PROCESS VALIDATION PROTOCOL

ACYCLOVIR STERILE

PROTOCOL No.: ……

This protocol is being executed along with the Batch Manufacturing Record

PROTOCOL PREPARATION

DEPARTMENT	NAME	SIGNATURE / DATE
Quality Assurance		

PROTOCOL APPROVAL

DEPARTMENT	NAME	SIGNATURE / DATE
Production		
Quality Control		
Quality Assurance		

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1.0 Objective

The objective of this Process Validation Protocol is to:

⇒ Define the validation process for Acyclovir Sterile.

⇒ Manufacture three validation batches of Acyclovir sterile Batch size of 110.00 Kg as per approved Master Production Record.

⇒ Generate Process Validation report to establish documented evidence that the product when manufactured at production scale operation meets all the Quality and Design specifications.

2.0 Functions and Responsibilities

Functional Area	Responsibility
P.D	To carry out the manufacturing operation as per BMR and record the online activity in BMR.
Q.C	To carry out the testing of the validation samples as per the standard test procedure (STP) and approved specifications.
Q.A	To collect the validation samples as per approved protocol and to monitor the process. Review of analytical reports. Compilation of validation data and report preparation, review & report Approval

3.0 Product / Process Description

3.1 Product Description:-

Product Name : Acyclovir Sterile.

Batch Size : 110.00 Kg

Reference : …….

Product specifications :

S. No.	Title	Specification No. †	STP No. †
RAW MATERIAL			
1.	Acyclovir USP.	RS009	RP009
2.	Sodium Hydroxide	RS015	RP015
3.	Eno Carbon	RS016	RP016
4.	WFI	RS001	RP001
5.	20 Lts Aluminum Canisters	PS002	PP002
IN-PROCESS SPECIFICATIONS			
6.	Acyclovir Sterile USP	IS003	IP003
FINISHED PRODUCT			
7.	Acyclovir Sterile USP	FS003	FP003

3.2 All applicable SOPs, STPs and all other related documentation should be referred.

† Current Version

3.3 Process Description:

3.3.1 Dispensing

Raw material to be used in the manufacturing shall be procured from the Approved / Provisional vendors and shall meet all the specifications laid down.

All the raw materials shall be dispensed in dispensing area of warehouse under contamination control station as mentioned in weighing record.

Check the weights and A.R.Nos. of all the dispensed materials in the manufacturing area as per the dispensing sheet.

3.3.2 Manufacturing formula.

The requirement of raw material is as follows:

Batch Size : 110 Kg.

3.3.3 Raw material quantity verification:

The quantity of dispensed raw material shall be verified by Production personnel in production area.

