CLEANING VALIDATION MASTER PLAN

CLEANING VALIDATION MASTER PLAN

1.0 APPROVAL:

This Cleaning Validation Master plan shall come into force only after approval from the following signatories:

	Name and Designation	Date and Signature
Prepared By:		
Reviewed By:		
Reviewed By:		
Reviewed By:		
Approved By:		
Authorized By:		

CLEANING VALIDATION MASTER PLAN

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CLEANING VALIDATION MASTER PLAN

3.0 INTRODUCTION:

3.1 PURPOSE

The purpose of this Cleaning Validation Mater Plan is to provide the requirements for validation of cleaning procedures so as to provide assurance that the cleaning procedures employed, effectively remove the residues of a product and the cleaning agent from the manufacturing equipment, to a level that does not raise patient safety concerns.

3.2 SCOPE

This document shall describe the plans to organize cleaning validation activities in Tablet Manufacturing Department.

3.3 DEFINITION

Worst case Product: A representative product from the product matrix chosen based on its toxicological evaluation (PDE), solubility (in water), lowest therapeutic dose and Cleanability as the candidate for cleaning validation.

Cleaning Validation: The methodology used to assure that a cleaning process removes the residues of the active pharmaceutical ingredients in the equipment, the cleaning aids utilized in the cleaning process and the microbial attributes.

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4.0 CLEANING VALIDATION TEAM AND RESPONSIBILITIES:

Validation team shall be responsible for execution of validation and verification exercise.

The following departments are responsible for the preparation and execution of the documents during cleaning validation activities.

DEPARTMENT	RESPONSIBILITIES
QUALITY ASSURANCE	1. Prepare and approve the Cleaning Validation Master plan 2. Prepare and approve the validation protocol and the report 3. Plan the cleaning validation, monitoring the validation activities and
PRODUCTION	1. Develop and approve the cleaning procedures of equipment's. 2. Support for identifying the hard to clean locations of equipment. 3. Arrange for cleaning of equipment.
ENGINEERING	1. Calculate the product contact surface area of equipment. 2. Support for identifying the hard to clean locations of equipment.
QUALITY CONTROL (CHEMICAL & MICROBIOLOGY)	1. Perform Analytical Method Validation for analysis of cleaning validation samples. 2. Testing and preparation of analytical reports.
R& D / TECHNOLOGY TRANSFER	1. Share the knowledge gained during product development for identifying cleanability rating of product. 2. Support for identifying the cleaning procedures for any specific product
TOXICOLOGIST	1. Provide support for toxicological evaluation of API molecule 2. Calculate PDE value for API 3. Provide support for routine review of toxicological evaluation of API molecule

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5.0 CLEANING VALIDATION POLICY:

This Cleaning Validation Master plan shall define the requirements for selecting the worst-case product for cleaning validation, development of acceptance criteria and selection of sampling methods residue recovery requirements and analytical method validation exercise and execution of cleaning validation activities.

This master plan shall identify the requirements for validation of cleaning processes.

The cleaning validation shall consist of the following steps:

a. Selection of worst-case product for cleaning validation.
b. Selection of worst-case equipment for cleaning validation.
c. Selection of sampling locations and sampling techniques.
d. Selection of analytical method.
e. Residue recovery studies
f. Sampling for cleaning validation

The Tablet Manufacturing facility manufactures multi-products using common equipments. Hence to avoid contamination of one pharmaceutical product into the other, the cleaning procedures shall be defined and validated. The product contact surfaces of equipment shall be free from contamination of active pharmaceutical ingredient and micro-organisms.

The cleaned equipment shall be monitored for physical contamination, chemical contamination and microbiological contamination. The physical contamination shall be monitored by visual observation of the cleaned equipment; chemical contamination shall be monitored using chemical testing method whereas microbiological contamination shall be monitored by suitable microbiological techniques.

The cleaning procedures for all critical processing equipment's in the manufacturing facility shall be validated. All the processing equipments coming directly in product contact shall be considered as critical.
Risk assessment shall be done for processing of the product with respect to contamination and cross contamination considering the technical and organizational control measure at the site.
Quality risk management (QRM) study shall be done to assure that process and controls implemented are robustly in place and take account of:

- Technical measure-Equipment design and cleaning procedures
- Organizational measure –Campaign processing and cleaning verification

Quality Risk management shall be used to evaluate planned changes to cleaning procedures to determine the potential impact on the product quality.

6.0 CLEANING PROCESS DESCRIPTION:

6.1 EQUIPMENT QUALIFICATION VERIFICATION

Equipment selected for cleaning validation shall be verified for following attributes before proceeding for the cleaning validation.

a. Qualification of Clean In Place (CIP)
b. Qualification of utilities such as Purified water used for cleaning process.
c. Calibration of critical process controlling instruments

6.2 DEVELOPMENT OF CLEANING PROCEDURES

User department shall develop the cleaning procedures based on the following:

a. Information received from the transferring site or R&D.
b. Cleaning procedure suggested by the equipment manufacturer.
c. Past experience.

