PROTOCOL

FOR

CLEANING VALIDATION

PRODUCTION BULK (API)

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1. OVERVIEW:

1.1 Introduction:

The purpose of this protocol for assurance of cleaning methodology to detect previous product residue from equipment/equipments parts. To provide the necessary documentary evidence that the cleaning procedure can reduce the residual contamination of previous product below the established limit so that such residue do not affect the quality and safety of the subsequent product to be manufactured in the same equipment.

1.2 Objective:

The objective of the cleaning validation protocol is to assure that the cleaning procedures of equipments, in-process containers in Production Bulk (API) facility can reproducibly remove residue of the product to levels below the established acceptance limits after manufacturing.

1.3 Scope:

The scope of this validation activity is limited to validate the cleaning process of equipments in production Bulk (API) department.

Reason for revision: Periodic cleaning verification is included in revalidation criteria.

1.4 Responsibility:

To conduct the cleaning validation study, a team shall be formed. The team shall contain the members from the Quality Control, Engineering, Production and Quality Assurance Departments. The Validation team is described through the following responsibility:

Quality Assurance	To prepare the protocol & report To provide the training To execute & supervise the study
Quality Control, Engineering, Production and Quality Assurance	To review the protocol To conduct the study To collect and analyze samples
Reviewer-1 : QC In-Charge / Designee	To review validation protocol. To review validation report.
Reviewer-2: CQA - Validation	To review validation protocol. To review validation report.
Approver-1: Head Production /Designee	To approve validation protocol. To approve validation report.
Approver-2: Head-QA/Designee	To approve validation protocol. To approve validation report.

2. EXECUTION TEAM:

Following personnel shall be responsible for the execution of validation study:

Production	:	To conduct the validation study as per protocol.
Quality Assurance	:	To monitoring the activity and collect the sample for chemical analysis as per protocol.
Quality Control	:	To conduct the microbiology monitoring, analysis of samples and reporting of results.
Engineering	:	To provide utility and maintenance support.

3. TRAINING RECORD:

3.1 Purpose:

The purpose of the training is to familiarize the trainees with the purpose and procedure of cleaning validation activity.

3.2 Scope:

This training is applicable to the protocol for cleaning validation.

3.3 Topics:

The following topics shall be covered during training: Identifying the responsibility of involved person.

4.3.1 Purpose & procedure of cleaning validation.
4.3.2 Documentation practices to be followed.
4.3.3 General precautions / guidelines to be followed during validation.

4. REQUIREMENT FOR CLEANING VALIDATION:

4.1 Documental Requirements:

S.No.	Document No.	Title of SOP
1.		Procedure for calibration of high performance liquid chromatography.
2.		Procedure for operation of high performance liquid chromatography (Model-Shimadzu).
3.		Procedure for operation of high performance liquid chromatography (Model-Waters).
4.		Bacterial endotoxin test procedure.
5.		Particulate matter testing.
6.		Bio burden testing by filtration method.
7.		Cleaning of Sparkler filter and Plate & frame filter
8.		Cleaning of Agitated Nutsche Filter Dryer-1
9.		Cleaning of Agitated Nutsche Filter Dryer-2
10.		Cleaning of Plate heat exchanger
11.		Cleaning of Crystallizer
12		Cleaning of Reactors

4.2 **Apparatus / Instrument Requirements:**

Polypropylene shaft (TEXWIPE), 10×10 cm^2 stainless steel coupon, Test tube (Glass bottle), WFI, Rinse Sample bottle.

5. SYSTEM/EQUIPMENT DESCRIPTION:

5.1 **API Solubility:**

5.1.1 **Imipenem**: Sparingly soluble in water.

5.1.2 **Cilastatin Sodium**: Soluble in water.

5.1.3 **Meropenem**: Sparingly soluble in water.

5.1.4 **Doripenem:** Sparingly soluble in water.

5.2 **Solubility Matrix:**

DESCRIPTION	SOLUBILITY (1g in listed ml)	mg/ml
Very soluble (VS)	Less than 1	>1000
Freely soluble (FS)	From 1 to 10	100 to 1000
Soluble (S)	From 10 to 30	33.33 to 100
Sparingly soluble (SPS)	From 30 to 100	10 to 33.33
Slightly soluble (SLS)	From 100 to 1000	1 to 10
Very slightly soluble (VSLS)	From 1000 to 10 000	0.1 to 1
Practically insoluble (PI)	More than 10 000	<0.1

5.3 **Equipment Description:**

The list of equipments and their part is given below with their surface area calculation for **Meropenem & Doripenem**:

