELF LIFE	BATCH SIZE	
				Kg	No. of Tablets
1.	*	100 mg	36 months	253.4	10,00,000
2.	*	100 mg	36 months	253.4	10,00,000
3.	*	100 mg	36 months	253.4	10,00,000

*** As per production plan.**

4.7 Location of Manufacturing: ……

4.8 Product Pack **:** Blister Pack of 30 tablets.

4.9 Acceptance Criteria for Critical Quality Attributes: Specification No. : **……**

S.No.	Parameters	In Process Specification	Release Specification
1.	**Description**	White, Circular, Biconvex, Uncoated Tablets.	White, Circular, Biconvex, Uncoated Tablets.
2.	**Identification**	N.A	Chemical reaction with ferric chloride test solution produce orange to red filtrate.
3.	**Weight of 20 Tablets**	5.068 gm ± 2 % (4.966 gm – 5.169 gm)	5.068 gm ± 2 % (4.966 gm – 5.169 gm)
4.	**Average weight**	253.4 mg ± 5% (240.73 mg – 266.07 mg)	253.4 mg ± 5% (240.73 mg – 266.07 mg)
5.	**Uniformity of weight**	NMT 02 Tablets out of 20 Tablets should deviate from the average weight by more than 5.0% and none should deviate by more than 10.0%.	NMT 02 Tablets out of 20 Tablets should deviate from the average weight by more than 5.0% and none should deviate by more than 10.0%.
6.	**Diameter**	7.90 mm – 8.10 mm	N.A
7.	**Hardness**	2 – 5 Kg/cm^2	2 – 5 Kg/cm^2
8.	**Thickness**	3.30 mm – 3.50 mm	N.A
9.	**Friability**	NMT 1.0 %	NMT 1.0 %
10.	**Dissolution Test**	N.A	2 Hrs: 50 %– 70 % of L.A 4 Hrs: 70 %– 90 % of L.A 6 Hrs: 90 %– 110 % of L.A
11.	**Assay**	N.A	**Pyridoxine Hydrochloride Content:** 90 % to 110 % of Labelled Amount. 90.0mg to 110.0mg of Labelled Amount.

5.0 REFERENCE DOCUMENTS:

S.No.	Reference Document	Document No.
1.	Master Formula Record	
2.	Batch Manufacturing Record	
3.	Batch Packaging Record	
4.	Finish Product Specification	
5.	Validation Master Plan	
6.	Performance Qualification of HVAC System	
7.	Performance Qualification of Water System	
8.	Performance Qualification of Vibratory Sifter	
9.	Performance Qualification of Fluid Bed Drier	
10.	Performance Qualification of Conta Blender	
11.	Performance Qualification of Rapid mixer granulator	
12.	Performance Qualification of Compression Machine	
13.	Performance Qualification of Blister Packing machine	

6.0 MANUFACTURING PROCESS

Sequential steps in the manufacturing process shall be followed as per the approved Manufacturing Instructions. Process Parameters during each manufacturing stage shall be monitored to demonstrate that product meets the Acceptance Criteria.

6.1 Process flow.

6.2 Process variable Influence Matrix

6.3 Raw and Packaging Materials acceptance criteria.

6.4 Equipment Details.

6.5 Manufacturing Checklist

6.1 Process Flow:

DISPENSING AND R.M QUANTITY VERIFICATION

⇓ [Weighing Balance]

SIFTING

⇓ [Vibratory Sifter]

DRY MIXING

⇓ [Rapid Mixing Granulator]

GRANULATION (WET MIXING)

⇓ [Rapid Mixing Granulator]

DRYING

IPQA TESTING ⇓ [Fluid Bed Drier]

SIFTING AND MILLING

⇓ [Multi-Mill / Vibratory Sifter]

MIXING AND LUBRICATION

⇓ [Conta Blender]

COMPRESSION

IPQA TESTING ⇓ [Compression Machine]

PRIMARY PACKAGING → **FP ANALYSIS**

IPQA TESTING ⇓ [Blister Packaging Machine]

SECONDARY PACKAGING

⇓

DISPATCH

6.2 Process variable Influence Matrix:

S.No.	Mfg. Steps	Influence
1.	**Dispensing** - % RH - Dispensing aids	Stability of Product
2.	**Sifting / Milling** - %RH - Mesh size - Sieve size - Speed of the Multimill	Pour Density and Tap Density
3.	**Granulation** - Mixing time - Granulation time - Amount of water added - Current drawn by Agitator - Current drawn by Chopper	Content Uniformity
4.	**Drying** - Inlet temperature - Exhaust temperature - Raking interval - % occupancy in bowl	Moisture content of Granules
5.	**Mixing and Lubrication** - % RH - RPM of Conta Blender - Mixing Time - % Occupancy of Conta blender	Content Uniformity
6.	**Tablet Compression** - % RH - Machine Speed - Weight Variation	In-process Tablet Compression characteristics
7.	**Blister Packaging** - Sealing Temperature - Machine Speed	Sealability and Stability of Product

6.3 Raw and Packaging Materials Acceptance Criteria:

Raw materials and Packaging Materials to be used in the manufacturing shall be procured from the approved vendor and shall meet all the laid specifications in the analysis prior to use. For this purpose all the raw materials shall have valid certification (Approval Tag put on containers by Quality Control) from Quality Control personnel before use for manufacturing.