6.3 BRIEF DESCRIPTION OF MANUFACTURING PROCESS

The dispensed materials are first sifted through the specified meshes and then mixed & granulated using the rapid mixer granulator. The wet granules are dried using Fluidized bed equipment. The dried granules are graded through Sifter cum Multimill. The lubricated granules can be transferred to the Compression machines to compressed the tablets. The compressed tablets can be transferred to the coating area (if applicable) and then packing area. The packaging lines are provided with adequate segregation between the lines.

In case of directly compressible tablets, the batch materials are blended using a Blender and further compressed using a Compression Machine.

In case of coated products, the compressed tablets are coated using a Coating Machine and further packed using a Blister Packing Machine.

6.4 BRIEF DESCRIPTION OF CLEANING PROCESSES USED FOR PROCESSING EQUIPMENT

The processing equipment’s coming in product contact shall be cleaned as per the approved procedures. The procedure includes cleaning with potable water, purified water. The detailed steps for dissembling of equipment parts and cleaning procedures are specified in the relevant SOPs.

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GENERAL CLEANING PROCESS FLOW CHART

Dismantling

↓

Cleaning with Potable Water

↓

Scrubbing with potable water

↓

Cleaning with Potable Water

↓

Final rinsing with Purified Water

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Drying using dryer / Compressed Air

6.5 CONTAMINATION TYPES

Contamination types shall be classified in following categories:

- **Chemical contamination** – This type of contamination results from residuals of an active pharmaceutical ingredient in the drug product.
- **Physical Contamination** – This type of contamination includes mechanical impurities and extraneous matter.
- **Microbial Contamination** – This type of contamination results from the Microorganisms contamination from the cleaning solvents employed for cleaning process and product processed on the equipment.

The cleaned equipment shall be monitored for all of the above stated contamination. The physical contamination shall be monitored by visual observation of the cleaned equipment. The chemical contamination and cleaning agent shall be monitored by chemical testing whereas microbiological contamination shall be monitored by suitable microbiological techniques.

7.0 SELECTION OF WORST CASE PRODUCT FOR CLEANING VALIDATION:

7.1 PRODUCT GROUPING

All the products manufactured at site shall be grouped together based on the equipment used for manufacturing. This product grouping shall be termed as “Product Matrix” as per Annexure-IV.

The “Product Matrix” shall include following which shall be considered for product grouping.

a. All the products manufactured for commercial distribution
b. Any product manufactured for dossier registration or feasibility at site or development trials or scale up.

The products which are manufactured only for dossier registration shall be clearly identified in the "Product Matrix" as "Product for Dossier Registration". These products shall be made inactive under "Inactive Product list" as per Annexure-IV.

Note: Products manufactured in commercial production area and pilot area shall be grouped separately.

7.2 IDENTIFICATION OF WORST CASE PRODUCT

The worst-case product for Cleaning Validation shall be selected based on the following:

a. Toxicological assessment of active(s) present in the product as per section 7.2.1.

b. Product characteristics based on total risk value for following attributes of product

- Solubility rating of Active Pharmaceutical Ingredient (API) in water.
- Cleanability rating for drug product
- Lowest therapeutic dose rating of API

Product matrix shall be prepared for entire manufacturing area to identify the worst-case product for cleaning validation Annexure-IV.

The product matrix shall be evaluated and revised whenever new product is introduced or new equipment is introduced, formula is changed or whenever any product is shifted to different equipment or manufacturing area.

Incase if the worst case product is coated, the product contact surfaces of equipment's shall be simulated with the powder blend of worst case product. This approach shall be utilized for equipment's such as Inspection Belt, De-blistering Machine and Blister Packing Machine.

Incase if the worst case product is manufactured in multiple strengths, then the highest strength shall be selected for the cleaning validation exercise. However this shall not be applicable if the multiple strengths are manufactured using a common blend.

7.2.1 EVALUATION OF WORST CASE PRODUCT FOR CLEANING VALIDATION BASED ON TOXICOLOGICAL ASSESSMENT OF PRODUCT /API(S):

All the products manufactured at site shall be evaluated for toxicological assessment to identify hazards associated with the product.

Toxicological assessments for each API molecule shall be evaluated as per the criteria mentioned in SOP for identifying the worst case for cleaning validation.
Toxicology assessment shall be performed by a subject matter expert.

Source of toxicological data collection: This shall be from the registered toxicological study data or medical literature.

The following hazards if any associated with the API shall be evaluated.

a. Genotoxic (specifically mutagenic) / Carcinogenicity
b. Reproductive and/or developmental toxicity
c. Serious target organ toxicity or other significant adverse effects at low doses
d. Sensitizing potential

The above toxicological hazard data collected for API molecule shall be presented as per Appendix I (under section H).

Each of the toxicological hazards identified for the molecule shall be evaluated through assigning following risk categorization.

a. Relatively Safe
b. Low Hazard
c. Moderate Hazard
d. Highly Hazardous

The API molecule having “Relatively Safe” and “Low Hazard” categorization shall be considered for cleaning validation based on product characteristics.