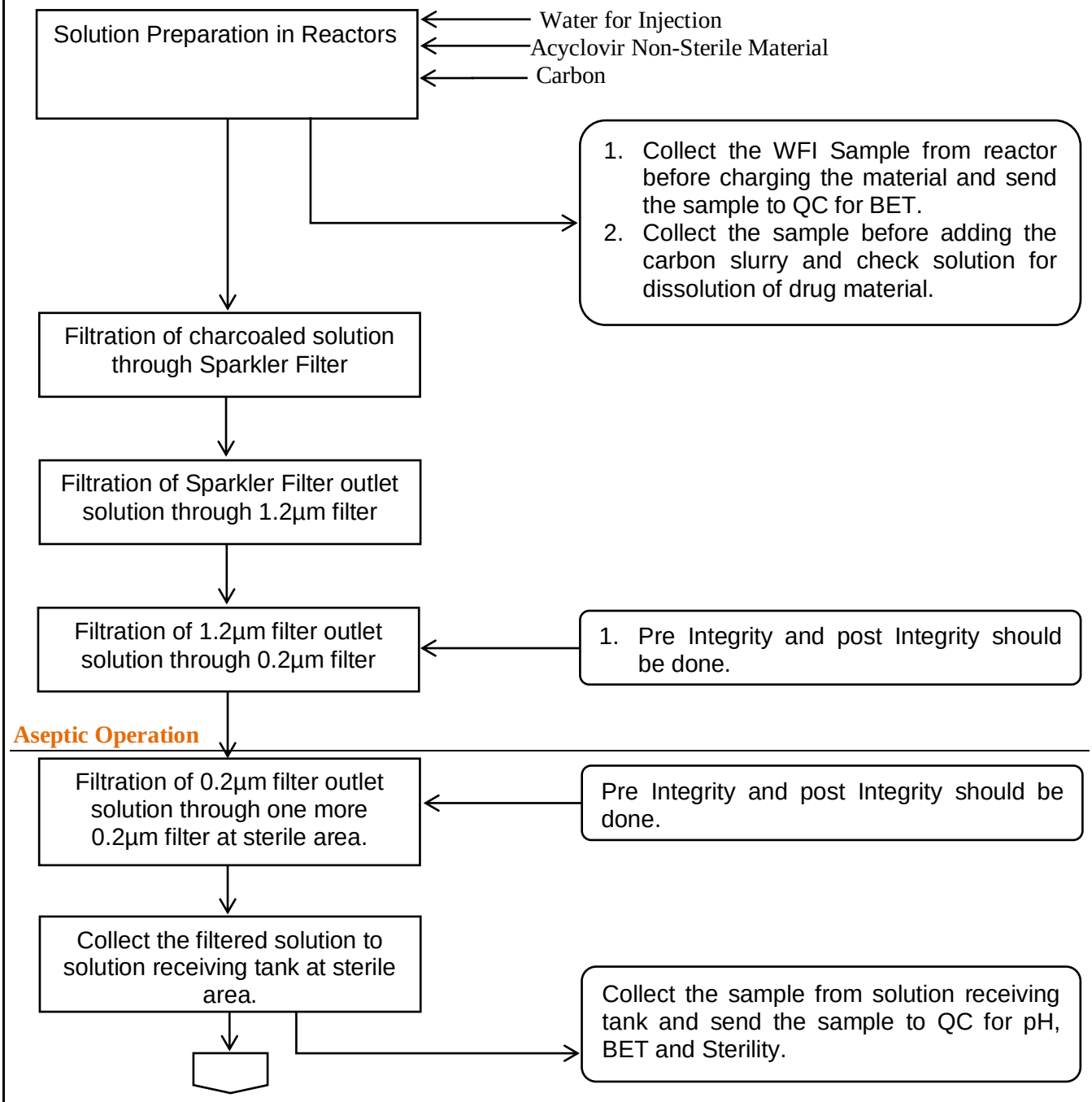
The requirement of raw material is as follows:

