SOP FOR CLEANING VALIDATION

1.0 OBJECTIVE:

1.1 To lay down the procedure to establish a guideline / approach to be followed for carrying out Cleaning Validation Studies.

2.0 SCOPE:

2.1 This SOP shall be used as a guideline to finalize cleaning validation methodology for validating the equipment cleaning procedures (manual, semi-automated and automated) used.

2.2 This SOP shall be used for the preparation and review of cleaning Validation Master plan, cleaning validation protocol and cleaning validation summary/Report.

2.3 This SOP shall also define the criteria for verification/revalidation of cleaning procedure, and revision of cleaning validation master plan.

3.0 RESPONSIBILITY:

3.1 It shall be the joint responsibility of the Validation team (Subject matter expert) to prepare the cleaning validation master plan and protocol and execute cleaning validation activity, which shall include the personnel from Quality Assurance, Quality control, Production, Warehouse and Engineering.

3.2 QC Head/ designee is responsible to provide details of physical properties of drug product required for evaluation of risk value.

3.3 Quality Assurance is responsible to provide technical support.

4.0 REFERENCE:

4.1 FDA Guide to inspection validation of cleaning process

4.2 MHRA (2015); Rules & Guidance for Pharmaceutical Manufacturers and Distribution.

4.3 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.

5.0 DEFINITION:

5.1 Marker/worst case API

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

5.2 Cleaning Verification

A single confirmation of equipment cleaning prior to release for product in use.

5.3 Cleaning Validation

It is documented evidence, which provides a high degree of assurance that a specific cleaning procedure will consistently clean a particular piece of equipment to a predetermined level of cleanliness. Validation has to be performed on three consecutive runs.

6.0 PROCEDURE:

6.1 Cleaning validation is a critical GMP requirement which confirms that cross contamination via product residues, cleaning agents and microbial contamination is contained to safe levels and that all processing and packaging equipment is suitably clean to pre-determined acceptable criteria by establishing cleaning methods.

6.2 Perform cleaning validation to assure that the materials that come in contact with equipment (including utensils) surfaces are not contaminated or adulterated. Consider the non-contact parts in close proximity to the production materials, which may contaminate or adulterate the product.

6.3 The following changes are examples of situations that may trigger the requirement for cleaning validation studies:

- Introduction of new product to the facility which is identified as “worst case product” based on matrix updation.
- Introduction of new equipment at site.
- Shift of product to another equipment/ manufacturing area / usage of additional equipment in the manufacturing process
- Revision in batch size
- Revision in cleaning procedure (e.g. cleaning agent, cleaning agent concentration).

(Refer Annexure- I: Cleaning Validation/Verification flow chart)

6.4 Three consecutive, successful verification runs have to be taken in consideration for the cleaning validation study. Validated analytical methods for the marker or the active pharmaceutical ingredient have to be used.

6.5 Microbial analysis has to be performed for each cleaning process. The possible variation in microbiological flora has to be considered.

6.6 Perform cleaning verification to assure that the equipment is suitable prior to the next use. Give special consideration to products manufactured with highly potent materials.

6.7 Verify all the equipments and utensils introduced to the Production facility for cleanliness prior to use. Inspect the machine visually for cleanliness.

6.8 Consider the ability to clean and validate the cleaning process during equipment specification, design and purchase.

6.9 Quarantine the equipments under evaluation for cleaning validation or verification until approval of cleaning results is documented and verified by QA. Do not release any product manufactured by that equipment for use until the Quality Assurance reviews all results, including those associated with cleaning validation. Interim summary report shall be prepared 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.

6.10 Before proceeding with the cleaning validation, ensure the following has been completed and are in place.

- Cleaning Validation Master Plan.
- Cleaning Validation Protocol.
- Analytical Method Validation for the Marker/Worst Case API selected.
- Residue recovery studies for the Marker/Worst case API selected.

6.11 Preparation of Cleaning Validation Master Plan

The validation master plan has to be prepared before proceeding with the cleaning validation study. The plan should be numbered as CVMP/ XXX/01

where

XXX denotes the department i.e. TAB for Tablets, CAP for Capsule, LIQ for Liquid.

01 denotes the first edition.

This master plan should contain the following sections but not limited to:

6.12 Cover Page:

This page should contain the document title along with the document number and Issue / Effective date.

6.13 Pre-approvals:

The approval page of the Master plan should contain the name, designation and signatures of personnel who are responsible for pre-approval of master plan.