All the API molecules from the product matrix having “Moderate Hazard” shall be considered for cleaning validation along with control measures during routine manufacturing of the product. Certain product shall require dedicated equipment / area and same shall be clearly identified

The API molecules having “Highly Hazardous” shall be considered for having dedicated area/equipment or dedicated facility. The products identified which requires dedicated facility shall not be included in the list as these are not manufactured in Tablet Manufacturing area.

The products falling under following shall be considered as highly hazardous.

a. Genotoxic (specifically mutagenic) compounds that are known to be, or highly likely to be, carcinogenic to humans. Compounds of this group are easily identifiable, since genotoxicity would be related to the pharmacology, e.g. as DNA alkylating cytostatics, and their use is usually restricted to oncology indications with respective warning statements in the Summary of Product Characteristics.
b. Compounds that can produce reproductive and/or developmental effects at low dosages, for example where evidence exists of such effects being caused by a clinical dose of <10 mg/day (veterinary dose equivalent 0.2 mg/kg/day) or dosages in animal studies of ≤1 mg/kg/day.
c. Compounds that can produce serious target organ toxicity or other significant adverse effects at low doses, for example where evidence exists of such effects being caused by a clinical dose of <10 mg/day (veterinary dose equivalent 0.2 mg/kg/day) or dosages in animal studies of ≤1 mg/kg/day.
d. Compounds with a high sensitizing potential.

The above list is not an exhaustive list and if evidence is available indicating that the product may cause adverse effects at low doses by other mechanisms it shall be considered as highly hazardous.

The compounds with a high pharmacological potency (Recommended daily dose of <1 mg) shall not be considered under toxicological evaluation as the product shall be identified for cleaning valuation based of its "Lowest Therapeutic rating" evaluation under Product characteristic as per section 7.3.

7.2.1.1 PDE DETERMINATION:

The PDE value shall be calculated for each API molecule handled at site.

Determination of a PDE shall be based on, hazard identification by reviewing all relevant toxicological data, critical effects, "No-Observed-Adverse-Effect Level (NOAEL)" and use of several factors to account for various uncertainties.

In certain cases when the data related to "No-Observed-Adverse-Effect Level (NOAEL)" is not available then "No-observed-effect level (NOEL)" or "Lowest-Observed Effect level" (LOEL)" shall be used for PDE calculation.

In certain cases NOEL shall be calculated using the LD_{50}.

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Formula to calculate PDE (Permitted Daily Exposure):

PDE is derived from the "No-Observed-Adverse-Effect Level (NOAEL)", No-observed-effect level (NOEL), or lowest-observed effect level (LOEL)

$$PDE = \frac{\text{NOAEL x Weight adjustment}}{\text{F1 x F2 x F3 x F4 x F5 x other modifying factor}}$$

The different modifying factors used for PDE determination shall be follows:

Factor details	Explanation / details to be used for PDE determination
F1	a. A factor to account for extrapolation between species b. 5 for extrapolation from rats to humans c. 12 for extrapolation from mice to humans d. 2 for extrapolation from dogs to humans e. 2.5 for extrapolation from rabbits to humans f. 3 for extrapolation from monkeys to humans g. 10 for extrapolation from other animals to humans
F2	A factor of 10 to account for variability between individuals
F3	a. A variable factor to account for toxicity studies of short-term exposure b. 1 for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys). c. 1 for reproductive studies in which the whole period of organogenesis is covered. d. 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents. e. 5 for a 3-month study in rodents, or a 2-year study in non-rodents. f. 10 for studies of a shorter duration.
F4	a. A factor that may be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the following factors are used: b. 1 for fetal toxicity associated with maternal toxicity c. 5 for fetal toxicity without maternal toxicity d. 5 for a teratogenic effect with maternal toxicity e. 10 for a teratogenic effect without maternal toxicity
F 5	A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.
F6 = Miscellaneous factor:	Based on review of toxicological literature and assessment of available data, miscellaneous factor shall be used to mitigate risk posed by any of uncertainties and variability.
Modifying factor:	In a situation where PDE (calculated by applying all the factors mentioned in guideline and as above) appears to be unacceptable or unrealistic (in relation with pharmacologic and toxicological effect and daily therapeutic dose of hazard) in opinion of Toxicologist and additional correction factor may be necessary to derive a more realistic and accurate PDE. In such a case additional modifying factor will be applied. This factor shall also be used for any other miscellaneous reason, data, observation, etc. not covered as above.

The scientific literature published shall be routinely reviewed to identify new information related to NOAEL, NOEL, LOEL used for PDE determination. If any new information is identified impact on the previous PDE determined along with an impact on cleaning validation shall be assessed.

7.3 EVALUATION OF WORST CASE PRODUCT FOR CLEANING VALIDATION BASED ON PRODUCT CHARACTERISTICS

The products which are categorized as "Low Risk" based on toxicological evaluation shall be evaluated for its worst case for cleaning validation based on the following:

a. Solubility rating of Active Pharmaceutical Ingredient (API) in water used in cleaning process (This is denoted as" A" in "Product Matrix").
b. Lowest therapeutic dose rating of API for Oral route of administration (This is denoted as" B" in "Product Matrix").
c. Cleanability rating of product (This is denoted as" C" in "Product Matrix").