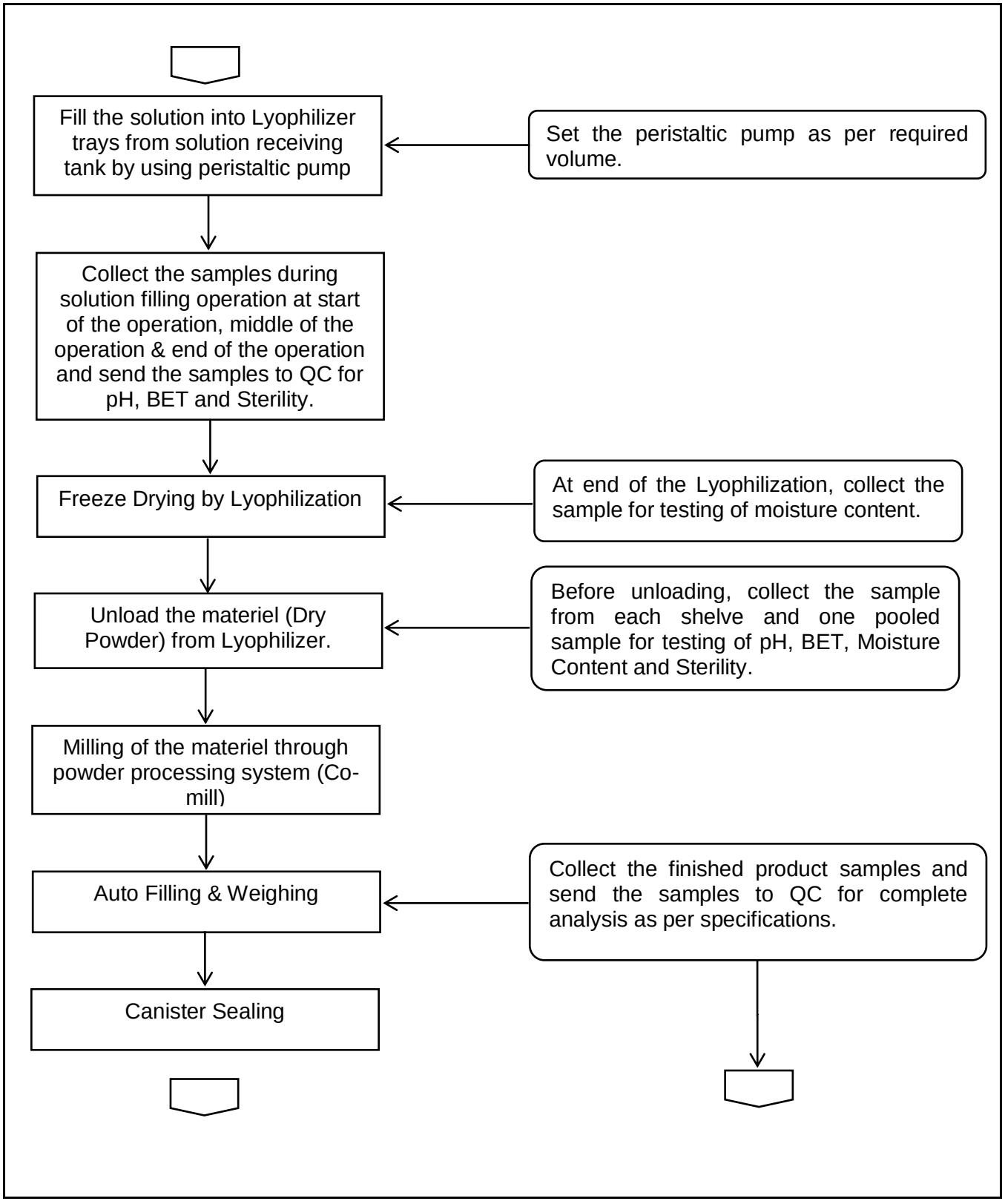
Ingredient	Quantity per Batch (kg)
Acyclovir, USP.	110.00*
ENO Carbon	0.500$
Sodium hydroxide	q.s
Water For Injection USP	424.00@