6.14 Table of Contents

Prepare a Table of Contents along with the page numbers (where each section can be found).

6.15 Introduction:

This section should cover the purpose and scope of the master plan. It should also cover the areas applicable, the criteria for preparation/revision of the plan, the criteria for revalidation/ verification.

6.16 Validation Team and The Responsibilities of the Personnel:

In this section, define the responsibility of the persons involved in the validation activity. The person responsible for preparation of validation plan/ protocols/report, review, approval and final report approval. The person responsible for execution of protocol and review of filled protocol shall also be defined.

6.17 Cleaning Validation Policy:

In this section mention steps involved in cleaning validation, brief description of the manufacturing process and processing equipment, and the cleaning procedure to be validated and the type of contaminants to be monitored.

Define the cleaning procedures (controlled and designed to be reproducible and justified) before the cleaning validation. Water or other solvents, which are used for final rinse, should be of the same quality, or better, as that used for manufacturing. Any reduced level of cleaning between batches within a campaign shall be justified and documented, and approved by QA. Full batch size of the product should be manufactured in the equipment to be cleaned.

6.18 Selection of worst case product:

This section shall give criteria for the evaluation and selection of the worst-case product for the cleaning validation activity based on:

- Toxicological assessment of product
- Risk rating assigned depending upon the product

Characteristics.

Select the worst-case product for cleaning validation based on the toxicological assessment of product /API(s) as per the Appendix-I:

Source of Data: Assessment made by toxicologist /Registered non-clinical or Clinical Data.

6.19 All the products manufactured at site shall be evaluated for toxicological assessment to identify if the product is hazardous nature based on clinical or non-clinical studies available from registered literature/site or regulatory data base or from approved contract giver etc. Decision for requirements for cleaning Validation should be taken as per reference Appendix-I.

6.20 Group the products based on the equipments used for the process.

6.20.1 Update the product matrix in case of following:

- New product introduction at site.
- Shift of product from one equipment train to another.
- Change in formulation (wherever applicable).
- Introduction of new equipment at site.

- Modification in existing equipment.
- Revision in cleaning procedure.

6.20.2 If two products are having the same rating, select the worst-case product based on following sequential order:

- Most insoluble API in the drug: (Example: Risk value of Metformin tablets 500 mg and Paracetamol 500mg Tablets is same i.e. 6 but Paracetamol is Sparingly soluble where as Metformin is Freely soluble, so Paracetamol is the worst case product).
- Most potent product: (Example: Risk value of X 40 mg Tablets and Y 80 mg Tablets is same but potency of Y is 80 mg and potency of X is 40 mg, so X is the worst case product)
- Most difficult to clean product. (If Risk value of two target product is same and also solubility rating and potency rating is same, then product which is difficult to clean, will be considered as worst case product)

6.20.3 If multiple concentrations of the same product are manufactured, select the highest concentration as the marker. If a multi-API product is selected so chose the one with the least soluble indicator compounds as a marker to demonstrate cleaning adequacy.

6.20.4 **Equipment Usage Matrix:** Wherein all equipments shall be listed based upon their usage for manufacturing. This matrix shall contain the worst case product for the particular equipment.

6.20.5 **Product matrix:** Wherein the entire product manufactured/ to be manufactured in the facility shall be listed along with active ingredient, lowest therapeutic dose, batch size, average weight and maximum daily dose.

6.21 Solubility

A solubility-rating shall be carried out based on the solubilities of the products with the water used for cleaning. Suggested rating numbers, with explanations, are presented in the table below:

S.No.	Category	Rating
1.	Very soluble	1
2.	Freely soluble	1
3.	Soluble	2
4.	Sparingly soluble	3
5.	Slightly soluble	4
6.	Very slightly soluble	5
7.	Practically insoluble	6

6.22 Selection of Acceptance Criteria

6.22.1 Selection of worst case Product for Cleaning Validation:

Acceptance Criteria: The acceptance criteria of chemical contamination for cleaning validation activity shall be determined by using following criteria:

Determination of acceptance criteria for the contaminant:

This section shall give acceptance criteria for Visual inspection, Chemical contamination and Microbiological contamination.

This section shall also provide the calculation of the Acceptance limits for carryover of residue of API, Detergent and Solvent (if used).

