CLEANING VALIDATION PROTOCOL FOR GLIMEPIRIDE 2 MG TABLETS FOR ACCEPTANCE CRITERIA CALCULATION AND CLEANING VALIDATION EXECUTION

PLANT	
PROTOCOL No.	
EFFECTIVE DATE	

CLEANING VALIDATION PROTOCOL FOR GLIMEPIRIDE TABLETS

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1.0 PROROCOL APPROVAL:

The protocol for Cleaning Verification of tablet manufacturing equipments has been initiated, checked and approved by the following functional heads. Further if any change in protocol are required, protocol will be revised and duly approved

Protocol prepared by:

Designation	Name	Sign	Date
Officer - Quality Assurance			

Protocol checked by:

Designation	Name	Sign	Date
Executive – Quality Assurance			

Protocol approved by:

Designation	Name	Sign	Date
Head – Production			
Head – Quality Control			
Head – Quality Assurance			
Plant Head			

2.0 PURPOSE:

CLEANING VALIDATION PROTOCOL FOR GLIMEPIRIDE TABLETS

Objective of cleaning validation is to establish and assure with documented evidence that define cleaning procedure for the respective equipments of facility can reproducibly remove residue of the products, microbial residues to the levels below predefined acceptance criteria.

3.0 SCOPE:

3.1 This Validation protocol shall be applicable for the Validation of cleaning procedures adopted for cleaning of equipments used for manufacturing of Glimepiride 2 MG Tablets API Glimepiride.

3.2 This protocol shall define the methods and documentation that shall be used to evaluate the suitability of the cleaning procedures in accordance with established acceptance criteria.

3.3 This protocol shall define methods used to determine the traces of leftover residue of previous product on the contact parts of equipments.

3.4 This Validation exercise shall be applicable for each product manufactured in Granulation-V.

3.5 The training documentation associated with the Standard Operating Procedures shall be verified prior to start of the cleaning verification study.

3.6 Pre- verification checks, analytical methods and acceptance criteria shall be verified for worst case API for evaluating the performance of the cleaning methods.

3.7 The equipments selected for cleaning verification shall be evaluated for residue of the previous API by visual inspection and chemical testing.

3.8 The rinse techniques shall be used to evaluate the left over residue of the previous API on the product contact surfaces of equipments.

3.9 The result obtained for each equipment shall be evaluated to verify that the specified acceptance is met.

3.10 The Standard Operating Procedures associated with the cleaning and testing shall be documented.

4.0 STUDY RATIONALE AND SELECTION OF WORST CASE PRODUCT:

Cleaning Validation is documented evidence, which provides a high degree of assurance that the cleaning method is consistent, reproducible and brings the residue levels below the total allowable carryover residue levels. Cleaning Validation shall ensure that the carryover of the active ingredient of earlier product in the next batch is within the acceptance criteria. The cleaning shall be done as per approved cleaning method. The procedures used for product changeover cleaning shall be validated for their effectiveness considering the worst case.

Glimepiride tablet (API : Glimepiride) is considered to be a worst case product as per the evaluation performed in Annexure-IV (Ver:01) to the cvmp.

Cleaning validation activity shall be performed by collecting the swab, rinse and microbiology samples on three cleaning cycles after the manufacturing of Glimepiride tablet.

Methanol shall be used as the desorption solvent for collecting the rinse sample from the contact surfaces of equipments.

The equipments shall be sampled for the residue of the previous product by visual inspection & chemical testing method and bioburden using validated analytical methods. Sampling shall be carried out using swab and rinse techniques.

The swab samples for chemical analysis of the equipment sampled shall be from such parts that are the most difficult to clean.

5.0 RESPONSIBILITY:

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

DEPARTMENTS	RESPONSIBILITIES
Production	• Execution of cleaning Validation. • Pre-approval & Post – approval of cleaning Validation Protocol.
Quality Assurance	• Preparation of cleaning Validation Protocol based on BMR and Cleaning Verification Plan. • Co-ordination with Production and QC to carryout Cleaning verification. • Monitoring and sampling at the different stages of cleaning as per Cleaning verification Protocol. • Preparation of cleaning verification Summary Report.
Quality Control	• Analysis of Cleaning verification Samples. • Preparation of Analysis Report and submission to Quality Assurance Dept.
Engineering	• Calibration of measuring devices and Preventive Maintenance of Machines as per schedule. • Rectification of Breakdown during Manufacturing (If any)

6.0 IDENTIFICATION OF EXECUTION TEAM MEMBERS:

Following personnel identified for the executing the qualification/ validation. And their training with respect to qualification and validation is completed and the evaluation is satisfactory.