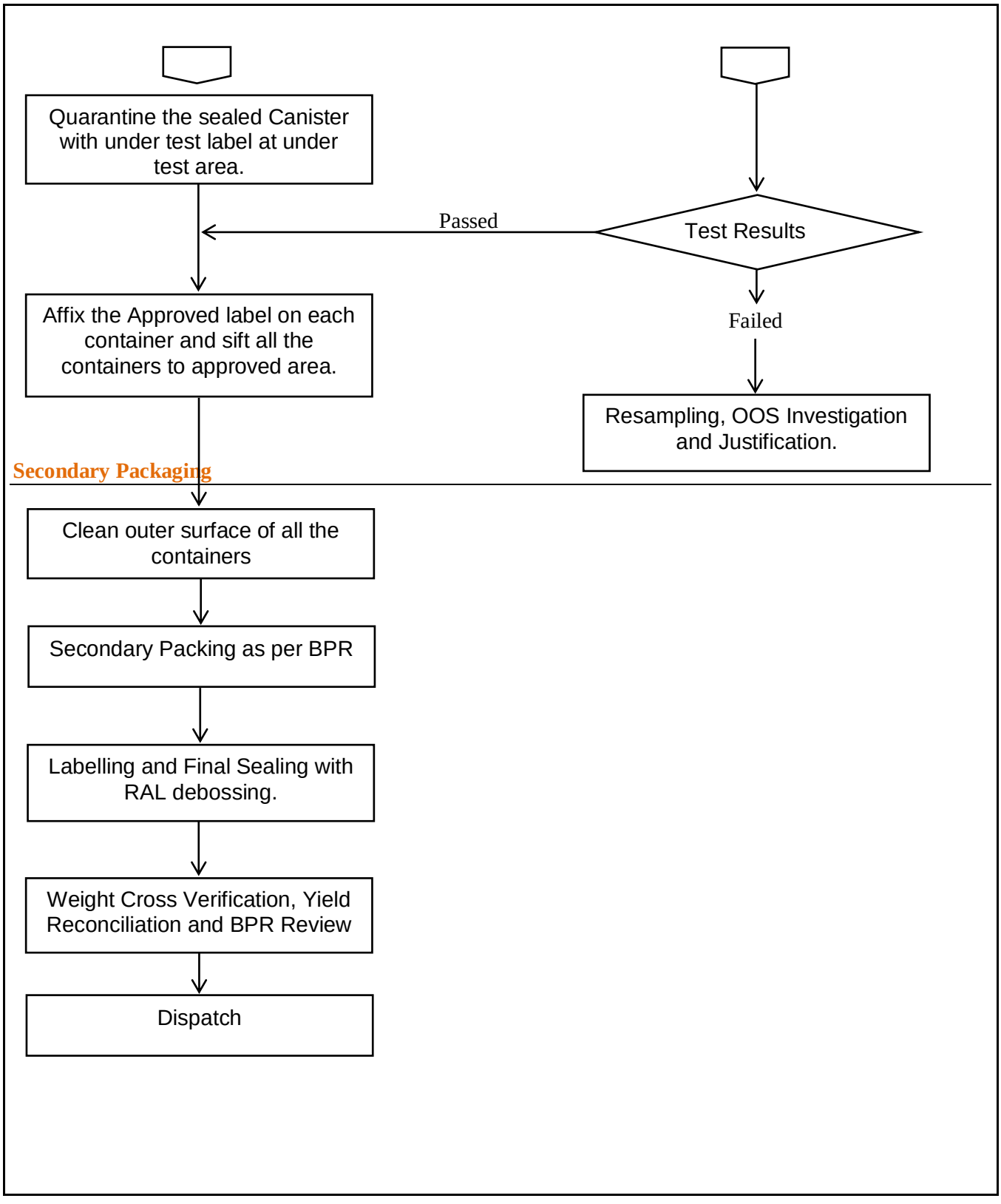
* : This quantity is based on 100%w/w assay.
@ : WFI shall be dispensed by production personnel, it will not appear in the final product except in traces.
NA : Not Applicable
q. s : Quantity Sufficient.

The dispensed raw material shall be transferred to the production.

4.0 Process Flow Diagram




Fill the solution into Lyophilizer trays from solution receiving tank by using peristaltic pump
Set the peristaltic pump as per required volume.
Collect the samples during solution filling operation at start of the operation, middle of the operation & end of the operation and send the samples to QC for pH, BET and Sterility.
Freeze Drying by Lyophilization
At end of the Lyophilization, collect the sample for testing of moisture content.
Unload the materiel (Dry Powder) from Lyophilizer.
Before unloading, collect the sample from each shelve and one pooled sample for testing of pH, BET, Moisture Content and Sterility.
Milling of the materiel through powder processing system (Co-mill)
Auto Filling & Weighing
Collect the finished product samples and send the samples to QC for complete analysis as per specifications.
Canister Sealing


Quarantine the sealed Canister with under test label at under test area.
Passed
Test Results
Failed
Affix the Approved label on each container and sift all the containers to approved area.
Resampling, OOS Investigation and Justification.
Secondary Packaging
Clean outer surface of all the containers
Secondary Packing as per BPR
Labelling and Final Sealing with RAL debossing.
Weight Cross Verification, Yield Reconciliation and BPR Review
Dispatch

5.0 Summary of critical process steps to be investigated

Process step	Process control parameters / variables
Quantity	Quantity of input and output of materials
Time	Time should comply with the standard or confirmative in study case.
Temperature	Temperatures of product dissolution, and drying.
Rpm	Rpm of the reactors,Comill