S.No.	Name of Equipment	Equipment ID	Calculated Surface Area (m^2)
1.	S.S. Reactor - 2		4.0
2.	Plate Heat Exchanger		16.0
3.	Sparkler Filter		1.846
4.	S. S. Reactor - 3		2.3
5.	Filtration Skid Process Line III		5.5
6.	Crystallizer		10.19
7.	ANFD – 1 / ANFD - 2		5.5
8.	Bin		0.6
9.	Co-mill & Auto Filling Machine		3.4
10	Equipment Line connection	NA	4.6
		Total Surface Area	53.936 m^2
			539360 cm^2

The list of equipment and their parts is given below with their surface area calculation for **Imipenem**:

S.No.	Name of Equipment	Equipment ID	Calculated Surface Area (m^2)
1.	S.S. Reactor - 2		4.0
2.	Plate Heat Exchanger		16
3.	Sparkler Filter		1.846
4.	Sparkler Filter		0.756
5.	S. S. Reactor - 3		2.3
6.	S. S. Reactor - 4		2.3
7.	Filtration Skid Process Line III		5.5
8.	Crystallizer		10.19
9.	ANFD – 1 / ANFD - 2		5.5
10.	Bin		0.6
11.	Co-mill & Auto Filling Machine		3.4
12.	Equipment Line connection	NA	4.6
	Total Surface Area		56.992 m^2
			569920 cm^2

The list of equipment and their parts is given below with their surface area calculation for **Cilastin**:

S.No.	Name of Equipment	Equipment ID	Calculated Surface Area (m^2)
1.	S.S. Reactor - 3		2.3
2.	Sparkler Filter		1.846
3.	S. S. Reactor - 4		2.3
4.	Filtration Skid Process Line III		5.5
5.	Crystallizer		10.19
6.	ANFD – 1 / ANFD - 2		5.5
7.	Bin		0.6
8.	Co-mill & Auto Filling Machine		3.4
9	Equipment Line connection	NA	4.6
	Total Surface Area		36.236 m^2
			362360 cm^2

☞ *If different capacity of equipments used in product, higher contact surface area shall be considered for calculation.*

6. CLEANING VALIDATION METHODOLOGY OR PROCEDURE:

6.1 General Recording Instructions:

6.1.1 Read the contents of the document thoroughly before proceeding for Execution of the activity (in case of doubts / contradictions / contact the approvers of the document for clarifications).

6.1.2 Recording of all the observations and data shall be done as per **SOP "Good Documentation Practices"**.

6.2 **Cleaning Methodology:**

6.2.1 The cleaning validation study shall be performed for three changes over batches taken for validation.

6.2.2 Cleaning procedure shall be evaluated for first three campaigns of all the new products, which is introduced in the premises.

6.2.3 Clean the equipments as per respective SOP.

6.2.4 Collect the swab and rinse sample as per sampling procedure.

6.2.5 The swab sampling location is defined in **Annexure – 01** (Sampling locations of equipment).

6.3 **Worst case product selection:**

6.3.1 Worst case product shall be selected by following criteria-

6.3.1.1 Solubility
6.3.1.2 Hardest to clean
6.3.1.3 Therapeutic dose

6.3.2 **Product matrix:**

Table-1

S. No.	Name of product	API	Therapeutic Daily Dose Maximum (TDD)(mg)	Minimum Batch Size (kg)	Solubility (in water)
1	Meropenem for Injection	Meropenem	6000	30	Sparingly soluble
2	Imipenem for Injection	Imipenem	4000	20	Slightly soluble
3	Cilastatin Sodium for Injection	Cilastatin Sodium	4000	40	Soluble
4	Doripenem for Injection	Doripenem	1500	25	Sparingly soluble

☞ *From above products (Table-1), Hardest to clean product is Imipenem for Injection.*

6.3.3 Maximum Allowable Residue (MAR) calculation:

6.3.4 **Dose Criteria:**

$$\mathbf{L1} = \frac{\text{Minimum therapeutic dose of product A x Safety Factor (L0)}}{\text{Maximum daily therapeutic dose of product B}}$$

6.3.5 **10 ppm Criteria:** 10 mg of product A in kg of product B

☞ *Where A is the product for which cleaning is to be performed and B is the next proposed product to be processed.*
☞ *L0 is the safe amount of residue that can be administered to a person on a daily basis for a long time.*
☞ *Safety factor is 1/10000th (0.0001) shall be considered for dose criteria.*

6.3.6 Maximum allowable carryover limit of product A in to total batch size of the product B (L2) as given below:

L2 = **L1** x Minimum batch size of product B

6.3.7 Maximum allowable carryover limit of product A per square centimeter (Sq.cm or cm^2) of surface area (L3) as given below:

$$\mathbf{L3} = \frac{\mathbf{L2}}{\text{Total product contact surface area of the equipments}}$$

☞ *While calculating the equipment surface area, +5% of the obtained values may be taken to prevent error due to manual measurements*

