PROCESS VALIDATION PROTOCOL

FOR

PRE AND PROBIOTIC CAPSULES

PROCESS VALIDATION PROTOCOL FOR PRE AND PROBIOTIC CAPSULES

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1.0 PROTOCOL APPROVAL:

PREPARED BY:

S.No.	NAME	DESIGNATION	SIGNATURE	DATE

REVIEWED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE

APPROVED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE

AUTHORIZED BY

S.No.	NAME	DESIGNATION	SIGNATURE	DATE

PROCESS VALIDATION PROTOCOL FOR PRE AND PROBIOTIC CAPSULES

2.0 OVERVIEW:

2.1 OBJECTIVE:

To validate the manufacturing process of Pre & Probiotic Capsules as per the Batch Manufacturing Record & Batch packing record to establish documentary evidence that the process will consistently produce a product, meeting its predetermined specifications and quality attributes by examining three consecutive batches.

2.2 SCOPE:

This protocol is applicable to the three batches of Pre and Probiotic capsules manufactured in capsule section to be taken for conducting Validation study.

2.3 RESPONSIBILITY:

Following functional groups shall be responsible for conducting validation study.

Production	:	Operating of equipments and the process as per BMR and BPR.
Engineering	:	Maintenance of facility, equipments and utilities as per the Batch requirement.
Quality Control	:	Testing of In-process and finished samples as per the specifications in Protocol.
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.

3.0 PRODUCT INFORMATION:

Generic Name	Pre & Probiotic Capsules
Product Code	
License No.	
Description	Grey/Yellow, Size "1" hard gelatin capsules in black colour.
Label Claim	Each Hard gelatin capsule contains: Lactobacillus acidophilus Lactobacillus bulgaricus Lactobacillus paracasei Lactobacillus Plantarum Lactobacillus casei Lactobacillus rhamnosus — 2.5 billion cfu Bifidobacterium bifidum Bifidobacterium longum Bifidobacterium breve — 1.25 billion cfu Streptococcus thermophilus — 0.50 billion cfu Enterococcus faecium — 0.75 billion cfu Lactitol monohydrate 100mg Approved colour used in capsule shells
Shelf Life	18 months
Batch Size	2,00,000 Capsules
Pack Size	10x10's Alu-PVC Blister
Storage Condition	Store in a cool & dry place, away from direct sunlight.

3.1 LIST OF RAW MATERIALS:

S.No.	ITEM CODE	INGREDIENTS	SPEC.	UOM	Qty/ Caps (mg)	QTY. used
1.		Lactobacillus acidophilus + Lactobacillus bulgaricus + Lactobacillus paracasei + Lactobacillus Plantarum + Lactobacillus casei + Lactobacillus rhamnosus + Bifidobacterium bifidum + Bifidobacterium longum + Bifidobacterium breve + Streptococcus thermophilus + Enterococcus faecium) NLT 5 Billion CFU per capsule	IHS	Kg	300.0	60.000
2.		Lactitol Monohydrate	IHS	Kg	100.0	20.000
3.		Size 1, Cap: Grey, Body: yellow with Cap in black colour.	IHS	Nos.	1.0	2,00,000

3.2 LIST OF PACKING MATERIALS:

S.No.	ITEMS	UOM	STD. QTY.
1.	160 mm printed Alu foil for blister packing	kg	10.500
2.	166 mm PVC foil for Blister packing	kg	52.500
3.	Printed Outer carton 10 x 10C	Nos	2050
4.	Shipper	Nos	28
5.	Bopp Tape	Nos	02

4.0 LIST OF REFERENCE DOCUMENTS:

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S.No.	DOCUMENT
1.	Master Formula Record
2.	Batch Manufacturing Record
3.	Batch Packing Record
4.	Bulk Product Specification
5.	Semi-Finished Product Specification
6.	Finished Product Specification

NOTE: Current revision / version of document to be referred

5.0 RATIONALE FOR IDENTIFICATION OF CRITICAL STEPS TO BE VALIDATED:

5.1 SIFTING:

Sift the …….. (HG) #30 and Lactitol Monohydrate through #30. Check if any material or agglomerates or foreign matter is retained on the screen.

5.2 BLENDING:

Load sifted material in octagonal blender and mix the blend for 15 minutes at 16 RPM to attain uniformity.

Variables: Blending time.

Blending Time: The homogeneous distribution of Drug content has an effect on content uniformity and dissolution profile.