The acceptance criteria of chemical contamination for cleaning validation are summarized in the following table:

Test	Acceptance Criteria
Visual appearance	Product contact parts should be visually clean.
Swab analysis	Swab visually clean and free from extraneous matter or oily residues.
Final rinse analysis	Sample visually clear and free from extraneous matter or oily residues.
API residues	Maximum allowable carryover limit (MACO) shall be determined with following three factors. **1. Toxicological data with PDE value** The PDE value/HBEL level should be calculated based on the toxicological data with suitable correction factor applied and this is converted to the "Safe Threshold Value" for carryover to the next batch. **2. Therapeutic data** with safety factor of 1/1000 of LTD **3. 10 PPM** criteria The least MACO derived from the above three criteria will be used for specifying the limit for API residue.
Solvent (used for the extracting of API removal from the equipment surface)	**Toxicological data:** The PDE value should be applied to Safe threshold value for carryover to the next product.
Levels of Microbial Residues	TAMC: NMT 30 CFU/100 cm^2

This section shall give criteria for the evaluation and selection of the worst-case equipment for the cleaning validation activity.

Group the equipments based on following:

- Identical (similar capacity and shape) and interchangeable pieces of equipment shall be grouped together.
- Equipment with the same operating principle and same cleaning procedure shall be grouped together.

6.22.2 **For product dedicated equipment** determination of the levels of product residues on the equipment may not be required, viz. Filter Bag, Punch and Die etc.

6.22.3 **For equipment that is not product dedicated** a documented evaluation of the toxicological data and therapeutic data for the API will be applied in the establishment of acceptance criteria for the levels of API residue on the equipment.

6.22.4 **Visual Clean Criteria:** All equipment surfaces should be clean to the un aided eye.

6.22.5 **Dose Criteria:** Not more than the 0.1% of normal therapeutic dose should appear in maximum daily dose of the product. Maximum Allowable Carry Over (MACO) calculation for API using dose criteria for swab and rinse method:

1. MACO for swab method shall be calculated as per the formula:

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

Where,

LTD = Lowest therapeutic dose (mg) Previous

1/1000 = Safety factor

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

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

Wt = Average weight of unit dose 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)

2. MACO for rinse method shall be derived by calculating maximum allowable contamination of API per equipment. The MACO for individual equipment shall be calculated using the formula:

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

where,

100 = Volume of rinse sample (ml)

ESA = Equipment surface area (cm2)

6.22.6 **10 ppm CRITERIA:** No more than 10 PPM of any product should appear in another product.

Maximum Allowable Carry Over (MACO) calculation for API using 10 ppm criteria for swab and rinse method:

For swab sample

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

where,

R = 10 (0.001% of the minimum batch size (MBS)

S = Minimum batch size of next considered product

U = Swab area (cm2) for swab sample calculation or Equipment surface area for rinse sample calculation

T = Equipment product contact surface area (cm2) for typical train of equipment.

6.22.7 PDE (Permitted Daily Exposure) Values Criteria:

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

For swab sample:

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

For Rinse sample:

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

Where

PDE = Permitted Daily Exposure (PDE) Values

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

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

Wt = Average weight of unit dose(gm)

Ss = Swab area cm2.

Se = Equipment product contact surface area (cm2) for

typical train of equipment.

ESA= Equipment surface area.

6.22.8 Methodology for PDE values

Determination of a PDE based on HBE involve:

- Hazard identification by reviewing all relevant data regulatory requirement.
- Hazard of API used in the formulation.
- Review of Literature; pharmacological and toxicological profile.
- Identification of critical effects.

- Determination of no observed adverse effect level (NOAEL) (or alternative toxicological parameter with proper justification) of critical effect.
- Define the use of several adjustment/ assessment factor to account for various uncertainties. Apply formula to determine PDE.

Criteria for Hazard identification

- Regulatory
- API in a shared facility manufacturing
- Chemical
- Worst to clean, longer time to clean
- May cause chemical reaction with next batch or may act as catalyst
- Pharmacological and toxicological (both human and animal)
- Narrow therapeutic index
- Genotoxicity
- Reproductive toxicity
- Carcinogenicity
- Sensitizing potential
- Highly toxic

Review of literature

- Available toxicology data, reference product insert, prescribing information.
- Review of all available animal and human data shall be performed
- Data can include but not limited to:
- Non-clinical pharmacodynamics data
- Non-clinical toxicological data
- Single, repeat dose toxicity study
- Carcinogenicity toxicity studies in vitro and in vivo genotoxicity study
- Reproductive and development toxicity studies
- Clinical data (therapeutic and adverse effect)

Application of Adjustment factors:

The PDE is derived by dividing the NOAEL for the critical effect by various adjustment factor (also referred to as safety, uncertainty, and assessment or modifying factors) to account the various uncertainties and to allow extrapolation to a reliable and robust no effect level in the human or target animal population.