Source of data collection for Solubility: The data shall be collected from Pharmacopoeia or Drug Master File (DMF) or Specification.

Source of data collection for Lowest therapeutic dose: The data shall be collected based on the therapeutic indication from the medical literature or Product Information Leaflet.

Source of data collection for Cleanability: The data shall be collected from the review of product matrix as follows

a. Products which API is practically insoluble shall be assigned higher rating.

b. Products which involves colored API and excipients and difficult to clean shall be assigned higher rating.

c. Products which API is soluble and free soluble in water and which can be easily cleaned shall be assigned lower rating.

Additionally Cleanability rating shall be assigned based on the knowledge gained during product development from R & D or information received from the product transferring site or past experience or knowledge gained during manufacturing of product manufactured for feasibility, scale up etc.

The rating for each parameter assigned for the product shall be multiplied (A x B x C) and total risk value shall be presented in Annexure-IV.

The total risk value for all the products grouped in the equipment train shall be evaluated and product with highest value shall be considered as worst case product for cleaning validation.

If two products are having the same total risk rating then the priority for selection of worst-case products shall be based on following sequential order:

a. Most insoluble API in the drug product.
b. Most potent product.
c. Most difficult to clean product.

The product matrix shall be evaluated and revised whenever a new product is introduced or new equipment is introduced.

Incase if the worst case product is manufactured in multiple strengths, then the highest strength shall be selected for the cleaning validation exercise. However this shall not be applicable if the multiple strengths are manufactured using a common blend.

8.0 SELECTION OF WORST CASE EQUIPMENT FOR CLEANING VALIDATION:

All the equipment in the manufacturing area shall be grouped to form an "Equipment Matrix" as per Annexure-V.

All the processing equipment's coming directly or indirectly in product contact shall be considered as critical.

In order to make the cleaning validation program manageable, the manufacturing equipments shall be grouped together so that the representative equipment in a group shall be selected for the cleaning validation. Identical equipment's such as similar capacity or similar shape shall be grouped together.

Equipment's or certain component or parts which are dedicated for the product shall not be considered for cleaning validation.

9.0 DETERMINATION OF ACCEPTANCE CRITERIA FOR CONTAMINANT:

9.1 SETTING OF ACCEPTANCE CRITERIA FOR CHEMICAL CONTAMINATION DUE TO API:

The amount of residue of previous product carry-over in the next manufactured product which shall be considered acceptable shall be based on following

a. Visual clean Criteria.
b. Maximum Allowable Carry Over based on Daily Dose Criteria
c. Maximum Allowable Carry Over based on 10 ppm Criteria
d. Maximum Allowable Carry Over based on PDE

Acceptance limit refers to the concentration of the active in another product, the surface concentration on the manufacturing equipment and the amount in the analyzed sample.

Acceptance limit by dose criteria shall be calculated for swab and rinse method.

9.1.1 Visual clean Criteria:

This acceptance criterion states that no residues shall be visible in the equipment after cleaning and drying.

Cleaned status of the equipments (dedicated equipments and non-dedicated equipments) shall be verified prior to swab test or rinse test for cleaning validation study.

All equipment surfaces should be clean to the unaided eye.

The product contact surface area of equipment shall be checked using a torch or light source. The production equipment shall be free from visible residues after cleaning. Visual inspection is a prerequisite for the further tests such as swab test or rinse test.

9.1.2 Maximum Allowable Carry Over based on Dose Criteria:

Not more than the 0.1% of normal therapeutic dose should appear in maximum daily dose of another product.

Swab sample:

The MACO (mg/swab) shall be calculated by using following formula

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

Where ,

LTD = Lowest therapeutic dose of previous product(mg)

1/1000 = Safety factor

D = Maximum daily dose of next considered product taken/Day (Tablets / day)

Wb = Minimum batch size of next considered product (gm)

Wt = Average dose weight of which Minimum batch size is selected (gm)

Ss = Swab area (cm^2)

Se = Total equipment product contact surface area for the equipment train (cm^2)

9.1.3 Maximum Allowable Carry Over based on 10 PPM Criteria:

No more than 10 PPM of any product should appear in another product.

Swab sample:

The MACO (mg/swab) shall be calculated by using following formula

$$\text{MACO (mg / swab)} = \frac{\text{R} \times \text{S} \times \text{U}}{\text{T}}$$

Where,

R = 10 mg

S = Minimum batch size in (Kg).

U = Swab area for swab sample

T = Equipment product contact surface area for typical train of equipment (cm^2)

9.1.4 Maximum Allowable Carry Over based on PDE (Permitted Daily Exposure) Values:

Acceptance limit calculation for API residues using Toxicological data based on PDE values

Swab sample:

$$\text{MACO (mg / swab)} = \frac{\text{PDE}}{\text{D}} \times \frac{\text{Wb}}{\text{Wt}} \times \frac{\text{Ss}}{\text{Se}}$$

Where PDE = Permitted Daily Exposure (PDE) Values

D = Maximum daily dose of next considered product taken/Day(Tablets / day)

Wb = Minimum batch size of next considered product (gm)

Wt = Average dose weight of which Minimum batch size is selected (gm)

Ss = Swab area (cm^2)

Se = Total equipment product contact surface area for the equipment train (cm^2)

9.1.5 Selection of Maximum Allowable Carry Over for cleaning validation

The MACO calculated for swab sample based on visual criteria, dose criteria and PDE shall be evaluated and least value shall be used for cleaning validation.