Test parameters: Description & Assay.

5.3 FILLING:

During filling the powder are filled into empty hard gelatin capsule shell. Each filled capsule is the final unit dose where all quality characteristics will be building into the process and hence it is a critical step need to be validated.

Variables: Filling Speed

Test Parameters: Appearance, Average net content, Uniformity of filled weight, Average weight of filled capsules, Locking length, Disintegration and Assay.

5.4 PACKING:

During packing operation, the capsules will be packed in the Alu-PVC Blister.

Variables : Temperature of the forming and sealing roller,

Test Parameters : Leak Test

6.0 PROCESS VALIDATION PRE-REQUISITE:

Following shall be the pre- requisite for process validation of Pre and Probiotic capsules.

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 packing process 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 SOP's shall be in place and training shall be completed on equipment operation, manufacturing instructions and sampling.

7.0 PROCESS EQUIPMENT:

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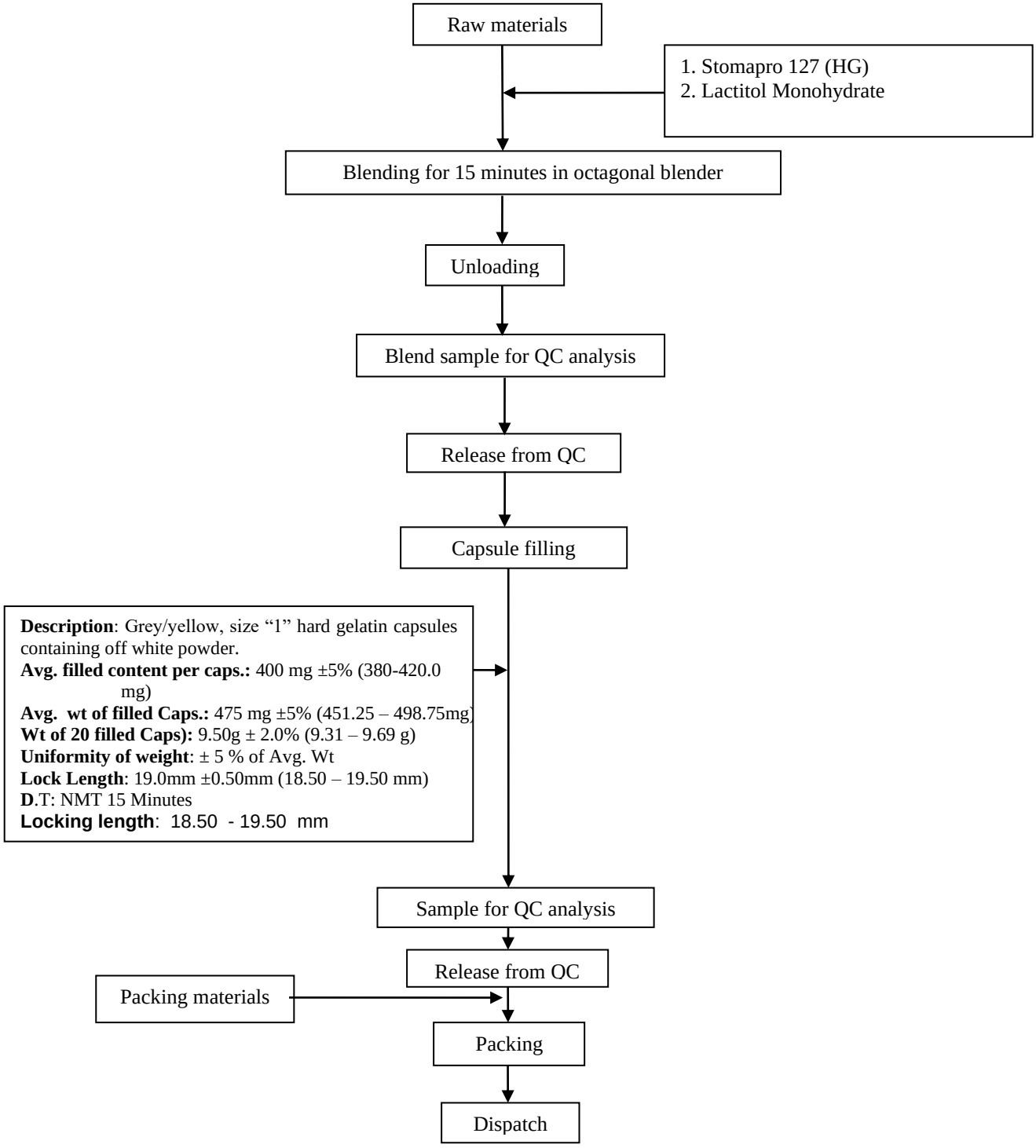
S.No.	EQUIPMENT/AREA	EQUIPMENT NUMBER/AREA
1.	Sifter & Sieves	
2.	Octagonal Blender 150 Ltrs	
3.	Capsule Filling Area	
4.	Capsule Filling Machine	
5.	Sorter & Elevator	
6.	De Dusting & Polishing Machine	
7.	Mini Capsule Sorter	
8.	Empty Capsule Sorter	
9.	Air Displacement Unit	
10.		
11.	Disintegration Test Apparatus	
12.	Blister Packing Machine	
13.	Leak Test Apparatus	

8.0 MANUFACTURING & PACKING PROCEDURE:

8.1 PROCESS FLOW CHART:



8.2 CRITICAL PROCESS PARAMETERS TO BE MONITERED DURING PROCESSING &

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PACKING

S.No.	PROCESS	PARAMETER	SPECIFICATION
1.	**Blending**	Blending time	15 minutes
		Assay	NLT 5.0 billion cfu (NLT 100%)
2.	**Filling**	Description	Grey/yellow, size "1" hard gelatin capsules containing off white powder.
		Average Weight of filled content	400 mg ± 5 % (380.0mg – 420.0mg)
		Average Filled Weight	475mg ± 7.5 % (451.25 – 498.75 mg)
		Weight of 20 Filled capsules	9.50 g ± 2.0 % (9.31 g to 9.69 g)
		Uniformity of weight (Filled capsule)	± 5 % of Avg. Weight
		Locking length	19.0mm±0.50mm (18.50mm – 19.50mm)
		Disintegration time	NMT 15 Minutes
		Assay Total viable count	NLT 5.0 billion cfu (NLT 100%)
3.	**Blister Packing**	Sealing roller Temperature	165^0 C – 190^0 C
		Forming roller Temperature	155^0 C – 175^0 C
		Leak test	Should pass the leak test.
		Knurling	For information
		Coding	For information
		Cut pocket	For information
		Broken capsules	For information
		Cutting	For information