6.4 Equipment Details:

S.No.	Equipment Name	Make	Equipment No.	Reference SOP No.
1.	Weighing Balance			
2.	Weighing Balance			
3.	Dispensing Booth			
4.	Weighing Balance			
5.	Vibratory Sifter			
6.	Rapid Mixer Granulator			
7.	Fluid Bed Drier			
8.	Multimill			
9.	Conta Blender			
10.	Tablet Compression Machine			
11.	Blister Packing Machine			

*** Used in Dispensing Area. + Used in Granulation Area.**

6.5 Manufacturing Checklist:

The following parameters of the unit operation shall be studied, monitored, evaluated and documented in the report.

S.No.	Unit Operation	Parameters	Operating Range
1.	Raw material Sifting	Screen size	40 mesh and 20 mesh
2.	Dry Mixing	Mixing time in RMG	10 min
3.	Wet Granulation	Granulation time	25 - 30 min
4.	Drying	Loss on Drying	NMT 1.0 %
5.	Post Drying Sifting and Milling	Sieve size for Sifting	20 mesh
		Screen size for Milling	2.0 mm
6.	Lubrication	Conta Blender Speed	6 rpm
		Conta Mixing Time	10 min
7.	Compression	Machine Speed	16 – 20 rpm
		Average Weight	253.4 mg (± 5%)
		Hardness	2.0 – 5.0 kg/cm^2
		Thickness	3.30 – 3.50 mm
8.	Blister Packaging	Sealing Temperature	180^{0}C – 210 ^{0}C

The Temperature and the Relative Humidity of the Processing Rooms should be NMT 25±2 Deg C and 55±5%/ 45±5% respectively.

7.0 SAMPLING AND TESTING PLAN WITH ACCEPTANCE CRITERIA:

STAGE	SAMPLING PLAN	TESTING PLAN	ACCEPTANCE CRITERIA
Dry Mixing	After 10 min of mixing, for determining the blend homogeneity, Sample quantity Equi. to 01gm shall be withdrawn from 10 different locations of Rapid mixer granulator using SS Sampler.	For determining the blend homogeneity.	**Pyridoxine Hydrochloride Content:** 95 % to 105 % of the Labelled amount. **RSD NMT 2.0 %.**
Drying	Approximately 2.0 g/Sample of the dried granules shall be withdrawn from 03 Sampling points comprising of Composite sample from Top, Composite sample from Middle and Composite sample from Bottom layers of FBD bowl and perform LOD separately from each sample. (Refer Picture for Sampling Locations as mentioned on Page No. 23 of 24.	Loss on drying of dried granules to be evaluated using IR Moisture balance.	NMT 1.0%.

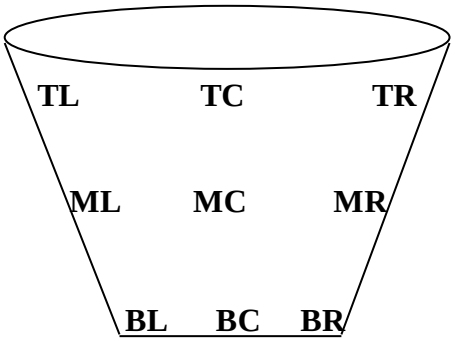
STAGE	SAMPLING PLAN	TESTING PLAN	ACCEPTANCE CRITERIA
Lubrication	After 10 min of Lubrication, for determining the bulk blend homogeneity Sample quantity Equi. to 01gm shall be withdrawn from 10 different locations of Conta blender using S.S Sampler. Picture for Sampling Locations as mentioned on Page No. 23 of 24.	For determining the bulk blend homogeneity.	**Pyridoxine Hydrochloride Content:** 95 % to 105 % of the Labelled amount. **RSD NMT 2.0 %.**
Lubricated Blend	For Physical parameters of Lubricated granules Composite samples of 50 gm Lubricated granules shall be with drawn.	For checking the physical parameters like Pour Density, Tap Density and Compressibility Index.	Tests done for informative purpose only.