6.3.8 Maximum allowable carryover limit of product A per swab area (L4a) is as given below:

L4a = **L3** x Swab area (sq. cm)

6.3.9 Concentration of residue in extracted swab sample (**L4b**) is given as below**:**

$$\mathbf{L4b} = \frac{\text{L3 x (area swabbed)}}{\text{Amount of desorbing solvent}}$$

6.3.10 Rinse concentration (**L4c**) of the active in any rinse solution is as given below;

$$\mathbf{L4c} = \frac{\text{L3 x (area rinsed)}}{\text{Amount of rinsing solvent}}$$

☞ *In case of swab sampling the calculation for chemical residue shall be performed by using 100 cm^2 surface area and 10ml as swab desorbing solvent (Water for injection).*

☞ *In case of rinse sampling the calculation for chemical residue shall be performed by using 100ml rinsing solvent (Water for Injection).*

6.4 **Maximum Allowable carryover (MACO) or Maximum Allowable Residue (MAR) determination:**

6.4.1 The minimum value obtained from 10ppm and therapeutic dose criteria shall be considered for acceptance limit of MAR in cleaning validation.

6.4.2 Worst case product is Imipenem for injection w.r.t. solubility (Slightly soluble in water) and hardest to clean.

6.4.3 Establishment of Acceptance Limits of Maximum Allowable Residue (MAR) calculation is as per **Annexure – 03** (Establishment of Acceptance Limits).

6.4.4 Worst case product is selected based on the least solubility of API in water. If the two or more products had the same solubility, the minimum therapeutic dose among those is considered as worst case product.

☞ *If the worst case product is not covered in all equipments, select next product as a worst case product based on worst case selection.*

- ☞ *For the products containing multi active ingredients, the active ingredient which has minimum therapeutic dose is considered for MAR calculation.*
- ☞ *Cleaning validation may consider may consider the next worst product, in case the actual worst product has not been manufactured since a long time.*

6.5 **Sampling Procedure and Test Methodology:**

6.5.1 **Physical verification:**

6.5.1.1 After completion of cleaning Production and QA personnel shall physically verify the equipment for cleanliness. It should be visually clean then only further activity shall be performed.

6.5.2 **Rinse Sample:**

6.5.2.1 Rinse the individual equipment as per respective SOP.

6.5.2.2 Send the entire samples along with blank sample to QC department for analysis of following test:

- Visual particles
- Sub visual particles
- Residue of previous product
- BET
- Bio burden

6.5.2.3 Depyrogenated container shall be used for BET sample collection.

6.5.2.4 Use the pre validated analytical method for analysis.

- ☞ *If samples are not analyzed immediately then samples are stores at 2 to 8°C and Samples shall be analyzed within 24 hours for chemical analysis.*
- ☞ *If samples are not analyzed immediately then samples are stores at 2 to 8°C and Samples shall be analyzed within 12 hours for microbial analysis.*
- ☞ *For bio burden sample use autoclaved bottle.*

6.5.3 **Swab Sample:**

6.5.3.1 Sampling locations (points) are selected based on the worst case criteria:

- Hard to clean area
- Inaccessible area

The sampling locations are defined in **Annexure – 01**.

6.5.3.2 Take the clean swab made up of Polyurethane foam having Polypropylene shaft (TEXWIPE) and put it in the test tube containing diluents and squeeze the swab along with the sides of test tube to remove the excess diluents from it.

6.5.3.3 Take out the wet swab from the test tube without touching the tip of swab.

6.5.3.4 Place the one side tip of swab at the identified location and apply it on the 10 x 10 cm^2 areas of the equipment/equipments parts (locations as defined in **Annexure – 01**). Swab samples are taken as shown in the **Figure – 01**.

- ☞ *In case of non-regular shape (e.g. cylindrical piping) simulate to the possible accessible area. Use appropriate swab holding devices to get the proper access of sampling points as described in the swab location.*

6.5.3.5 Put the swab stick into the test tube without touching the tip.

6.5.3.6 Label the test tube with the information of Swab sample, equipment part name, Sampling location, product name, batch no., sampled by and date.

