CLEANING VALIDATION PROTOCOL & REPORT
(MEFENAMIC ACID IP)

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

CLEANING VALIDATION PROTOCOL & REPORT FOR ORAL LIQUID (MEFENAMIC ACID)

INDEX

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1. PROTOCOL PRE APPROVAL:

Prepared By	Name	Signature	Date
Quality Assurance			
Approved By			
HOD - Quality Control			
HOD - Production			
HOD - Engineering			
HOD - Quality Assurance			

2. INTRODUCTION:

Cleaning Validation is documented evidence, which gives high degree of assurance that the cleaning method is consistent and reproducible and brings the residue levels below the total allowable carryover residue levels.

The cleaning methods must be validated to demonstrate the efficacy of the cleaning methods during product changeover. It is important to ensure that the carryover of the active ingredient of earlier product in the next batch is within the acceptance criteria. The validated cleaning method shall ensure that there is no cross contamination of the product in the next product.

The cleaning after product changeover is done as per approved cleaning method. These methods shall be validated for their effectiveness considering the worst case.

3. OBJECTIVE:

This validation protocol shall be applicable to validate the cleaning method used to clean the Stirrer Tank, Sugar tank, Mfg. tank, Transfer pump, and Storage tank, Filter press and Basket filter Homogeniser, and Filling machine used in manufacturing plant. This protocol will define the methods and documentation that will be used to evaluate the efficacy of the cleaning procedures in accordance with acceptance criteria used considering the worst scenario with respect to solubility, potency and batch size.

4. SCOPE:

The scope of this protocol is to evaluate the acceptability of cleaning procedure used for the cleaning equipment in Stirrer Tank, Sugar tank, Mfg. tank, Transfer pump, and Storage tank, Filter press and Basket filter, Homogeniser, and Filling machine using well-established analytical and Microbiological method to determine the chemical and microbiological burden. This will also cover the responsibilities, sampling plan, acceptance criteria and analytical method.

The equipments shall be sampled for the residue of the earlier product by visual inspection and chemical testing method, residue of the detergent by chemical testing method and bio burden using validated analytical methods. Sampling shall be carried out using swab.

The Analytical method used for analysis of residue traces after cleaning shall be validated for limit of detection, specificity and linearity at the minimum. The microbiological test method shall be concurrently validated using positive and negative controls.

5. RESPONSIBILITY:

The validation group comprising of a representative from each of the following departments shall be responsible for the overall compliance of this protocol:

DEPARTMENTS	RESPONSIBILITIES
Production	• Approve the validation protocol and the report. • To follow & effectively cleaning as per Standard Operating Procedure • Identify the equipment's hard to clean areas. • Arrange for cleaning of used equipment • Provide all the information to build the data base.
Quality Assurance	• Preparation of Cleaning validation Protocol • Co-ordination with Production and QC to carryout Cleaning validation • Monitoring and sampling at the different stages of cleaning as per Cleaning validation Protocol • Compilation of report • Preparation of a Cleaning validation Summary Report • Approve the validation protocol and the report.
Quality Control	• Analysis of Cleaning validation Samples. • Preparation of Analysis Report and submission to Quality Assurance Dept.
Engineering	• Verify the accuracy of the drawing. • Calculate the product contact area. • Assist in the identification of equipment hard to clean locations.

6. SLECTION OF PRODUCT:

6.1 Selection of worst case product for cleaning validation study

The worst case product selection from product matrixing criteria are solubility of product, potent drugs, minimum daily dose, batch size.

The Products falling under these criteria are listed below:

S.No.	Active	Criteria	Reason
1.	Mefenamic Acid IP	Solubility minimum daily dose criteria	The selection of this product due to : 1. To cover all stages up to bottle filling. 2. On the basis of minimum daily dose and solubility matrix.

7. PRODUCT DETAIL

Product: **MEFENAMIC ACID IP**

8. EQUIPMENT DETAIL

The following equipments are to be used for Manufacturing and packing of the product.

8.1 List of Equipment to be validated:

S.No.	Title	SOP No.
1.	Operation and cleaning of Sugar tank	
2.	Operation and cleaning of Mfg. tank	
3.	Operation and cleaning of Transfer pump	
4.	Operation and cleaning of Storage tank	
5.	Operation and cleaning of Homogeniser	
6.	Operation and Cleaning of Filling machine	

8.2 Equipment Data Base:

The swab samples of the equipment sampled shall be from such parts that are the most difficult to clean which are listed below.

Equipment	Product contact surface area (cm^2)	Rinse Water volume (Lit.)
Stirrer Tank	5494.57	5
Sugar tank	120201.5	100
Mfg. tank	120853.7	100
Transfer pump	1623.64	5
Storage tank	130906.4	100
Filter press	1095.75	10
Basket filter	1623.31	10
Homogeniser	1873.35	20
Filling machine	1857.20	25

Total contact surface area for API = 385529.42 cm^2

9. CALCULATION OF MAXIMUM ALLOWABLE CARRY OVER (MACO):

Solubility and Minimum Therapeutic Daily Dose criteria as per matrix:

$$\text{Maximum Allowable Carry Over (mg per batch)} = \frac{\text{MTD x SF x MBS x 1000}}{\text{MDD}}$$

Where,

MTD : Minimum Therapeutic Daily Dose of Previous Product

SF : Safety factor (1/1000)

MBS : Minimum Batch Size of Next product in liter

MDD : Maximum daily dose

MACO calculation for Mefenamic acid as per matrix:

$$\text{MACO} = \frac{50\text{X } 1/1000 \text{ X}500\text{X}1000}{500} = 50 \text{ mg.}$$

Swab Limit: $= \frac{\text{MACOx25}}{\text{Surface area}} = \frac{50 \times 25}{385529.42} = 0.003242$ mg/swab

=3.24 ppm

10. ACCEPTANCE CRITERIA:

A. For Visual Inspection Criteria:

- There shall not be any visual evidence from a distance of 30 cm for previous product on the product contact parts and other equipment surface after cleaning.

B. 10 ppm Criteria:

- Not more than 10 ppm.
  = 10 x Batch size= 10x500 =5000 ppm

C. Dose Criteria: Not more than 1/1000th dose of any product, which shall appear in the maximum daily dose of another product manufactured subsequently.

For Microbial Contamination:

S.No.	Swab Sample	Acceptance limit
1.	Total Bacterial Count	NMT 100 CFU/gm/ml
2.	Total Fungal Count	Should be absent

Based on these acceptance criteria lowest value shall be considered for determination of cleaning validity.

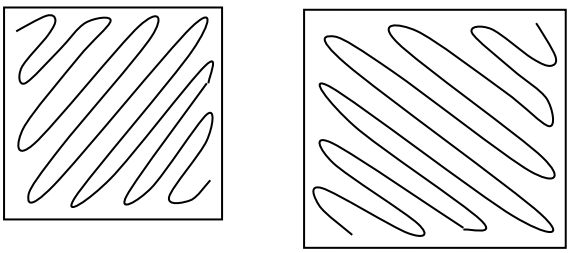
11. SAMPLING PROCEDURES & SAMPLING PLAN:

I. SAMPLING PROCEDURE

- Prior to swab sampling, cleaned equipment shall meet "Visual Clean" criteria.
- After cleaning of the equipment visual inspection shall be done and recorded in report.
- After successful Visual Inspection swab sampling shall be carried out.
- Use Hand gloves and mask during sampling.

II. For Swab Sampling:

The Swabbing shall be done in horizontal or vertical strokes like below shown procedure in the marked area assuring that the entire area is swabbed.



- After swabbing, rinse the swabbing location by purified water to remove the traces of solvent.

Sampling procedure for Residue for chemical analysis:

During sampling, Chemist should wear hand gloves. Take specified solvent in a test tube. Dip non-sterile swab (Absorbent cotton swab stick) in specified solvent to wet/ moisten the swab and squeeze. Swab critical areas of the specified equipment as per protocol. Swab sampling area. Swabs used for sampling should be dipped in the same solvent. Stopper the test tube immediately. Put identification label to the test tubes.

Sampling Procedure for Microbial Analysis:

During sampling, Chemist should wear sterile hand gloves. Take 5ml of sterile distilled water in a sterile test tube. Dip the swab in sterile distilled water to wet/moisten the swab. Squeeze the swab slightly by pressing the swab on the inside wall of the test tube. Swab critical areas of the specified equipment as per protocol.

Keep the swab sample after sampling in a sterile empty test tube.

Stopper the test tube Put identification number, location number and date of sampling, Take the Stoppered test tubes to QC for Microbial testing.

B). For Rinse Sampling:

- Rinse the entire equipment with the specified quantity of the Purified water and collect the rinse in a clean container. Remove appropriate quantity of rinse sample and filter through what man No. 2 filter paper.

11.1SWAB RECOVERY:

Once the acceptance limit of cleaning validation is determined swab recovery study should be carried out. Product solutions of 50%, 100% and 150% of the acceptable limit are prepared and spiked on the model surface equivalent to the swab surface area. Surface is dried under gentle airflow and sampled as per the standard swabbing technique, as used for sampling during validation. The swab is tested by UV method. The percentage recovery should not be less than 80% Recovery.

III. SAMPLING PLAN:

a. Swab sample for chemical/Microbial analysis

Name of Equipment	Product Contact Surface Area (In cm^2)	Sampling Locations
Stirrer Tank	5494.57	1. Stirrer 2. Inner Surface of Stirrer Tank 3. Lid
Sugar tank	120201.5	1. Bottom valve 2. Lid 3. Stirrer 4. Inner surface 5. Top dish
Mfg. tank	120853.7	1. Bottom valve 2. Lid 3. Stirrer 4. Inner surface 5. Top dish
Transfer pump	1623.64	1. Inlet 2. Out let
Storage tank	130906.4	1. Bottom valve 2. Lid 3. Stirrer 4. Inner surface 5. Top dish
Filter press	1095.75	1. Filter plate 2. Inlet 3. Outlet
Basket filter	1623.31	1. Inlet 2. Outlet 3. Screen
Homogeniser	1873.35	1. Inlet 2. Discharge chute
Filling machine	1857.20	1. Inlet line 2. Filling nozzle 3. Storage vessel 4. Hose 5. Silicon Tube

12. Cleaning Verification:

Cleaning verification of the equipment train shall be done results shall be summarised as per below table:

S.No.	Equipment used in Manufacturing	Visually Clean/or not clean
1.	Stirrer Tank	
2.	Sugar tank	
3.	Mfg. tank	
4.	Transfer pump	
5.	Storage tank	
6.	Filter press	
7.	Basket filter	
8.	Homogeniser	
9.	Filling machine	

Opinion: The visual inspection of the equipment after the manufacture of MEFENAMIC ACID IP Complies / Does not comply w.r.t. acceptance limit.

Checked By
(Sign. /Date)

Reviewed By
(Sign. /Date)

12.2 Microbiological Analysis Report:

AFTER 1ST BATCH MANUFACTURING

S.No.	Equipment No.	Location of swab area	Bacterial counts	Yeast & moulds
1.	Stirrer Tank	1. Stirrer		
		2. Inner Surface of Stirrer Tank		
		3. Lid		
2.	Sugar tank	1. Bottom valve		
		2. Lid		
		3. Stirrer		
		4. Inner surface		
		5. Top dish		
3.	Mfg. tank	1. Bottom valve		
		2. Lid		
		3. Stirrer		
		4. Inner surface		
		5. Top dish		
4.	Transfer pump	1. Inlet		
		2. Out let		
5.	Storage tank	1. Bottom valve		
		2. Lid		
		3. Stirrer		
		4. Inner surface		
		5. Top dish		
6.	Filter press	1. Filter plate		
		2. Inlet		
		3. Outlet		
7.	Basket filter	1. Inlet		
		2. Outlet		
		3. Screen		
8.	Homogeniser	1. Inlet		
		2. Discharge chute		
9.	Filling machine	1. Inlet line		
		2. Filling nozzle		
		3. Storage vessel		
		4. Hose		
		5. Silicon Tube		

Opinion: The microbial contamination of cleaned equipment after the manufacturing of MEFENAMIC ACID IP complies / does not comply w.r.t. acceptance limit.

Checked By
(Sign. /Date)

Reviewed By
(Sign. /Date)

12.3 Microbiological Analysis Report:

AFTER 2ND BATCH MANUFACTURING

S.No.	Equipment No.	Location of swab area	Bacterial counts	Yeast & moulds
10.	Stirrer Tank	1. Stirrer		
		2. Inner Surface of Stirrer Tank		
		3. Lid		
11.	Sugar tank	1. Bottom valve		
		2. Lid		
		3. Stirrer		
		4. Inner surface		
		5. Top dish		
12.	Mfg. tank	1. Bottom valve		
		2. Lid		
		3. Stirrer		
		4. Inner surface		
		5. Top dish		
13.	Transfer pump	3. Inlet		
		4. Out let		
14.	Storage tank	1. Bottom valve		
		2. Lid		
		3. Stirrer		
		4. Inner surface		
		5. Top dish		
15.	Filter press	4. Filter plate		
		5. Inlet		
		6. Outlet		
16.	Basket filter	4. Inlet		
		5. Outlet		
		6. Screen		
17.	Homogeniser	1. Inlet		
		2. Discharge chute		
18.	Filling machine	1. Inlet line		
		2. Filling nozzle		
		3. Storage vessel		
		4. Hose		
		5. Silicon Tube		

Opinion: The microbial contamination of cleaned equipment after the manufacturing of MEFENAMIC ACID IP complies / does not comply w.r.t. acceptance limit.

Checked By
(Sign. /Date)

Reviewed By
(Sign. /Date)

13.0 DOCUMENTATION

I Validation Protocol
II Analytical Reports QC
III Analytical Reports Micro

14.0 ABBREVIATIONS

QC	:	Quality Control
QA	:	Quality Assurance
PPM	:	Parts Per Million
NMT	:	Not More Than

15.0 SUMMARY & CONCLUSION

15.1Summary:_____

15.2Conclusion:_____

16.0 FINAL APPROVAL:

Approved By	Name	Signature	Date
HOD - Quality Control			
HOD - Production			
HOD - Engineering			
HOD - Quality Assurance			