9.1.6 Maximum Allowable Carry Over for rinse sample

The MACO (mg/equipment) shall be calculated by using following formula

$$\text{MACO (mg / equipment)} = \frac{\text{MACO (mg per swab)}}{100} \times \text{ESA}$$

Where,

100 = Swab surface area

ESA = Equipment surface area (cm^2)

9.2 FOR MICROBIOLOGICAL EXAMINATION:

The acceptance criteria for the Microbiological examination shall be not more than 30CFU/100cm^2 .Swab samples for microbiological examination shall be collected using sterile swab sticks.

9.3 SETTING OF ACCEPTANCE CRITERIA FOR CHEMICAL CONTAMINATION DUE TO DESOPTION SOLVENT USED FOR SAMPLING:

The maximum allowable carryover (MACO) of solvent in rinse sample shall be calculated using the following formula

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

Where ,

PDE = Permitted daily exposure of solvent selected for sampling

D = Maximum daily dose of next considered product taken/Day(Tablets / day)

Wb = Minimum batch size of next considered product (gm)

Wt = Average dose weight of which Minimum batch size is selected (gm)

ESA = Equipment surface area (cm^2)

Se = Total equipment product contact surface area for the equipment train (cm^2)

10.0 SELECTION OF SAMPLING METHOD AND LOCATION:

10.1 SELECTION OF SAMPLING METHODS:

The samples shall be collected following during cleaning validation for estimation of residual contamination on the surface of equipment

a. Determination of Active Pharmaceutical Ingredient (API)
b. Determination of Desorption solvent used during sampling of API
c. Determination of Microbial quality on surface

The following sampling methods shall be adapted for determining the residual contamination on the surface of the equipment being tested for its cleanliness.

a. Swab sampling Method
b. Rinse sampling Method

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10.1.1 SELECTION OF SAMPLING METHOD FOR ESTIMATION OF API:

10.1.1.1 SWAB SAMPLING METHOD:

Swab sampling method shall involve removal of residue on the product contact surfaces of equipment using a swab dipped in a suitable desorption solvent (Solvent in which the API is soluble).

This method shall be based on the physical removal of residue left over on a piece of equipment after it has been cleaned and dried.

The swab sampling shall be a preferred method of sampling as it shall give the precise contamination status of the equipment surface, especially for the surfaces which are hard to clean, easily accessible and dried out surfaces.

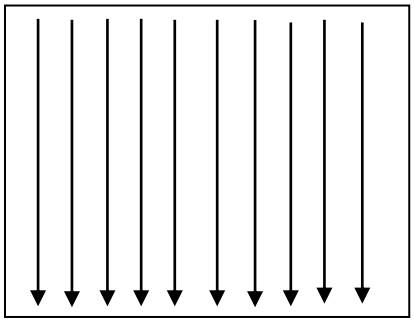
Advantages of direct swab sampling shall be that areas hard to clean and which are reasonably accessible can be evaluated, leading to establishing a level of contamination or residue per given surface area.

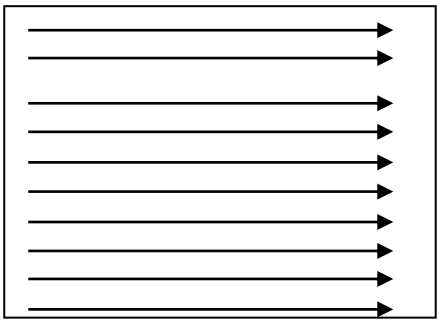
Additionally, residues that are "dried out" or are insoluble shall be sampled by physical removal.

The volume of the solvent used for the sampling shall be selected to allow for the detection of contaminant by the analytical method selected.

The swab sample shall be collected over an area of 10X10cm (100 cm^2). However in some equipment, area of 5 x 5 cm (25 cm^2) or 4 x 4 cm (16 cm^2) shall be taken depending upon the symmetry or size of sampling location of respective equipment.

The swab shall be taken from a measured surface area by the use of a template of specified dimensions as per the following diagrammatic sketch.





In case of uneven surfaces, area shall be calculated and approximately an area equivalent shall be sampled.

The swab shall be pre-saturated with a desorption solvent and shall be squeezed prior to taking swab samples to prevent the dripping of solvent on the sampling area. The swab sample shall be collected per the above procedure and same shall be placed back in a glass test tube containing desorption solvent. The sample collected shall be sent to Quality Control for analysis.

10.1.1.2 RINSE SAMPLING METHOD:

The rinse sampling shall be adopted for the surfaces, which are inaccessible or for the equipment parts which are not usually dismantled during the cleaning process and for the difficult to reach locations.

Two advantages of using rinse samples shall be that larger surface areas and inaccessible systems are sampled and evaluated.

Rinse sample shall be collected using a suitable desorption solvent (Solvent in which the API is soluble). Desorption solvent selected shall be such that it is soluble in Purified water and can be removed effectively after sampling

The volume of the solvent used for the sampling shall be selected to allow for the detection of contaminant by the analytical method selected.

10.1.2 SAMPLING METHOD FOR DETERMINATION OF TRACES OF DESORPTION SOLVENT USED FOR SAMPLING

Rinse sampling method shall be used for determination of traces of desorption solvent on the product contact surfaces of equipment.

If organic solvent is used for the collection of rinse sample then equipment shall be cleaned with the Purified Water to remove the traces of desorption solvent.

In such cases residual contamination due to desorption solvent shall be collected by using the Purified Water.

10.1.3 SAMPLING METHOD FOR DETERMINATION OF MICROBIAL CONTAMINATION

Swab sampling method shall be used for determination of microbial contamination. The swab sample shall be collected using sterile swab.

10.2 SELECTION OF SAMPLING LOCATIONS FOR CHEMICAL ANALYSIS

The product contact areas, which are difficult or hard to clean, shall be selected for sampling. These areas shall be corners, joints, bents etc.

Sampling locations shall be selected based on following criteria:

- **a.** Design of equipment and material of construction.
- **b.** Flow of product throughout the equipment.
- **c.** Locations difficult to disassemble and most difficult to clean areas.
- **d.** Access to equipment sampling location
- **e.** Recovery of the analyte.

Swab sampling of the surface is designed to collect samples from different parts of the equipment surface for the presence of residues. The number of swab sampling locations per equipment shall be selected so as to provide a high degree of confidence on complete removal of previous product residues. In case of a small product contact surface, total surface of equipment shall be considered for sampling.

In cases where swab sampling is not possible, for example restricted access, swabbing may be substituted by the analysis of final rinse solutions. Rinse samples shall be also used to determine the carryover of residues over a large surface area.

10.3 SELECTION OF SAMPLING LOCATIONS FOR MICROBIAL SAMPLING

The sampling location for microbial sampling shall be selected based on the following criteria:

a. Areas that may contain residual moisture, temperature, crevices or rough surfaces.
b. Locations where microbial contamination likely to occur and adversely affect product quality.
c. Sites most likely to support microbial growth.
d. Site that represent the most inaccessible or difficult to decontaminate.

10.4 SAMPLING SEQUENCE

After the visual inspection, sampling shall be performed in the following sequence:

a. Rinse for residual testing of cleaning agent
b. Swab for microbiology testing
c. Swab for residual testing of API
d. Rinse for residual testing of API

10.5 SELECTION OF SWABBING MATERIAL

Swabbing material used for cleaning validation shall not give any interference with the API during analysis.

Swabbing material shall be selected based on the following criteria:

a. Compatibility with swabbing solvent
b. Compatibility with targeted substance (API)
c. Compatibility with desorption solvent
d. Shredding properties.
e. Recovery studies.

10.6 SELECTION OF DESORPTION SOLVENT FOR SWAB AND RINSE SAMPLE:

Desorption solvent used for cleaning validation shall not give significant interferences in the analysis of the target substance.

Solvent shall be selected based on following criteria:

a. Solubility of active in the solvent.
b. Compatibility of the selected solvent with the equipment surfaces.
c. Compatibility with swabbing material.

The equipment supplier shall be consulted if required to determine the suitability of selected solvent for sampling. If any organic solvents are selected for sampling, the residue of organic solvent on the equipment surfaces shall be determined prior to release of equipment for use and requirements for the same shall be incorporated in the respective protocols.

After sampling the equipment's selected for cleaning validation shall be cleaned as per the respective cleaning SOP to remove the traces of solvent used for sampling.

10.7 PRODUCT DEDICATED PARTS / EQUIPMENT:

The parts of equipment or whole equipment which are difficult for cleaning or determination of the levels of product residues on these parts/ equipment cannot be determined with accuracy, in such case same shall be identified as product dedicated.

The product dedicated parts shall not be applicable for cleaning validation.

The product dedicated parts shall be identified through product code identifying the product for which it is used.
The product dedicated parts / equipment shall be covered as a part of Microbial monitoring.

11.0 SIMULATION OF DIRTY EQUIPMENT HOLD TIME AND CLEANED EQUIPMENT HOLD TIME:

11.1 SIMULATION OF DIRTY EQUIPMENT HOLD TIME

During cleaning validation, dirty equipment hold time shall be simulated. Equipment's shall be kept in un-cleaned condition after manufacturing of the worst case product and then cleaning shall be performed to simulate the Dirty equipment hold time as a worst case condition. Dirty equipment hold time study shall be performed for at least one cleaning validation run.

11.2 CLEANED EQUIPMENT HOLD TIME:

Cleaned equipment hold time shall include the time interval from end of cleaning to start of use for process. Cleaned equipment hold time study shall be established through microbiological controls.