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Calculation of permitted daily exposure (PDE) Value:

PDE Value is calculated using the formula as follows:

$$\text{PDE} = \frac{\text{NOAEL x Weight adjustment}}{\text{F1xF2xF3 x F4 x F5 x other modifying factor}}$$

Following are the details of factor used for addressing the sources of uncertainty:

F1 = A factor to account for extrapolation between species

- F1 = 5 for extrapolation from rats to humans
- F1 = 12 for extrapolation from mice to humans
- F1 = 2 for extrapolation from dogs to humans
- F1 = 2.5 for extrapolation from rabbits to humans
- F1 = 3 for extrapolation from monkeys to humans
- F1= 10 for extrapolation from other animals to humans

F2 = A factor of 10 to account for variability between individuals

F3 = A variable factor to account for toxicity studies of short-term exposure

F3 = 1 for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys).

- F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.
- F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents.
- F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents.
- F3 = 10 for studies of a shorter duration.

In all cases, the higher factor has been used for study duration between the time point , e.g. a factor of 2 for 9 month rodent study.

F4 = 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:

- F4 = 1 for fetal toxicity associated with maternal toxicity
- F4 = 5 for fetal toxicity without maternal toxicity
- F4 = 5 for a teratogenic effect with maternal toxicity
- F4 = 10 for a teratogenic effect without maternal toxicity

F5 = 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: As per toxicological literature review and assessment of available data a miscellaneous factor will be used to mitigate risk posed by any of uncertainties and variability.

Modifying factor:

In a situation where PDE (calculated by applying all the factor 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 will also be used for any other miscellaneous reason, data, observation, etc. not covered as above.

- All products used in different equipment will be matrixed, the PDE values will be obtained on all molecules used at site.
- Based on the toxicological evaluation, molecules with severe toxicity shall be given a high risk rating.
- The higher risk rating will trigger the requirement for worst case identification for cleaning validation. Certain specialized procedures like containment, use of dedicated equipment and plan to manufacture the product once or twice in a year in campaign basis as possible and increase in the testing swabs / rinse points of non-dedicated equipment post manufacturing of the sever toxicity molecule.

6.22.9 Note:

1) For MACO values of greater than 10 ppm by considering the batch size: Acceptance criteria shall be 10 ppm.

2) For MACO values of less than 10 ppm by considering the batch size: Acceptance criteria of MACO shall be followed as per Dosage criteria (1/1000th of therapeutic dose) or PDE criteria which have less MACO value.

6.22.10 Acceptance Limit Calculation for Solvent using Toxicological Data

Calculation of Maximum Allowable Carry Over (MACO) for solvent:

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

Where,

PDE = Permitted Daily Exposure (PDE) Values

D = Maximum daily dose

Wb = Minimum batch size in gm.

Se = Equipment product contact surface area (cm2) for typical train of equipment

Wt = Average weight of unit dose(gm)

6.22.11 Microbiological Considerations:

The acceptance criteria for cleaned equipments shall be derived from the compendial microbiological attribute requirements for products.

The acceptance criteria established should be stringent enough to ensure that the residual bioburden from clean equipment will not add significantly to the bioburden of the product.

6.23 Selection of sampling locations for chemical and microbiological analysis:

This section should contain the rationale behind selection of sampling location. The list of sampling locations for chemical analysis & microbiological examination shall be updated in protocol.

Sampling locations shall be selected based on following criteria:

- Design of equipment.
- Flow of product throughout the equipment.
- Locations difficult to disassemble.

6.23.1 For microbial swabbing the "worst case" will focus on areas that may contain residual moisture, temperature, crevices or rough surfaces. The impact of storage time before cleaning and the time between cleaning and equipment use should be established.

Note: Due to difficulty in cleaning Fluid Bed Dryer bags are allocated to a single product and thus they are considered as "dedicated bags".

6.24 Sampling Method:

This section should contain the procedure for collection of swab and rinse samples, selection of solvent for rinse sampling and method for determination of residue of solvent remained on the equipment surface after collection of rinse samples.

6.25 Sampling Procedure:

6.25.1 **Based** on the evaluation of need for cleaning validation protocol shall be prepared to execute the cleaning validation activity.