6.5.3.7 Send the test tube to the QC department for analysis of following test:

- Residue of previous product
- BET
- Bio burden

6.5.3.8 Use the pre validated analytical method for analysis.

☞ *If samples are not analyzed immediately then samples are stores at 2 to 8°C and Samples shall be analyzed within 24 hours for chemical analysis.*

☞ *If samples are not analyzed immediately then samples are stores at 2 to 8°C and Samples shall be analyzed within 12 hours for microbial analysis.*

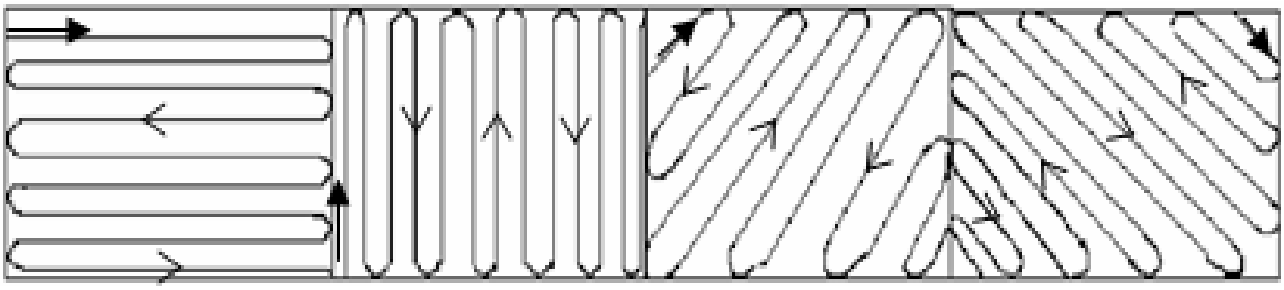


Figure – 01

6.6 **Recovery, LOQ and LOD Study:**

Recovery study, LOQ and LOD study is performed as per the analytical cleaning method validation protocol.

6.6.1 Analytical Method Validation protocol for Imipenem for Injection by HPLC.

6.6.2 Analytical Method Validation protocol for Doripenem for Injection by HPLC.

6.6.3 Analytical Method Validation protocol for Meropenem for Injection by HPLC.

6.6.4 Analytical Method Validation protocol for Cilastatin for Injection by HPLC.

6.6.5 **Testing Plan:**

6.6.5.1 **Rinse sample:** Visually inspect to particulate matter and analyze the rinse sample by suitable HPLC method for residue of previous product in the sample. BET shall be analyzed as per GTP and bio burden shall be analyzed as per GTP. Use the pre validated analytical method for analysis.

6.6.5.2 **Swab sample:** Analyze the swab sample by suitable HPLC method for residue of previous product in the sample. BET shall be analyzed as per GTP and bio burden shall be analyzed as per GTP. Use the pre validated analytical method for analysis.

6.6.5.3 **During Product Change over Testing**: Visual checking, particulate matter, residue of previous product, BET and Bio burden.

6.6.5.4 **During Change over Testing:** Visual checking, particulate matter and BET.

☞ *Particulate matters to be check firstly, if it is complying then proceed for next analysis.*

☞ *For sampling and dispensing different accessories to be used for each different product.*

7. ACCEPTANCE CRITERIA:

7.1 Should be visually clean.

7.2 Should be free from visible particle and sub visible particle ≥ 10µ: NMT 25/ml
≥ 25µ: NMT 3/ml

7.3 For the product contact surfaces, the least MAR in the product grouping obtained shall be considered as acceptance chemical residue limit (as per **Annexure – 03:** Establishment of Acceptance Limits).

7.4 For the product non-contact surfaces such as external surface of equipment etc., an acceptance chemical residue limit of 100 PPM per swab shall be considered.

7.5 The acceptance limit for microbial load is as follows:

- Bacterial Endotoxin Test shall be < 0.125 EU/ml.
- Bio burden shall be less than < 10 CFU / 100ml.

8. REVALIDATION CRITERIA:

Process to be revalidated in any of the following case:

8.1 Equipment change with different design specification.

8.2 Major modifications / changes to the equipments.

8.3 Change in the cleaning procedure.

8.4 Change in the manufacturing process.

8.5 Addition of new molecule.

8.6 MACO value decreased.

8.7 **Periodic verification:**

8.7.1 Periodic verification shall be done once in a year (± 30 days) with product, precisely the worst case product to cover all the equipments for those equipment on which worst case product is not taken, consider the worst case product from the group of products sharing that equipment.

☞ *Periodic verification may consider the next worst product, in case the actual worst case has not been planned during the review period.*

☞ *Periodic verification shall be carried out as per approved protocol.*

9. OBSERVED NON-CONFORMANCE (IF ANY):

All the non-conformance shall be addressed as per “Reporting and Monitoring of Process Non-Conformance in the Automated Quality Management System Software SOP”.

10. VALIDATION REPORT:

On completion of the cleaning validation, evaluation of the test results shall be carried out for achievement of the acceptance criteria. A summary report shall be prepared clearly stating the outcome of the cleaning validation against the predetermined acceptance criteria.

11. ABBREVIATIONS:

11.1	MACO	:	Maximum Allowable Carry Over
11.2	MAR	:	Maximum Allowable Residue
11.3	HPLC	:	High Performance Liquid Chromatography
11.4	NMT	:	Not More Than
11.5	BET	:	Bacterial Endotoxin Test
11.6	TDD	:	Therapeutic Daily Dose
11.7	MBS	:	Minimum Batch Size
11.8	SF	:	Safety Factor
11.9	cm^2	:	Centimeter Square
11.10	CFU	:	Colony Forming Unit
11.11	EU	:	Endotoxin Unit
11.12	PPM	:	Parts Per Million
11.13	LOQ	:	Limit of Quantitation
11.14	LOD	:	Limit of Detection
11.15	WFI	:	Water for Injection
11.16	API	:	Active Pharmaceutical Ingredient

12. LIST OF ANNEXURE:

Annexure No.	Annexure Title
01	Sampling location of equipment
02	Visual inspection for cleaning validation / verification
03	Establishment of Acceptance Limits
04	Equipment / equipment parts cleaning record

13. REFERENCE DOCUMENT (IF ANY):

13.1 Management of Validation/Qualification documents in DMS.
13.2 Quality Policy.
13.3 Cleaning Validation Programme.
13.4 Preparation of Validation and Qualification Protocol and its Control.

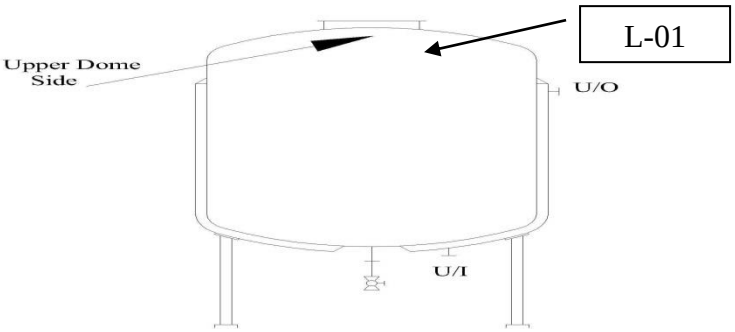
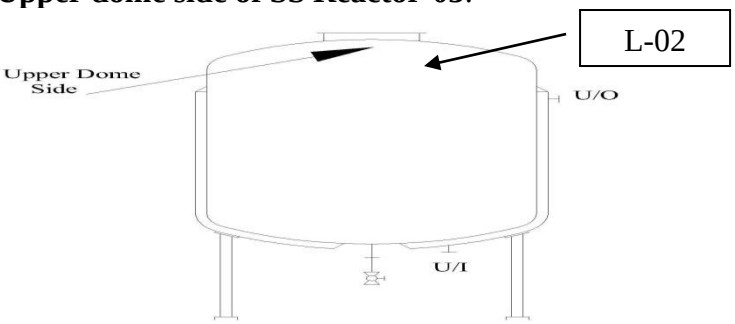
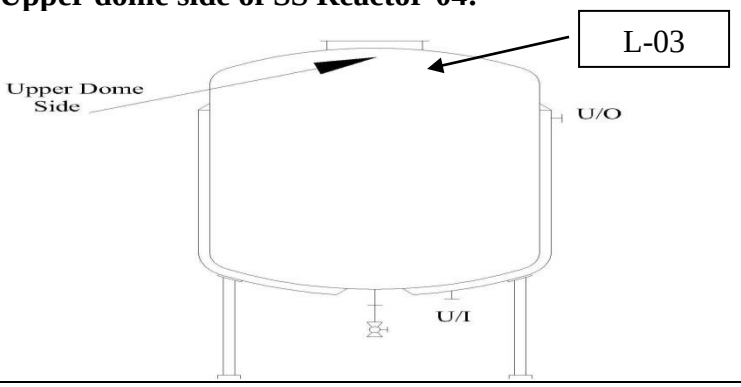
14. REVISION HISTORY:

Superseded Protocol		S. No.	Step No.	Changes made
Protocol No. / Version No.	Effective Date			

Superseded Protocol		S. No.	Step No.	Changes made
Protocol No. / Version No.	Effective Date			

Annexure – 01: Sampling location of equipments

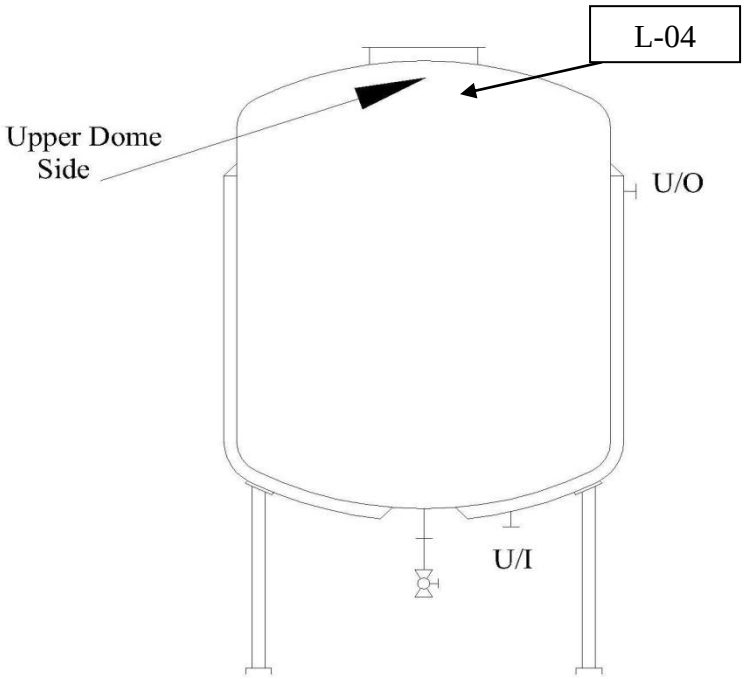
Equipment Name:	SS Reactor- 02, 03, 04	**ID No.:**	

Location Photo	**Location Identification & rational for selection**
Upper dome side of SS Reactor-02: 	L-01: Hard to clean area and physical verification is not feasible.
Upper dome side of SS Reactor-03: 	L-02: Hard to clean area and physical verification is not feasible.
Upper dome side of SS Reactor-04: 	L-03: Hard to clean area and physical verification is not feasible.

Done by (Signature & Date)	**Checked by (Signature & Date)**

Equipment Name:	Crystallizer	**ID No.:**	
Location Photo		**Location Identification & rational for selection**	

Upper dome side of Crystallizer:

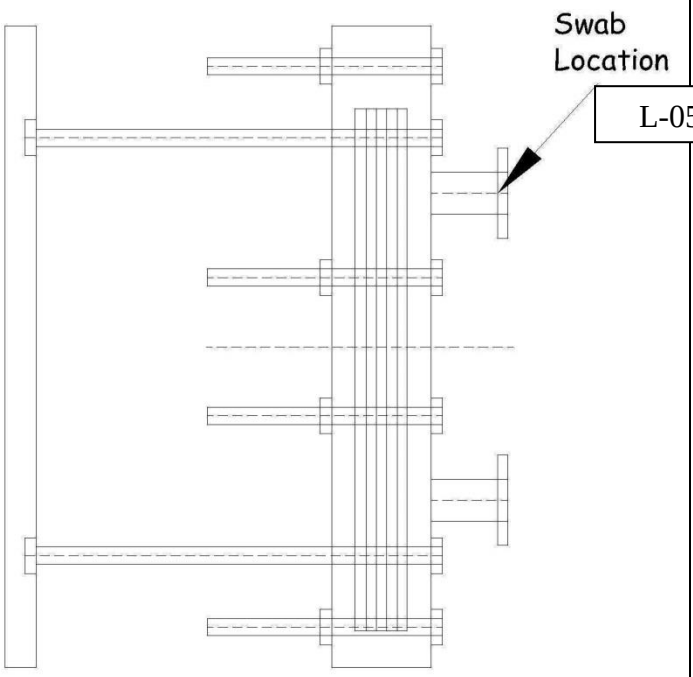


L-04: Hard to clean area and physical verification is not feasible.

Done by (Signature & Date)	Checked by (Signature & Date)

Equipment Name:	Plate Heat Exchanger	ID No.:	
Location Photo		Location Identification & rational for selection	

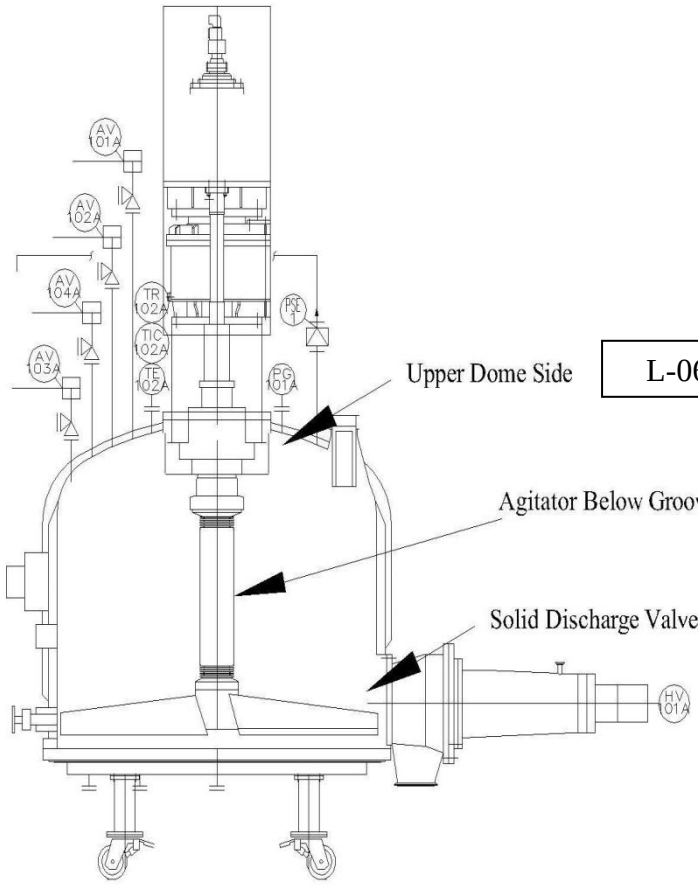
Outlet of Plate Heat Exchanger:



L-05: Hard to clean area and physical verification is not feasible.

Done by (Signature & Date)	Checked by (Signature & Date)

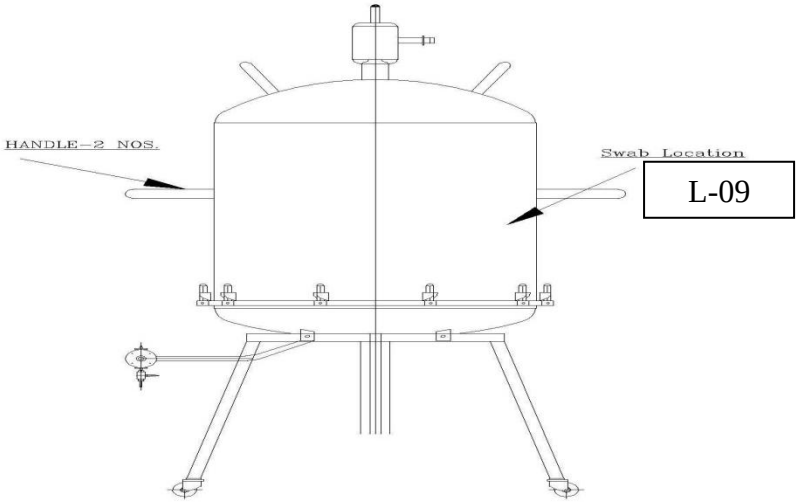
Equipment Name:	Agitated Nutsche Filter Dryer	ID No.:	

Location Photo	Location Identification & rational for selection
	L-06: Hard to clean area and physical verification is not feasible. L-07: Hard to clean area and physical verification is not feasible. L-08: Hard to clean and maximum chance deposition of groves of bellow.

Done by (Signature & Date)	Checked by (Signature & Date)

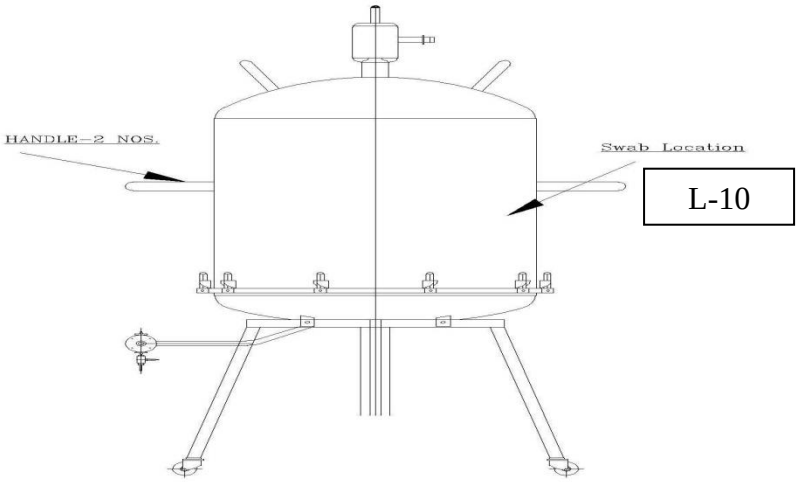
Equipment Name:	Sparkler Filter	ID No.:	
Location Photo		**Location Identification & rational for selection**	

Body of Sparkler Filter:



L-09: Maximum time to contact on the product.

Body of Sparkler Filter (PB/SPF-02):

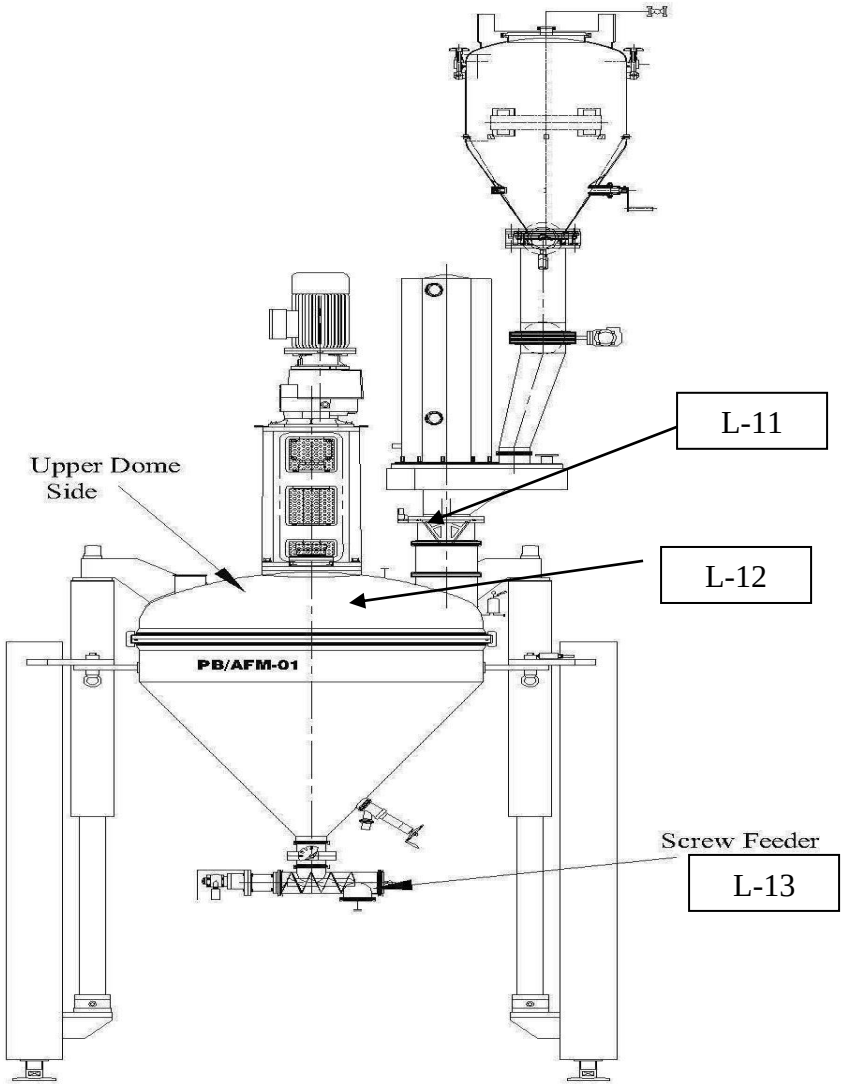


L-10: Maximum time to contact on the product.

Done by (Signature & Date)	Checked by (Signature & Date)

Equipment Name:	Co-mill & Auto Filling Machine	ID No.:	

Location Photo	Location Identification & rational for selection



L-11 (Sieve of the Co-Mill): Hard to clean, maximum chance to deposition of product on mesh pores

L-12: Hard to clean and physical verification is not feasible.

L-13: Hard to clean, maximum chance to deposition of product on mesh pores.

L-14 (Filtration skid inside housing): Hard to clean surface.
L-15 (Inside housing of aseptic area filter): Hard to clean surface.
L-16 (Unloading bin 01/02): Hard to clean and physical verification is not feasible

Done by (Signature & Date)	Checked by (Signature & Date)

Annexure – 02: Visual inspection for cleaning validation / verification

S.No.	Product Name/ Batch No.	Equipment Name	Equipment ID No.	Part Inspected	Visually clean (Yes/No)	Checked by Sign/Date

Annexure – 03: Establishment of Acceptance Limits

Product B →			Therapeutic Dose	Meropenem for Injection	Imipenem for Injection	Cilastatin Sodium for Injection	Doripenem for Injection	Worst Case MAR Value	Remarks
Product A ↓				DOSE	DOSE	DOSE	DOSE		
		Therapeutic Dose (gm)		6000	4000	4000	1500		
		Batch Size (kg)		30	20	40	25		
	1	Meropenem for Injection	Surface Area		569920.0	362360.0	569360.0		
			6000		0.526	1.656	1.756	0.526	
	2	Imipenem for Injection	Surface Area	569360.0		362360.0	569360.0		
			4000	0.351		1.104	1.171	0.351	
	3	Cilastatin Sodium for Injection	Surface Area	569360.0	569920.0		569360.0		
			4000	0.351	0.351		1.171	0.351	
	4	Doripenem for Injection	Surface Area	569360.0	569920.0	362360.0			
			1500	0.132	0.132	0.414		0.132	
							Minimum Value	**0.132 (mg/swab)**	

Annexure – 04: Equipment / equipment parts cleaning record

S.No.	Product Name/ Batch No.	Equipment /equipment part name	Equipment ID No.	WFI loop pressure	Cleaning		Cleaning done by (Sign/Date)	Checked by Sign/Date
					From	To		