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Department	Name	Signature	Date
Quality assurance	*	*	*
Production	*	*	*
Engineering	*	*	*
Quality control	*	*	*

7.0 PREVIOUS PRODUCT DETAILS:

7.1 Product: Glimepiride Tablets

7.2 Product Design:

Active Ingredient as Worst Case	Glimepiride
Pharmacopoeial Grade	IP
Strength	2 mg
Label Claim	Each Uncoated Tablet Contains: Glimepiride IP…..……. 2 mg
Weight/ Tablet	150.00 mg

7.3 Batch Size : 5,00,000 Tablets

7.4 Method Detail:

Specific Analysis (HPLC)

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Ref. Method Validation Document No. (Protocol No) : …… **Residue Recovery Study Protocol No. : ……**	
Parameters	**Results**
Specificity	There is no interference of blank and swab stick solution with Glimepiride peak
LOQ & LOD	LOD- 0.01 ppm LOQ- 0.025 ppm
Linearity & Range	The correlation coefficient was found within the limits (not less than 0.999), hence method is liner over the working range (LOQ to 0.4 ppm concentration).
Accuracy (Recovery)	LOQ (0.025) ppm - 81.2% , 0.05 ppm- 97.5 %, 0.1 ppm-99.4 % and 0.4 ppm -101.2 % The % recovery at each level is not less than 75.0 % .
Solution Stability	Cumulative % RSD between zero hours and 24 hours ------ 2.12 %

8.0 EQUIPMENT DETAIL AND CLEANING PROCEDURE:

Equipment to be used for manufacturing and packing of Glimepiride Tablets (API-Glimepiride) and cleaning has to be carried out as per instructions given in respective SOP of the equipment.

Refer to Annexure-I

9.0 ACCEPTANCE CRITERIA AND SAMPLING PLAN:

9.1 Calculation of acceptance criteria for Chemical contamination

9.1.1 Dose criteria:

The maximum allowable carryover (MACO per 100 cm^2) for swab sample shall be calculated using the following formula:

$$\text{MACO (mg /100 cm}^2\text{)} = \frac{\text{LTD/1000}}{\text{D}} \times \frac{\text{Wb}}{\text{Wt}} \times \frac{\text{Ss}}{\text{Se}} \times \text{R}$$

Where,

Parameter	Data for Calculation	Product Name
MACO = Maximum allowable carry over		

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LTD	=	Lowest therapeutic dose of previous product	1 mg	(Glimepiride) TABLETS
D	=	Maximum daily dose (units/day) of any product to be manufactured in the same equipment train	8Tablets / Day	……..
Wb	=	Minimum batch size (in mg) of any subsequent product to be manufactured in the same equipment train (Next product B)	75.00 Kg.	(Glimepiride) Tablets
Wt	=	Highest unit dose weight (mg) of any product to be manufactured in the same equipment train.	1277.25 mg.	…….
Ss	=	Swab area (cm^2)	100 cm^2	
Se	=	Equipment product contact surface area (cm^2) for typical train of equipment	438960.11 cm^2	
R	=	Recovery factor of active ingredient chosen for validation purpose (NLT 75%)		

$$\text{MACO (mg /100 cm}^2\text{)} = \frac{1/1000}{8} \times \frac{75.00 \times 1000 \times 1000}{1277.25} \times \frac{100}{438960.11} \times 0.75$$

MACO (mg /100 cm^2**) = 0.0013**

9.1.2 10 ppm Criteria:

The maximum allowable carryover (MACO per 100 cm^2) for swab sample shall be calculated using the following formula:

$$\textbf{MACO (mg /100 cm}^{2)} = \frac{\textbf{10 x Wb x Ss}}{\textbf{Se}} \textbf{ X R}$$

Where,

Parameter		
MAC	=	Maximum allowable carry over
Wb	=	Minimum batch size (in mg) of any subsequent product to be manufactured in the same equipment train (Next product B)

Ss	=	Swab area (Cm^2)
Se	=	Equipment product contact surface area (cm^2) for typical train of equipment
R	=	Recovery factor of active ingredient chosen for validation purpose (NLT 75%)

$$\text{MACO (mg /100 cm}^2\text{)} = \frac{10 \times 75 \times 100}{438960.11} \times 0.75$$

MACO (mg /100 cm^2) = 0.13

9.1.3 Toxicity Criteria

$$\textbf{MACO (mg /100 cm}^2\textbf{)} = \frac{\textbf{LD}_{50} \textbf{ x 0.0005 x AAW x SF x Wb x Ss}}{\textbf{D x Wgt. x SE}} \textbf{ x R}$$

Where,

Parameter			Data For Calculation	Product Name
MACO	=	Maximum allowable carry over		
LD_{50}	=	Lethal dose (toxicity) of previous product	10000 MG/KG	(Glimepiride)
0.0005	=	Empirical factor		
AAW	=	Average adult weight	50 kg	
S	=	Safety factor	0.001	
D	=	Maximum daily dose (units/day) of any product to be manufactured in the same equipment train.	8 Tablets / Day	……
WB	=	Minimum batch size (mg) of any subsequent product to be manufactured in the same equipment train	75.00 Kg.	Glimepiride
WT	=	Highest unit dose weight (mg) of any product to be manufactured in the same equipment train	1277.25 mg.	……..
SS	=	Swab area (cm^2)	100 cm^2	

Parameter			Data For Calculation	Product Name
SE	=	Equipment product contact surface area (cm^2) for typical train of equipment	438960.11 cm^2	
R	=	Recovery factor of active ingredient chosen for validation purpose (NLT 75%)		

$$MACO\ (mg/100\ cm^2) = \frac{10000 \times 0.0005 \times 50 \times 0.001 \times 75 \times 1000 \times 1000 \times 100}{8 \times 1277.25 \times 438960.11} \times 0.75$$

MACO (mg /100 cm^2) = 0.31

From above MACO (mg/swab) 0.0013 values to be considered, which is least calculated with respect to Dose criteria, 10 ppm and Toxicity criteria.

9.2 Calculation of acceptance criteria for traces of Glimepiride in rinse sample

The maximum allowable carryover (MACO) per equipment shall be calculated using the following formula:

$$\textbf{MACO (mg / equipment)} = \frac{\textbf{0.0013}}{\textbf{100}} \times \textbf{ESA}$$

Where ,

0.0013 = MACO (mg per 100 cm^2)

100 = Swab sampling area (cm^2)

ESA = Equipment surface area (cm^2)

Enclosed Annexure-II

9.3 Calculation of acceptance criteria for traces of Methanol in rinse sample

The maximum allowable carryover (MACO) of Methanol for rinse sample shall be calculated using following formula

$$\textbf{MACO (mg / equipment)} = \frac{\textbf{PDE/1000}}{\textbf{D}} \times \frac{\textbf{Wb}}{\textbf{Wt}} \times \frac{\textbf{ESA}}{\textbf{Se}} \times \textbf{CF}$$

$$MACO\ (mg / equipment) = \frac{30/1000}{} \times \frac{75 \times 1000 \times 1000}{} \times \frac{ESA}{} \times 0.75$$

8 1277.25 438960.11

Parameter			Data For Calculation	Product Name
MACO	=	Maximum allowable carry over		
PDE	=	Permitted daily exposure of methanol	30 mg	
D	=	Maximum daily dose (units/day) of any product to be manufactured in the same equipment train	8 Tablets / Day	……..
Wb	=	Minimum batch size (in mg) of any subsequent product to be manufactured in the same equipment train (Next product B)	75.00 Kg.	……..
WT	=	Highest unit dose weight (mg) of any product to be manufactured in the same equipment train.	1277.25 mg	…….
ESA	=	Equipment surface area (Cm^2)		
Se	=	Total equipment product contact surface area (cm^2) for equipment train	438960.11 cm^2	
CF	=	Correction factor chosen for verification purpose 0.75 (NLT 75%)		

Enclosed Annexure-III

10.0 PROCEDURE:

10.1 Clean the equipment identified for cleaning verification as per the approved cleaning procedures as per section 8.0

10.2 Record the cleaning details in the respective datasheet in **Annexure-IV**.

10.3 Intimate Quality Assurance for collecting the samples.

10.4 **Visual inspection**

10.4.1 After final cleaning of the equipment, visually inspect the product contact parts of the equipment for cleanliness.

10.4.2 Use torch for inspection, if the surfaces of the equipment are difficult to inspect.

10.4.3 Product contact surfaces of equipment should appear visually clean with no traces of product or any extraneous matter.

10.4.4 Record the results in the **Annexure-IV.**

10.5 **Sampling sequence**

After the visual inspection, perform the sampling in following sequence:

a. Swab for microbiological contamination
b. Swab for chemical contamination
c. Rinse for chemical contamination for Glimepiride
d. Rinse for chemical contamination for Methanol

10.6 Carry out the sampling activity using powder free gloves.

10.7 Label the sample containers indicating,

- Name of the previous product.
- Equipment Identification number.
- Sample ID. Number
- Date and Sampled by.

10.8 **Swab sampling for microbiological contamination.**

10.8.1 Collect the swab samples from each equipment from the sampling location.

10.8.2 Swab sampling locations and acceptance criteria for microbiological analysis **Refer to Annexure-V.**

10.8.3 Record the sampling details in **Annexure-VI**

10.8.4 Collect the swab as per SOP …….

10.8.5 Analyze the sample as per SOP ……

10.8.6 Record the results as per **Annexure-VII.**

10.9 **Swab sampling for chemical contamination for Glimepiride**

10.9.1 Collect the swab samples of each equipment and acceptance criteria from the sampling location as per **Annexure-VIII**.

10.9.2 Moisten swab stick in the test tube containing 10 ml of methanol.

10.9.3 During sampling drain the excess methanol from the swab stick by pressing it against the sides of the test tube.

10.9.4 Collect the swab sample from the 10 cm x 10 cm area of the plate by first vertical stokes and then flap the swab stick to the other side and give horizontal strokes as per the below diagram. Carefully lift the swab stick after each stroke.

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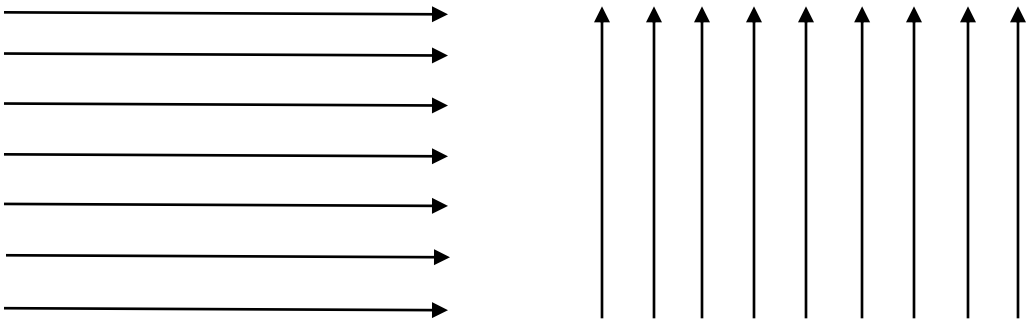

10.9.5 Transfer the swab back into the test tube containing 10 ml of Methanol and cover the test tube.

10.9.6 Record the sampling details in **Annexure-IX.**

10.9.7 Transfer the swab sample to Quality Control for analysis.

10.9.8 Analyze the sample as per the analytical method given in Protocol No. **……..**

10.9.9 Record the results in **Annexure-X.**

10.10 **Rinse sampling for traces of Glimepiride**.

10.10.1 Rinse the equipment with relevant quantity of Methanol specified in **Annexure-II.**

10.10.2 Collect the rinse samples of each equipment glass container ensuring that the rinse sample is uniform.

10.10.3 Record the sampling details in **Annexure-XI**

10.10.4 Transfer the rinse sample to Quality Control for analysis.

10.10.5 Record the results in **Annexure-XII.**

10.11 **Cleaning of equipments after Rinse sampling with methanol.**

10.11.1 Clean the equipment identified for cleaning Validation as per the approved cleaning procedures as per section 9.0.

10.11.2 Record the cleaning details after rinse with methanol in the **Annexure-XIII**.

10.12 **Rinse sampling for traces of Methanol**

10.12.1 Rinse the equipment with relevant quantity of Purified water as specified in **Annexure-III**.

10.12.2 Collect the rinse samples of each equipment using the quantity of Purified Water.

10.12.3 Collect the rinse samples in a glass container ensuring that the rinse sample is uniform. Close the container.

10.12.4 Record the sampling details in **Annexure-XIV**

10.12.5 Transfer the rinse sample to Quality Control for analysis.

10.12.6 Analyze the sample as per the analytical method given in Protocol No. **……..**

10.12.7 Record the results in **Annexure-XV.**

11.0 DEVIATION & JUSTIFICATION/ CORRECTIVE ACTION:

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S.No.	Deviation details	Justification(s) / Corrective action(s)	Remarks (Acceptable/ Not acceptable)
1.	*	*	*
2.	*	*	*

*To be recorded in the report

Comments: .....

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Checked By: _____
(Sign & Date)

Verified By: _____
(Sign & Date)

12.0 SUMMARY:

Note: Use additional pages if required.

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Checked By: _____ Reviewed By: _____
(Sign & Date) (Sign & Date)

13.0 CONCLUSION:

Note: Use additional pages if required.

CLEANING VALIDATION PROTOCOL FOR GLIMEPIRIDE TABLETS

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