6.25.2 **Before** proceeding for sampling the Visual Inspection criteria should be met.

6.25.3 **Design** the sampling technique and plans in such a manner so as to provide information about completeness of equipment cleaning.

6.25.4 **Use** swab sampling technique for sampling of traces of cleaning agent.

6.25.5 Use swab and rinse sampling technique for sampling of chemical residue and use swab sampling technique for sampling of microbial residues on the equipment.

6.25.6 Check the equipment or utensils for visual cleanliness before sampling, use torch if required. Presence of extraneous matter, dust, stains shall require re-cleaning and swab sample shall not be collected in such conditions.

6.25.7 **Sampling for detection of microbial residues.**

Swab the sampling points as identified in the sampling plan. Hold a device, which marks the area as 100 cm^2, and then slowly swab this entire area with the sterile swab and put this swab in a sterile test tube.

6.25.8 **Sampling for detection of chemical residues.**

- Swab the sampling points as identified in the sampling plan with a swab dipped in a suitable solvent for the identified marker. Hold a device, which marks the area as d cm2, and then slowly swab this entire area with the swab and put this swab in a glass test tube. Collect suitable solvent for identified marker from the QC.
- Take a fixed amount of the rinse solvent for taking the rinse so as to cover the entire surface area of the equipment. Collect the total rinse in a suitable container and then take required amount of the rinse sample in a glass test tube.

6.25.9 **Sampling for detection of chemical residues of solvent used for collection of rinse sample**

Purified water shall be used for final rinsing. Solvent are used only for the collection of rinse samples during the cleaning validation study.

If organic solvent is used for the collection of rinse sample then clean the equipment again after collection of rinse sample as per the procedure for product to product changeover mentioned in the SOP of respective equipment.

In such cases, rinse sample shall be collected by using the purified water as solvent for the determination of residue of solvent remained on the equipment surfaces after cleaning.

The acceptable limits for the residues of the solvent shall be mentioned in the Cleaning validation protocol.

Re-clean the equipment by giving a rinse to the equipment with an adequate amount of Purified Water. Analyze the samples for traces of solvent used for sampling.

Reporting of results:

While recording the amount of traces / residue of API, solvent the observed value should be multiply with recovery of the analyte (R) and the final value should be compared against the MACO derived for cleaning validation.

Result= Observed value x R

6.25.10 Consider the following points while finalizing the sampling plan (document the sampling plan in the protocol).

- Design of equipment and material of construction.
- The recovery of the analyte.
- Most difficult to clean areas as worst cases including minimum detection and variability limits.
- Techniques appropriate to the analysis planned (e.g. marker residue)
- Access to equipment sampling location and safety.

Maximum holding times for samples (Dirty equipment hold time and clean equipment hold time).

6.26 Analytical Method Validation:

This section must describe about the validation of analytical method to be used for estimation of API residue, cleaning agent and solvents should be validated.

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

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

6.26.1 The analytical **method** should be validated for various parameters such as

- Specificity
- Limit of Detection (LOD) and Limit of Quantification (LOQ)
- Linearity
- Accuracy

- Precision
- Range
- Intermediate Precision
- Solution Stability

6.26.2 Residue recovery test:

This section must describe about the requirement of residue recovery test. A separate protocol needs to be prepared and the study needs to be carried out for the worst case API selected by using both swab and rinse technique. The recovery factor should be NLT 75%.

6.26.3 Documentation:

This section shall define the need of various documents which are required for executing the cleaning validation. The format of the document shall be given in detail.

6.27 Continuous monitoring post validation

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

6.27.2 It is a requirement that during Product changeover cleaned equipments should be visually inspected for cleanliness by the Production & Quality Assurance personnel. The line clearance should be given independently by both Production & Quality Assurance Personnel by verification against a line clearance checklist.

6.27.3 During Product changeover the swab samples should be collected & analysed for detection of API residues to check the cleaning method efficiency.

6.27.4 The periodic review of all validated cleaning procedures should consist of a documentation review and may include but is not limited to:

- A review of any changes to products, processes, equipment and facility.
- A review of cleaning validation documents to assess any gaps verses current standards.

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

6.28 Summary report

The requirement of summary report shall be defined in this section.

6.29 Change control & revalidation

Any change shall be documented and revalidated if required.

6.30 References

The various references used for cleaning validation shall be listed in this section.