6.0 List of Manufacturing Equipment:

S. No.	Name of the Equipment	Equipment No.	Operation SOP No.	Cleaning SOP No.
1.	Lyophilizer	PDE-002	PD043†	PD023†
2.	Autoclave	PDE-003	PD025†	PD013†
3.	Dry Heat Sterilizer	PDE-001	PD027†	PD014†
4.	Solution preparation tank	PDE-029	PD026†	PD045†
5.	Solution preparation tank	PDE-030	PD026 †	PD045 †
6.	Solution holding vessel	PDE-031	PD026 †	PD045 †
7.	Process line Cartridge Filter (1.2µm)	PDE-034	PD015 †	PD015 †
8.	Process line Cartridge Filter (0.2µm)	PDE-035	PD015 †	PD015 †
9.	Process line Cartridge Filter (0.2µm)	PDE-036	PD015 †	PD015 †
10.	Sparkler Filter	PDE-033	PD046 †	PD047 †
11.	Peristaltic Pump	PDE-038	PD066 †	PD066 †
12.	Powder Processing System	PDE-052	PD069†	PD070 †
† Current effective version to be referred				

6.1 Testing equipment used

Only calibrated testing equipment will be used

6.2 Manufacturing facility

6.3 Environmental conditions.

- Temperature : NMT 25^0C.
- RH : NMT 35% & 55% as per product requirement.

7.0 Finished product specifications for release

S.No.	TEST	SPECIFICATION
1.	Characters: 1.1 Appearance 1.2 Solubility	A white or almost white, crystalline powder, Freely soluble in water
2.	**(a) Identification:** a) **By HPLC**	The retention time of the major peak in the chromatogram of the sample solution corresponds to that in the chromatogram of working standard in assay test.
	b) By Chemical Method:	It gives a reaction of sodium.
3.	Clarity of solution 1g in 10ml water	The solution is clear and absorbance<0.1 AU at 430 nm
4.	Related Substances (By HPLC)	
	a) Guanin (Imp-B) b) Impurity at RRT 0.7 c) Any other specified impurity e) Any Unspecified Impurity f) Sum of all Impurities	Not more than 1.0% Not more than 0.15% Not more than 0.5% (each) Not more than 0.1% Not more than 1.0%(other than guanine)
5.	Water content (by KF) determined on 0.5g sample	Not more than 5.5%w/w
6.	pH(50 mg/ml)	11 to 12
7.	Assay (By HPLC)	NLT 98.0% and NMT 101.0% on the anhydrous basis.
8.	**ADDITIONAL TESTS**	
I.	Residual Solvents: Ethyl acetate Methanol	 5000ppm 3000ppm
II.	Bulk Density (un-tapped)	Informative
	Tapped Density 100 Taps	Informative
III.	**Bacterial Endotoxins**	NMT 0.174 EU/mg
IV.	**Sterility test**	Should pass the test

V.	**Particulate matter:** Visible Particulate Matter Sub-visible Particulate Matter 10 micron or larger 25 micron or larger.	 Free from any visible particulate matter 6000 600
Storage Condition: Preserve in well closed containers, protected from light, in a dry place, at a temperature not exceeding 25ºC.		

Finished product Specification No. FS003†

† Current version will be used for reference

8.0 List of analytical methods

S. No.	Analytical test	Method
01.	Identification	By HPLC
		By UV
		By Chemical Method
02.	Assay	By HPLC
03.	Related compounds	By HPLC

9.0 Proposed in process controls with acceptance criteria

In Process Set Parameters	
BET	Should be pass
Moisture content	NMT 5.5 % w/w
Assay	98.0 % to 101.0

9.1 Three consecutive pivotal batches will be manufactured as described in Batch Production Record and Process Validation Protocol.

9.2 Manufacturing controls to be monitored.

9.3 Testing equipment used.

9.4 Only calibrated testing equipment shall be used.

10.0 Process Validation Methodology:

10.1 Three batches will be manufactured as described in Batch Production Record and Process Validation Protocol.

10.2 Manufacturing controls to be monitored

S.No.	Name of the Equipment	Equipment No.	Operation SOP No.	Cleaning SOP No.
1.	Lyophilizer			
2.	Autoclave			
3.	Dry Heat Sterilizer			
4.	Solution preparation tank			
5.	Solution preparation tank			
6.	Solution holding vessel			
7.	Process line Cartridge Filter (1.2µm)			
8.	Process line Cartridge Filter (0.2µm)			
9.	Process line Cartridge Filter (0.2µm)			
10.	Sparkler Filter			
11.	Peristaltic Pump			
12.	Powder Processing System			
† Current effective version to be referred				

10.3 Testing equipment used

Only calibrated testing equipment will be used.

10.4 Process Steps

Step No.	Process Stage	Process control Step		Expected response	Responsibility
	Solution preparation	pH		Should meet the specification	Production
	Filtration through Sparkler Filter	Removal of Carbon		No carbon particles should pass through the filter	Production
	After solution receiving	pH, Sterility and BET		Results should meet the specification	Microbiology
	During solution filling into Lyophilizer trays	pH, Sterility and BET	Start	Results should meet the specification	Microbiology
			Middle		
			End		
	During Lyophilization Cycle	All Set parameters		Lyophilizer Set parameter should be as per BMR	Production
	End of Lyophilization Cycle	Moisture Content		Moisture should meet the in process specification	Production
	Materiel Unloading from Lyophilizer	pH, Sterility, BET, Moisture and Assay	Sampling should be done as per sampling pan	Results should meet the specification	Microbiology
	During Milling	RPM of the Co-Mill		NMT 230	Production
	During Filling	Fill weight		As per BMR	Production

10.5 Compilation of Observed responses and Test results of samples collected shall be made in the formats provided in Appendices.

11.0 SAMPLE TEST PLAN

Process Stage	**Process Variable**	**Samples**				**Testing Needed**	**Testing Method †**	**Acceptance Criteria**
		No. of samples to be taken	**Type of Container / Bag**	**Sample size**	**No. of samples to be tested**			
Solution Preparation	Adjustment of pH	01 sample from bottom of the reactor	Glass Container	20 ml	01	pH	IP003	Should meet the Specification
After Solution Receiving	Sterility of Product	01 sample from bottom of the tank	Sterilized Glass Container	130 ml	01	pH, Sterility and BET	IP003	Should meet the Specification
Solution Filling into Lyophilizer trays	Sterility of Product	Start Middle End	Sterilized Glass Container	390 ml	03	pH, Sterility and BET	IP003	Should meet the Specification
End of the Lyophilization Cycle	*Sterility and purity of the Product	01 sample from each tray and one pooled sample	Sterilized Glass Container	360g	12	pH, Sterility, BET, Moisture Content and Assay	IP003	Should meet the Specification
During Milling and Container filling	*Sterility and purity of the Product	Start Middle End Pooled Sample	Sterilized Glass Container	400g	03	Complete Analysis	FP003	As per specification

† Current version will be used for reference.

* Sample shall be collected in twice of the sample quantity.

12.0 Environmental Monitoring

12.1 Environmental monitoring shall be done during manufacturing process as mentioned in BMR.

12.2 Operating procedure. All reports shall be attached to the Validation report.

† Current version will be used for reference.

13.0 Methods for recording and evaluating the results

Compilation of Observed responses and Test results of samples collected shall be made in the report

14.0 Stability Studies Requirements

Stability studies will be performed on the packed product as per the Stability Protocol.

15.0 Deviations if any

In case any deviation from the approved validation protocol, during the validation Studies, the same shall be recorded with justification in the validation report.

16.0 Process Validation Report Compilation

After completion of validation study, the validation team shall prepare the report. All the reports generated during the validation study shall be part of validation document. Validation report shall be reviewed and approved by the validation core committee.

Data generated during the Process Validation studies, test results etc., shall be presented in a comprehensive process validation report.

The process validation protocol shall be certified with compiled validation report by Head-Production, Head- QC, Head MB and Head QA.

17.0 References

- Batch Manufacturing Record
- In process and finished product specifications
- Test Methods

18.0 Abbreviations

QA	:	Quality assurance.
QC	:	Quality control.
P.D	:	Production.
MPR	:	Master production record.
STP	:	Standard test procedure.
PVP	:	Process validation protocol.
RPM	:	Rotations per minute.
SOP	:	Standard Operation Procedure