12.0 SELECTION OF THE ANALYTICAL METHOD:

After the selection of the worst-case product for validation study, the analytical methods shall be developed for the detection of active, cleaning agent and solvent used for sampling.

The analytical method shall be validated for following parameters:

a. Specificity
b. Limit of Detection (LOD) and Limit of Quantification (LOQ)
c. Linearity
d. Accuracy
e. Precision
f. Range
g. Intermdiate precision
h. Solution Stability

The requirements of the analytical validation include but are not limited to the details below:

a. The ability to detect the target API and solvent at levels consistent with the acceptance criteria.
b. The ability to detect the target substances in the presence of other materials that may also be present in the sample.
c. Stability of the API over time should be considered.
d. Surface recovery / spike studies (Residue recovery test) from all relevant materials of construction of product contact parts of the equipment's.
e. Studies for the extraction method used in the analytical methodology.

The rationale for selection of an analytical technique shall be based on following criteria:

a. Simple – The method shall be practical and rapid and as much as possible use instrumentation existing at the site.
b. Allow easy sample preparation
c. Validated

The instruments that shall be used for validation of analytical method and the testing of the swab samples of active in quality control department shall be in calibrated status during the testing.

13.0 RESIDUE RECOVERY STUDY:

The residue recovery test shall be performed to check the effectiveness of sampling methods in recovering the proportion of the residue present on the equipment surface.

The residue recovery study shall be demonstrated on all the possible material of constructions of equipments selected for the cleaning validation study. The details of MOC coming in contact with the product shall be specified in the respective protocols.

The residue recovery studies shall be performed at the MACO level and concentration of active in the solvent being analyzed

The residue recovery studies shall simulate the material of construction and surface smoothness of parts of equipment.

The residue recovery shall be performed by challenging the known concentration of the active ingredient selected for the cleaning validation on the test plate of known dimension. The sample shall be collected simulating the sampling methods that shall be used during cleaning validation. The residue recovery sample for the recovery of the active shall be analyzed by using the validated analytical method. The details of this procedure shall be specified in the respective protocols.

The amount recovered shall be recorded as percentage of the total amount charged on the surface.

The sampling method shall be considered acceptable if the recovery is more than 75%. In case of certain surfaces such as rubber lower recovery up-to 50% shall be considered acceptable and same shall be defined during the study.

14.0 DETERMINATION OF PRODUCT CONTACT SURFACE AREA OF EQUIPMENT:

The product contact surface area (cm^2) for each equipment shall be calculated by engineering department in coordination with equipment supplier.

The surface area shall involve measurement of dimensions of different parts and calculation of surface area using the formulas applicable for the shape. In certain cases if the equipment supplier has provided the surface area as part of equipment qualification, then same shall be verified and used for cleaning validation.

15.0 NUMBER OF RUNS FOR CLEANING VALIDATION:

Cleaning validation shall be performed on three consecutive runs with the worst case product.

16.0 CONTINUOUS MONITORING POST VALIDATION:

The verification of cleaning procedures shall be performed at-least once in 3 years. This verification shall be performed for only one run using the worst case product identified from the Appendix I to CVMP.

If there is no plan for manufacturing of worst case product during the scheduled verification activity, then the total risk rating of products shall be evaluated from the matrix to identify the immediate next worst case product.

The effectiveness of the cleaning procedure for each piece of equipment shall be continuously monitored post validation.

During product changeover, the cleaned equipment's shall be visually inspected for cleanliness by the Production & Quality Assurance personnel. The line clearance shall be given independently by both Production and Quality Assurance Personnel and same shall be documented in a line clearance checklist. During product changeover the swab samples shall be collected and analyzed for detection of API residues.

The periodic review of all validated cleaning procedures shall be performed for following but is not limited to:

a. Review of any changes to products, processes, equipment and facility.
b. Review of cleaning validation documents to assess any gaps verses current standards.

If a cleaning procedure is deemed to be ineffective during the periodic review of the cleaning procedures or during product changeover line clearance, then re-validation shall be required.

17.0 DOCUMENTATION:

17.1 PLAN FOR COMPLETION OF VALIDATION DOCUMENTATION

Validation protocol shall be prepared for validation of cleaning procedures of the equipment used for manufacturing of the product. The protocol shall be prepared as per the formats specified in the relevant SOP's and Cleaning Validation Master Plan. The protocol shall be executed only after it is pre-approved for use.

The raw data generated during the validation activity shall be compiled and form a part of the validation documentation. The raw data shall be checked and verified by at least two persons and it shall be compared against the specified acceptance criteria.

All validation failures shall be immediately recorded in the relevant sections of the protocols. They shall be either accepted with proper justification or corrective action shall be taken.

The corrective action shall be verified for their effectiveness through the additional retesting requirements and specified acceptance criteria. All the data shall be documented.

17.2 DOCUMENTATION FORMAT:

17.2.1 Approval Page:

This page shall contain the following information:

- Protocol name.
- Protocol number and the revision number
- Name, date, signature and area of responsibility of person preparing, checking and approving the protocol for the execution/implementation.
- Protocol issue date

17.2.2 TABLE OF CONTENTS

This page shall contain the details of contents along with the page numbers.

The table of contents and sections should be presented according to military/legal outline format, that is:

1….
1.1….
1.2…….
1.2.1……

17.2.3 SCOPE

This section describes the purpose of the protocol. In general it is sufficient to explain that the purpose is to validate the cleaning method which gives evidence that the equipment are thoroughly cleaned and meet the predetermined specifications.

Description: This section serves to describe the functioning of the Cleaning method as well as what characteristics of the method we will be testing. It can contain:

- A brief description of the equipments especially those in contact with the product and study rationale.
- List for all the equipments including the hard to clean areas for each.
- Calculation of acceptance criteria
- The checks to be performed as a part of a particular qualification activity and review of SOP's.
- Sampling Procedure.
- All the checks shall be given detailing the tests, test procedures, test equipments, acceptance criteria, observations and conclusions.
- Verification of Acceptance Criteria
- Review of all the test results and their comparison with the acceptance criteria summary report and conclusion.
- Interim summary report shall be prepared if three runs are not consecutive, based on chemical result for releasing of equipment for further processing and final summary report will be prepared after getting the results of both chemical and microbial results.

17.2.4 STUDY RATIONALE AND SELECTION OF WORST CASE PRODUCT

This section serves to describe the functioning of the Cleaning method as well as what characteristics of the method will be tested. It shall contain:

- A brief description of the equipment and the standard operating procedures used for the operation, cleaning and sanitization of the equipments.
- Sampling plan, acceptance criteria and analytical methods.
- All the checks shall be given detailing the tests, test procedures, test equipment acceptance criteria, observations and conclusions.

17.2.5 VALIDATION TEAM AND THEIR RESPONSIBILITIES

This section serves to describe the responsibility of person preparing, checking and approving the protocol for the execution/implementation.

17.2.6 ACCEPTANCE CRITERIA AND SAMPLING PLAN

This section serves to describe the calculation of acceptance criteria and sampling plan.

17.2.7 PROCEDURE

This section serves to describe the procedure for sampling and sequence of sampling.

17.2.8 DOCUMENTATION AND RESULTS

This section serves to describe the data sheets for documentation of sampling and results.

17.2.9 SUMMARY

After completion of cleaning validation activity, the summary report shall be prepared. The summary report shall contain the verification that all the planned activities are completed. The summary reports shall have the final sign-off of the report by QA and from initial approval authorities or from current individuals those now have those responsibilities.

The summary reports shall be reviewed and approved by the responsible persons.

17.2.10 TRAINING

All the training conducted on the standard operating procedure shall be documented in this section.

17.2.11 CERTIFICATION

This section serves to describe the certification of the cleaning validation studies.

17.2.12 REFERENCES

References for the specific acceptance criteria or the details and test programs selected for validation shall be documented in this section.

17.2.13 KEY WORDS AND GLOSSARY

Reference of any key words shall be mentioned in this section.

18.0 CHANGE CONTROL AND REVALIDATION

The change implemented at site shall be evaluated for its impact through a flow chart as per Annexure I of SOP.

The "Equipment matrix and product matrix as per Appendix I to this CVMP shall be evaluated and revised in-case of following:

- **a.** New product introduction at site
- **b.** Change in the formulation of the product
- **c.** New equipment introduction at site
- **d.** Shift of product to another equipment or manufacturing area or use of additional equipment in the manufacturing process.
- **e.** Modification of product contact parts of the equipment.
- **f.** Revision of cleaning procedures.

Any change to the cleaning method shall be documented and any significant change shall be validated using adequate predefined protocols.

The cleaning procedures shall be evaluated for their validation status every three years by executing one cleaning verification run using the worst case product identified in the cleaning validation evaluation matrix. If the worst case product identified is not manufactured during the cleaning verification due period, then the next product shall be selected for cleaning verification based on the risk value identified in the cleaning validation evaluation matrix.

Based on the evaluation a need for revalidation of cleaning procedures shall be identified.

In-case of new product introduction, new equipment introduction and shift of product to another area / equipment the impact on the acceptance criteria set for the cleaning validation shall be evaluated. Based on the evaluation a need for revalidation of cleaning procedures shall be identified.

The parameter which affects the MACO used for cleaning validation shall be evaluated for following parameters along with it impact on the previously executed cleaning validation studies.,

- **a.** Lowest therapeutic dose
- **b.** Maximum daily dose
- **c.** Minimum batch size
- **d.** Total equipment product contact surface area for the equipment train

This CVMP shall be revised after every 3 years.

19.0 REFERENCES:

19.1 Martindale

19.2 Indian Drug Review (IDR)

19.3 Current Index of Medical Specialties (CIMS)

19.4 SOP for "Cleaning Validation"

19.5 Annex 15: Qualification and Validation, Eudralex

19.6 European Medicines Agency; Guidelines on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.

19.7 FDA Guide to inspection validation of cleaning process.

19.8 Guidance on aspects of cleaning validation in active pharmaceutical ingredient plants- Active Pharmaceutical Ingredients Committee (APIC)

20.0 REVISION HISTORY:

CVMP No.	Version No.	Changes done