STAGE	SAMPLING PLAN	TESTING PLAN	ACCEPTANCE CRITERIA
Compression	Samples to be collected after particular time intervals as per BMR for Regular Inprocess checks and also for following study conditions: ➢ Slow speed and Fast speed. ➢ Half, Full and Near to End Hopper.	➢ Weight of 20 Tablets ➢ Individual Wt. variation ➢ Thickness ➢ Hardness ➢ Friability	➢ 4.97 – 5.17 gm ➢ 240.73–266.07mg ➢ 3.30 – 3.50 mm ➢ 2.0 – 5.0 kg/cm^2 ➢ NMT 1.0%
	40 Tablets to be collected at Initial, Middle and End of Tablet Compression operation.	Compliance to Test for Assay and Dissolution as per Finished Product Specification.	**For Assay:** 90 % to 110 % of the Labelled amount. 90.0mg to 110.0mg of the Labelled amount. **RSD NMT 2.0 %.** **For Dissolution:** **2 Hrs-** 50 %– 70 % of Labelled amount. **4 Hrs-** 70 %– 90 % of Labelled amount. **6 Hrs-** 90 %–110 % of Labelled amount. **RSD NMT 5.0 %.**

STAGE	SAMPLING PLAN	TESTING PLAN	ACCEPTANCE CRITERIA
Packaging	Sample to be collected after regular interval for Inprocess checks. (e.g.: Leak test) Leak test shall be done also at following Sealing temperatures: ➢ 180 Deg C ➢ 190 Deg C ➢ 210 Deg C	Leak Test	No moisture should found inside the pocket of Blister.
	10 X 30 Tablets to be collected during Packaging operation.	Compliance to the Approved Finished Product Specification and Test for Microbiological Analysis	**As per Finished Product Specification No.:** …….. **For Microbiological Analysis:** SOP/…….

Figure 1: Sampling Location from FBD Bowl

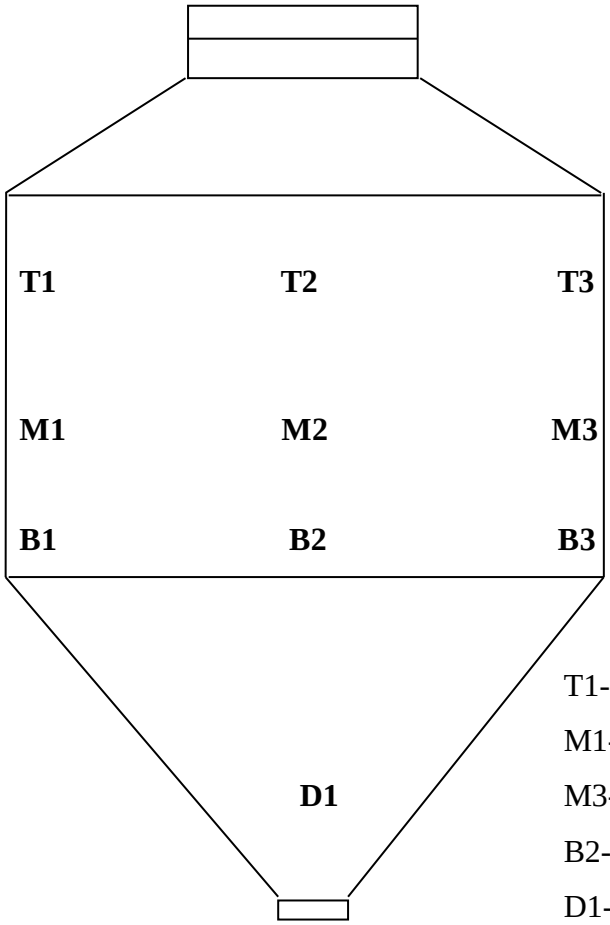
Withdraw samples from Top, Middle and Bottom as per the figure from FBD Bowl and record Loss on drying.



T = Top, M= Middle, B= Bottom.
L = Left, C= Centre, R= Right.

Figure 2: Sampling Location from Conta blender

Withdraw the samples from Top, Middle, Bottom and Discharge port as per figure from Conta blender after 10 minutes and record the corresponding time of Mixing.



T1- Top Left, T2- Top Centre, T3-Top Right.
M1- Middle Left, M2- Middle Centre,
M3- Middle Right. B1- Bottom Left,
B2- Bottom Centre, B3- Bottom Right.
D1- Discharge Port.

8.0 EVALUATION OF RESULTS AND CONCLUSION:

A summary report shall be prepared to summarise the results of the Validation Studies. On the basis of evaluation of results, a conclusion shall be drawn to state the adequacy of the process to carry out the manufacturing of Pyridoxine Sustained Release Tablets.

9.0 REFERENCES:

USP 31 NF 26, 21 CFR Part 211, EU GMP and WHO GMP Guidelines

10.0 ATTACHMENTS:

Annexure –I: Sampling Matrix.