9.0 VALIDATION SAMPLING PLAN

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

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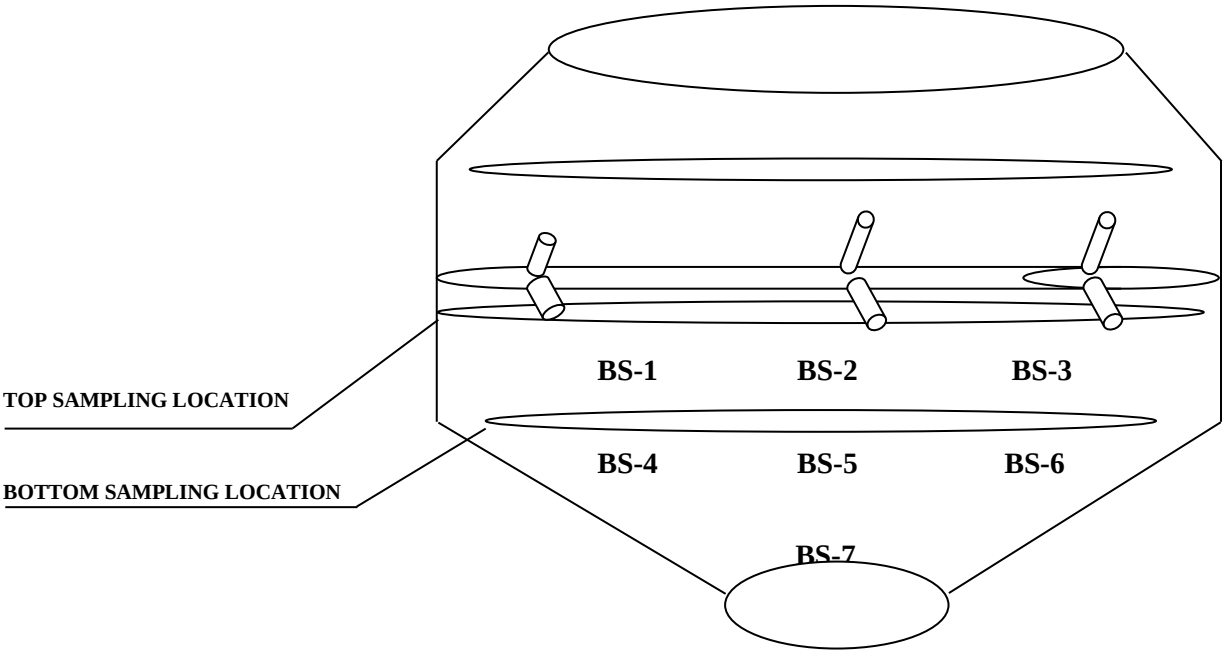
UNIT OPERATION	SAMPLING POINT	SAMPLE QUANTITY	SAMPLE CODE	CONTROLLED PARAMETER	MEASURED RESPONSE
Blending	Sample shall be drawn from 04 locations of the blender at intervals of 05 min, 10 min, 15min as per the sampling plan	05 g each from each sampling location	• BS-1-Top left • BS-2-Top middle • BS-3-Top right • BS-4- Bottom left • BS-5- Bottom middle • BS-6- Bottom right • BS-7- Near Discharge Port	• Blending time • Blender RPM	• Description • Assay
Intermediate Process Containers	Sample 12g from top, middle and bottom layer composite sample after unloading the material into Intermediate Process Containers.	20 g	IS_1	-----	• Description • Moisture content • Assay
Filling	3 Different RPMs (RPMs are going to fixed at the time of filling)	60 capsules at each sampling point. (3X60 capsules)	------	•Filling Speed	• Appearance • Avg. Fill weight • Avg. Weight • Weight Variation • Locking Length
	3 Different stages (Initial, middle & near to end of the process)	60 Capsules at each sampling location. (3X60 Capsules)	CS_1 CS_2 CS_3		• Appearance • Avg. Fill weight • Avg. Weight • Weight Variation • Locking Length
Filled Capsule (Composite)	Composite sample after completion of filling	60 Capsules	IS_2	----------	• Appearance • Avg. Fill weight • Avg. Weight • Weight Variation • Locking Length • D.T. • Assay • MLT
Blister Packing	Withdraw blisters after every 2 hour intervals for leak testing	Number of blisters that are taken for leak testing shall represent each cavity of the sealing rollers.	BPS_5	• Machine Speed • Sealing Roller temperature	• Leak Test

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

9.1 SAMPLING LOCATIONS FOR OCTAGONAL BLENDER:

After completion of mixing for the defined period of time, the samples shall be collected from different locations as shown in diagram.

- BS-1-Top left
- BS-2-Top middle
- BS-3-Top right
- BS-4- Bottom left
- BS-5- Bottom middle
- BS-6- Bottom right
- BS-7- Near Discharge Port



10.0 VALIDATION ACCEPTANCE CRITERIA:

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The Pre & Probiotic Capsules stands validated if various critical steps meet the following acceptance criteria:

STAGE	PARAMETER	ACCEPTANCE CRITERIA
Blending	Description	Off White Granules
	Assay: Each 400 mg granules contains: Total viable count	NLT 5.0 billion CFU
Filling Stage	Description	Grey/Yellow, size "1" hard gelatin capsules containing off white powder.
	Average weight	475 mg ± 5% (451.25 – 498.75mg)
	Average Fill	400 mg ± 5% (380.0mg – 420.0mg)
	Uniformity of average fill	±5% of Average fill
	Disintegration time	NMT 15 Minutes

11.0 YIELD VERIFICATION:

S.No.	Stage	Yield % Acceptance Criteria
1.	Packing	NLT 98 %

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:

PROCESS VALIDATION PROTOCOL FOR PRE AND PROBIOTIC CAPSULES

ABBREVIATED FORM	EXTENDED FORM	ABBREVIATED FORM	EXTENDED FORM
PVP	Process Validation Protocol	BMR	Batch Manufacturing Record
MPR	Master Packing Record	“	Inches
Lac.	Lacs	Spec.	Specification
Ltrs.	Liters	mm	Millimeter
MFR	Master Formula Record	ID	Identification
BPR	Batch Packing Record	HVAC	Heating Ventilation and Air Conditioning.
&	And	^{0} C	Degree Centigrade
No.	Number	Mins.	Minutes
Kg	Kilogram	#	Mesh
BP	British Pharmacopoeias	IHS	In House Specification
mg	Milligram	w/w	Weight by weight
Eq.	Equivalent	UOM	Unit of Measurement