6.31 Revision of cleaning validation master plan

6.31.1 Revise the cleaning validation master plan upon any change in the policy for cleaning validation.

6.31.2 The Cleaning validation master plan shall be updated upon introduction of any new product falling outside the product matrix, change in the cleaning procedure and change in the equipment train. At the time of revision, the version number shall be changed to next version.

6.31.3 The cleaning validation shall be verified once in three years ± 3 months. This verification shall be consisting of a single run.

If the verification study could not be carried out due to non-manufacture of the marker batches, the alternate API (marker) shall be selected based on CVMP.

6.31.4 Review of chemical and microbiological reports:

Review the reports for chemical and microbiological analysis and verify that equipments under the scope of the study are complying to the predefined limit.

6.32 Handling of Non-Conformances

6.32.1 Any significant changes to the approved cleaning validation protocol during execution e.g. acceptance criteria, operating parameters etc. should be documented as deviation.

6.32.2 In case of any unexpected results which fail to meet the pre-defined acceptance criteria the matter shall be reported to the QA Head.

6.32.3 An Unplanned Deviation shall be raised to identify the root cause of the obtained results as per SOP, “Handling of Incidence Deviations”. The corrective action and preventive action shall be defined and implemented as per SOP, “Corrective and Preventive Action (CAPA).”

6.32.4 The corrective actions shall be reviewed for the impact on the cleaning validation study.

6.33 Quality Risk Management and Control

6.33.1 Quality risk management (QRM) study should assure that process and controls implemented are robustly in place and take account of:

- Technical measure- e.g. Premises and equipment design and installation
- Organizational measure – e.g. campaign processing, cleaning verification

6.33.2 Quality risk management should be used to evaluate planned changes to cleaning procedures to determine the potential impact on the product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance and on any other system to avoid unintended consequences and to plan for any necessary process validation, verification or qualification reports.

6.33.3 Changes should be authorized and approved by responsible persons.

6.33.4 Supporting data, for example, copies of documents should be reviewed to confirm that the impact of the change has been demonstrated prior for approval.

7.0 ANNEXURES:

ANNEXURE No.	TITLE OF ANNEXURE	FORMAT No.
Annexure-I	Cleaning Validation/Verification Flow Chart.	
Annexure-II	Template for collecting information required for worst case evaluation.	

8.0 DISTRIBUTION:

- Controlled Copy No. 01 Quality Assurance
- Controlled Copy No. 02 Quality Control
- Controlled Copy No. 03 Head Production
- Controlled Copy No. 04 Head Warehouse
- Controlled Copy No. 05 Head Engineering
- Controlled Copy No. 06 Head Information Technology
- Controlled Copy No. 07 Head Personnel & Administration / HR
- Controlled Copy No. 08 Head Purchase / Commercial
- Controlled Copy No. 09 Head Production Planning & Inventory Control
- Controlled Copy No. 010 Head Environment Health & Safety
- Master Copy QA Department

9.0 ABBREVIATIONS:

SOP	Standard Operating Procedure
No.	Number
QA	Quality Assurance
QC	Quality Control
API	Active Pharmaceutical Ingredient
LTD	Lowest Therapeutic Dose
MACO	Maximum Allowable Carry Over
SOP	Standard Operating Procedure
NOEL	No observed effect level
PDE	Permitted Daily Exposure
QA	Quality Assurance
QC	Quality Control
STV	Safe Threshold Value
TWA	Total Weighted Average
OEL	Occupational Exposure Limit
CVMP	Cleaning Validation Master plan.
HBEL	Health Based Exposure Limit
TAMC	Total Aerobic Microbial Count
CFU	Colony Forming Unit
LOAEL	Low Observe Adverse Effect Level
LOEL	Low Observe Effect Level

10.0 REVISION HISTORY:

CHANGE HISTORY LOG

Revision No.	Details of Changes	Reason for Change	Effective Date
00	**New SOP**	**Not Applicable**	

ANNEXURE–I
Cleaning Validation/Verification Flow Chart.

It will be prepared in separateA3 paper sheets

SOP FOR CLEANING VALIDATION

ANNEXURE–II

Template for collecting information required for worst case evaluation

Name of Active Pharmaceutical Ingredient in Drug product:

Toxicological Evaluation	

PHYSICAL PROPERTIES	
Physical appearance of drug product	
Solubility	
Cleanability	
Lowest Therapeutic Dose	

Information Collected from Formulation and Development ☐ / Technology Transfer ☐

Name	Designation	Sign	Date

Information Collected from other sources
1.
2.

Prepared by: Checked by: