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CLEANING VALIDATION MASTER PLAN

PHARMA DEVILS
(Oral Solid Dosage & Injectable Facility)

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1.0 APPROVAL & AUTHORIZATION:

This Quality Document **"CLEANING VALIDATION MASTER PLAN"** is sets out the requirements of the organization in respect to Plant and elaborates on Cleaning Validation Activity being followed in all the relevant area in …….

PREPARED BY:

DESIGNATION	NAME	SIGNATURE	DATE
OFFICER/EXECUTIVE (QUALITY ASSURANCE)			

REVIEWED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (QUALITY CONTROL)			
HEAD (ENGINEERING)			
HEAD (OPERATIONS)			

APPROVED BY:

DESIGNATION	NAME	SIGNATURE	DATE
HEAD (QUALITY ASSURANCE)			

AUTHORIZED BY:

DESIGNATION	NAME	SIGNATURE	DATE
GENERAL MANAGER (QUALITY ASSURANCE)			

2.0 INTRODUCTION:

…… is engaged in manufacturing of following dosage form:
In General Category (Tablets, Hard Gelatin Capsules, Soft Gelatin capsules, Dry Syrups), In Injection Block (Dry Powder Injections, Three Piece Eye/Ear Drops, Ampoules, Forming Filling Sealing), In Ointment section (Ointment, Lotion, Cream, Gel Liniment).

This Cleaning Validation Master Plan demonstrates the approach of …….. for Cleaning Validation to meet the current National and International regulatory guidelines.

At ……., the Cleaning procedure is automatic as well as manual for each piece of equipment. The Cleaning procedure adopted is not product or molecule specific but equipment specific, as per the procedure outlined in the respective equipment specific SOP.

The Cleaning Validation Master Plan is designed to provide guidelines for planning, execution and successful completion of the Cleaning Validation program. As the cleaning procedure is Automatic (CIP) & Manual, hence training of personnel shall be performed before the Cleaning Validation.

3.0 PURPOSE:

The Cleaning Validation Master Plan shall function as an umbrella guidance document for all the Cleaning Validation Protocols, program and procedures adopted to ensure that all the equipments utilized for the manufacturing of different dosage forms (Tablets, Hard Gelatin Capsules, Soft Gelatin capsules, Dry Syrups, Dry Powder Injections, Three Piece Eye Drops & Ear Drops, Ampoules, FFS, Ointment, Lotion, Cream, Gel Liniment) as mentioned above are cleaned up to the level to prevent contamination that would alter the Safety, Identity, Strength, Purity and/or Quality of the drug product.

4.0 SCOPE:

This Cleaning Validation Master Plan is applicable to the solid oral dosage forms (Like Tablets, Capsules, and Dry Syrups manufactured in General Block at …… It shall also be applicable to the I-Block, where Dry Powder Injections, Three Piece Eye Drops & Ear Drops, Ampoules & FFS along with Q-Block where Ointments, Lotion, Cream, & Gel Liniment are manufactured.

This CVMP shall also be applicable to all the sections, which shall come in future, with appropriate addendum at that point of time to this CVMP.

On introduction of new equipment/product, it shall be evaluated with the guideline provided in Cleaning Validation Master Plan for determination of requirement of Cleaning Validation.

5.0 RESPONSIBILITIES:

Quality Assurance Department:

Quality Assurance Department shall be responsible for:

- Preparation, Executing and reviewing the Cleaning Validation Protocol.
- Coordinating with production department for the collection of the samples as specified in the protocol.
- Ensuring that the equipment is cleaned to the levels specified in the respective protocol.
- Swab/Rinse sampling of equipments for Chemical & Microbial analysis.
- To prepare, review and approve the Cleaning Validation Report.
- To provide and supervise training programs.

Quality Control Department:

Quality Control department shall be responsible for:

- Reviewing the Cleaning Validation Protocol and report.
- Development of validated analytical method of sufficient sensitivity as mentioned in the Cleaning Validation Master Plan.
- Swab & Rinse sampling for microbiological analysis.
- Analyzing the samples withdrawn during the execution of the Cleaning Validation protocol.

Production Department:

Production department shall be responsible for:

- Reviewing the Cleaning Validation Protocol and Report.
- Provide training to the manufacturing personnel for cleaning of equipment.
- Executing the Cleaning Validation Program.

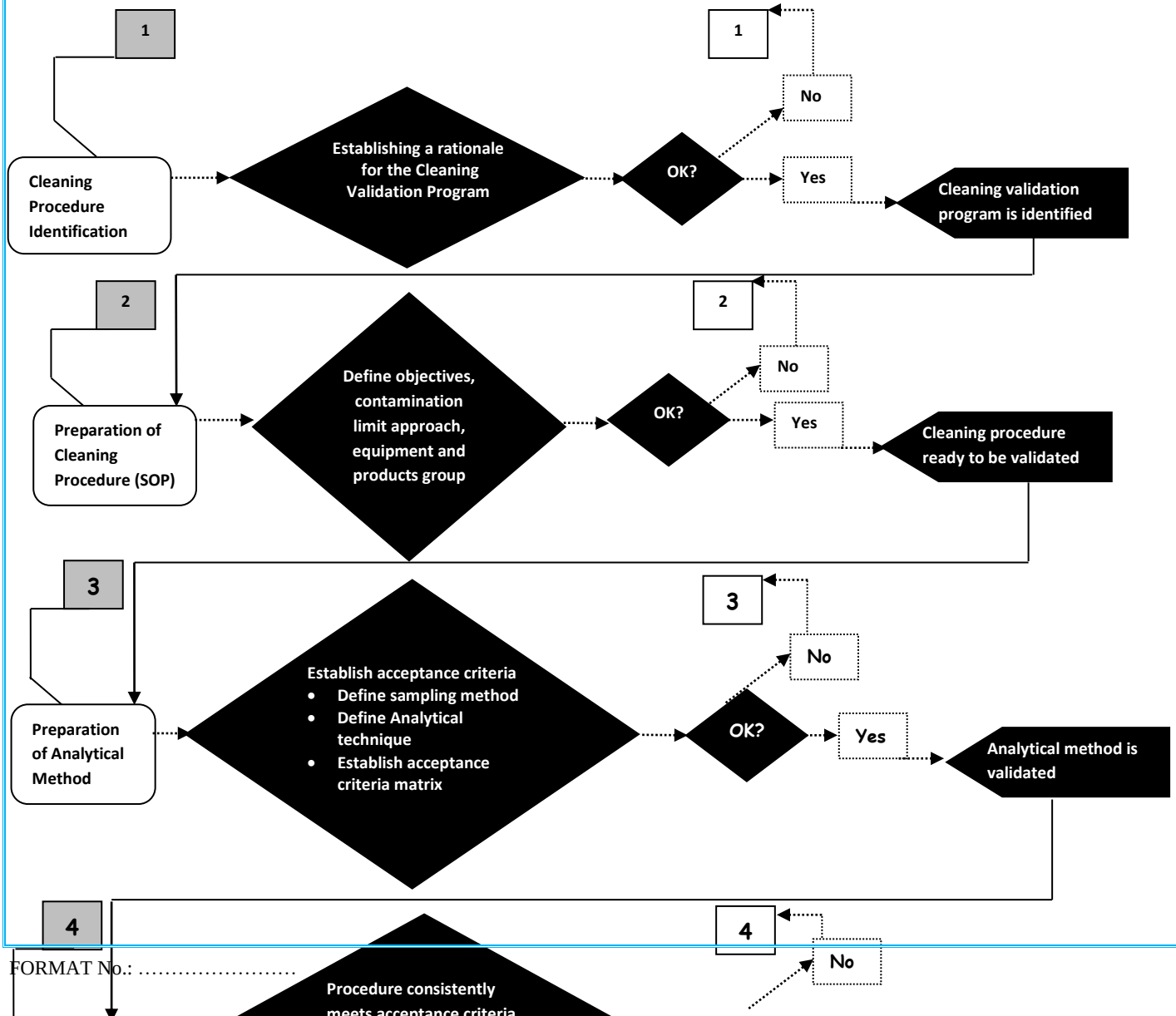
Engineering Department:

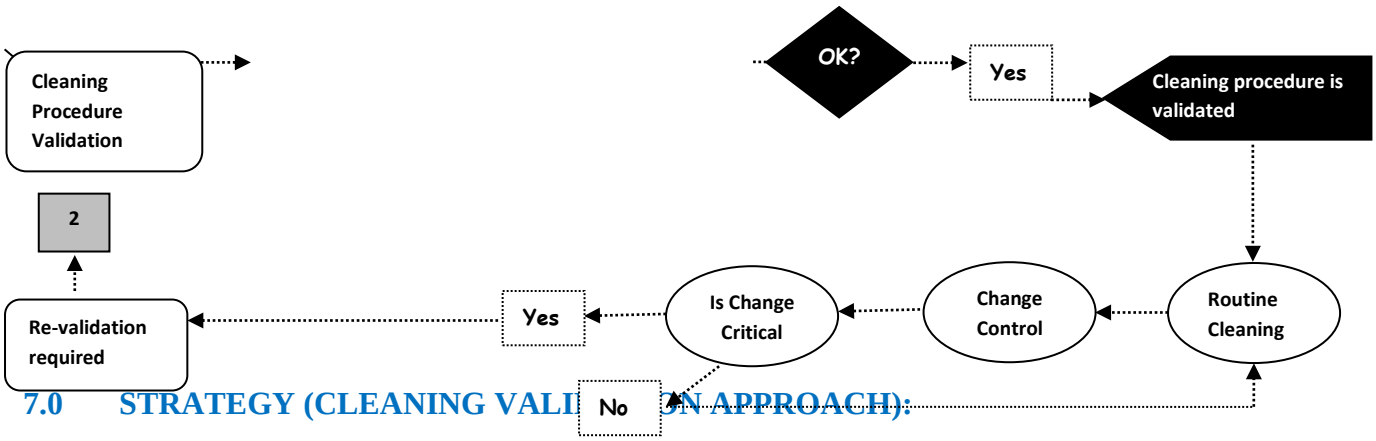
Engineering department shall be responsible for:

- Providing the contact surface area for equipments, being used in the products.

- To operate and maintain the facilities and utilities, so as to maintain the conditions appropriate to the requirement of the product/process and environment, during the execution of Cleaning Validation Protocol.

6.0 CLEANING VALIDATION ACTIVITY FLOW:





7.0 STRATEGY (CLEANING VALIDATION APPROACH):

Cross contamination is understood to be the accidental mixing of one product with another of a different type. If the contaminant is highly toxic or very potent in small dosages, the consequences can be particularly dangerous. Thus, Cleaning Validation has become subject of increase review.

Cleaning is Physical or Chemical removal of undesirable substances. These undesirable substances are generally referred to as contaminants. The contaminants of critical importance normally are the remnants of Active Pharmaceutical Ingredients (API) previously processed in the equipment.

Cleaning must be demonstrated to be effective in order to provide assurance that unacceptable levels of contamination are not carried over to the next product.

The purpose of Cleaning Validation is to provide assurance as to the effectiveness of the cleaning procedures in removing product residue, residue of Cleaning Agents and viable microorganisms from the equipment surfaces to predetermined acceptable levels, such that it does not affect the quality and safety of other products manufactured in the same equipment.

A more important benefit from conducting Cleaning Validation activity is the identification and correction of potential problems, previously unsuspected which could compromise the safety, efficacy or quality of subsequent batches of drug product manufactured with the equipment or the set of equipments. For equipment used in more than one process, Cleaning Validation will provide evidence that product cross contamination will not occur, and assure the quality and safety of product manufactured.
Type A Cleaning Validation of Campaign batches to be performed between same batches while Type B Cleaning validation shall be performed for cleaning performed between product changeovers.

7.1 Product/Equipment Matrixing:

Due to complexity of manufacturing of multiple products and multi product use of the same equipment, a Matrixing approach shall be applied for Cleaning Validation based on scientific rationale. In this approach, cleaning procedure for each product shall not be validated individually;

The most Potent, most Toxic and the most Insoluble (In water) drug product with the highest batch size shall be selected for the Cleaning Validation purpose.

Based on the Solubility, Potency & Toxicity criteria, one product shall be selected as a worst case product among the products manufactured.

Additionally, the value of the acceptance limit derived for the product shall also be considered for classifying the product as a worst case. Train of equipments shall be identified based on equipment capacity and the batch size. The equipment with the largest capacity shall be considered for the cleaning validation/verification. For equipments with different capacities but similar in design and operating principle and where cleaning procedures are equivalent, Cleaning Validation to be performed for minimum & maximum size of the equipment.

Following criteria shall be taken into consideration for the selection of product/equipment:

- Active Pharmaceutical Ingredient's solubility (Difficult to clean and high dose).
- Low dose drug product i.e. Product with potent drug.
- Toxicity of the Active drug.
- Equipment train and its capacity.
- Based upon evaluation of above criteria, product matrix shall be developed and the 'Worst Case' product shall be selected and used for cleaning validation program.

Change of Cleaning Agent in cleaning procedure, change in equipment which does not fit into the established equipment train shall require revalidation.

7.2 Cleaning Validation Approach:

The following may be adopted for conducting the cleaning validation exercise:

- **Validation of cleaning procedure for each product-**
  Involves validation of cleaning procedure for each piece of equipment for each product manufactured.

- **Matrix approach**

Involves testing the cleaning of a product/selection of products that have been identified/chosen as representing the worst-case scenario in the facility. The factors that can be considered for identification of a particular product are Toxicity/Potency, Solubility in cleaning solvent, difficult to clean, acceptance limits etc.
The matrix approach based on the worst case scenario shall be adopted for the cleaning validation exercise.

Rationale:
Matrix approach involves testing the cleaning of a product that has been identified as the worst-case product. This approach is based on the fact that the cleaning procedure adopted is equipment specific & not product specific, and that if it is satisfactory in removing the residue of the worst-case product to levels below the acceptance limits, it will be effective for other products as well.

7.3 Selection of the Worst-Case Product:

The worst case product shall be identified based on the following criteria:

- The solubility of the active ingredient of the previous product in the water used for equipment cleaning.
  Rationale:
  Lesser the solubility of the active ingredient in the cleaning solvent, the greater is the challenge to remove it.

- Where more than one active ingredient is involved and the formulation is difficult to clean; only the active ingredient, which is insoluble in water and having higher Potency & Toxicity shall be evaluated.
  Rationale:
  Lesser the solubility of the active ingredient in the cleaning solvent, the greater is the challenge to remove it.

- If two or more such products emerge as worst case, the product with higher concentration of the drug shall be considered as the worst case.
  Rationale:
  Higher the concentration of the drug on the equipment surfaces the greater is the challenge for the cleaning procedure to remove the drug to concentration levels below the acceptance limits.

- A matrix containing the characteristics and parameters listed below shall be prepared and the worst-case product identified:

- Product name
- Active ingredient
- Batch size
- Dose weight
- Solubility in the cleaning solvent
- Smallest Recommended Daily Dose
- Largest Recommended Daily dose

- **The worst-case product shall be selected from the matrix based on:**
  - The lowest solubility of the active ingredient in cleaning solvent.
  - Amongst the products with lowest solubility of the active in cleaning solvent (water), difficult to clean products are selected.
  - If higher strength product is manufactured, cleaning validation shall be conducted on the cleaning performed after the manufacture of the higher strength product.

7.4 Selection of Equipments:

- **Selection of the worst-case equipment:**
  To make the cleaning validation program manageable, the manufacturing equipment shall be grouped, according to the listed criteria, so that one piece of equipment in a group may represent the entire group. The cleaning validation study shall be performed on this representative piece of equipment.

- **Criteria for grouping & identifying the worst-case equipment:**
  Identical, interchangeable piece of equipment having the operating principle & design may be grouped together.
  Rationale:
  Equipment with the same operating principle and design having the same cleaning procedure, with or without different product contact surface area, can be grouped, if they can be interchangeably used.

- **Equipment surface area:**
  - The equipment with the larger surface area shall represent the worst case.
    Rationale:
    For calculating the maximum allowable carry over residue the higher surface area shall be considered. Since the equipment surface area is in the denominator of the equations for

calculation of the limits, higher the value; lower/stringent will be the value of the acceptance limit derived from the calculations.

- Small utensils like Scoop and Sampling thief shall be covered under other major equipments.
  Rationale:
  The surface area of such small equipment is very less and has simple design, which is very easy to clean. The value of 10% additional surface area shall be calculated for the major equipments of equipment train and the final area shall be taken into consideration for calculation to cover the surface area of small utensils.

- The Cleaning Validation studies should take into account the hard to clean locations in each selected piece of equipment, in addition to the main parts of the equipment.

- Cleaning validation on dedicated equipment includes studies on residual cleaning agent only.

7.5 Cleaning Validation Methodology:

The Cleaning Validation methodology to be adopted involves the following stages:

- Selection of the worst case product
- Calculation of the acceptance limits for the active ingredient and cleaning agent (if used).
- Selection of the sampling method
- Selection and development of the analytical method
- Establishment of hold times.

7.6 Cleaning Verification:

- Cleaning verification approach shall be applied for the unique condition where the product being manufactured for the first time is not fitting/does not exist in the established product/equipment matrix, until cleaning procedure has been validated or it is one time activity/event the product will not be manufactured in the same manner on the commercial scale equipment.

- Cleaning verification approach shall also be applied while introducing/replacing any equipment of the train, after appropriate evaluation. Based on evaluation, verification shall be performed, if required, for particular equipment until cleaning procedure has been validated.

- Cleaning verification shall establish/demonstrate the proper removal of target product residue (approved detergent and wherever applicable, microbial load) by which it shall not alter the

Safety, Identity, Strength, Purity and/or Quality of subsequent drug product being manufactured in the same equipment.

- Selection of swabbing position based on the experience for difficult to clean location of equipment or history for worst-case sampling while Rinse sampling shall be done for those locations which are hard to reach.

- Method adopted shall be qualified for the sensitivity and Swab recovery/Rinse recovery.

7.7 Cleaning Techniques:

- **Type A Cleaning:** The equipments are cleaned with common cleaning procedures. It consists of manual removal of adhered material using nylon brush, and then after the surface is wiped with dry lint free cloth.

- **Type B Cleaning:** The equipment cleaning consists of manual removal of adhered powder using nylon brush, water and a solution of 2.0% v/v Extran MA-02 solution may be used as cleaning agent to remove adhered residue and then the surfaces are rinsed with potable water till the rinse water is free from visible froth, even on shaking, lastly the equipment shall be rinsed with Purified water. Then the equipment is dried by wiping with clean lint free cloth or using the filtered compressed air.

- **Water Quality:** Water to be used for the cleaning of manufacturing equipment is Purified water or WFI at room temperature for final rinse.

- **Ancillary Equipment:** Ancillary equipments are utilized along with the main equipment illustrated in the equipment train. They aid in clean manufacturing process in terms of product transfer, excipients holding and granulating solution preparation. Examples of ancillary equipment are solution tanks, agitator assembly and scoops.

- Cleaning validation shall be established for ancillary equipment e.g. Scoops, Sampling thief to the extent that these are visually clean mainly because the impact of the leftover residue of previous product, based on the total surface area is too small to have any significant impact on the Acceptance value of entire equipment train.

7.8 Selecting the Sampling Method:

- **Swab Method (Direct Sampling):**

Swab sampling shall be the preferred method since areas difficult to clean and which are reasonably accessible can be evaluated. Additionally, residues that are insoluble can be sampled by physical removal.

Since worst-case approach is taken for validating cleaning procedure by evaluating insoluble actives swab sampling is usually chosen. For microbial evaluation also, swab method is chosen since curved surfaces can be easily sampled.

Swab recovery study shall be performed to determine the ability of the swab to quantitatively remove residue from the surface sampled. This shall be performed as part of the validation of analytical method. Recovery of the target residue shall not be less than 70% after taking into account interference of swabbing material while using solvent in which target API residue is soluble. This recovery factor shall be used for final calculation of the residue limits.

The equipment's hard to clean locations are identified, based on cleaning experience and the equipment design. Sampling shall be done from the equipment product contact surfaces, including hard-to-clean locations. Sample surface area should be large enough to allow the recovery of the target active in a quantity sufficient to be detected by the analytical method. An area of 5 x 5 cm^2 shall be sampled. Stainless steel/Teflon sampling frames shall be used on flat accessible surfaces to demark the area to be swabbed.
For hard-to-clean smaller areas (curved surfaces), wherever feasible, **the whole area shall be swabbed**. As a manual operation and inherently personnel dependent, the persons performing the sampling and the recovery study shall be trained and given precise instructions in order to obtain reproducible results.

- **Rinse Method (Indirect Sampling):**

  Rinse water sampling involves taking a sample of an equilibrated post-final rinse that has been re-circulated over all surfaces. This method allows sampling of a large surface that are inaccessible or that cannot be routinely disassembled. Rinse method provides an overall picture.

  Although Rinse recovery factor is uncertain but can be performed to determine the ability of the rinse to quantitatively remove residue from the surface sampled. This shall be performed as part of the validation of analytical method. Recovery of the target residue shall not be less than 70% after taking into account interference of swabbing material while using solvent in which target API residue is soluble. This recovery factor shall be used for final calculation of the residue limits.

7.9 Evaluation of Cleaning Procedures:

- To evaluate the cleaning procedure and to give evidence of cleaning effectiveness following methods shall be used:
  A. Visual inspection,
  B. Swab sample and Rinse sample (wherever applicable).

- Method adopted for the analysis of sample shall be validated.

- Visual inspection shall be performed upon completion of the cleaning procedure. Swab sampling shall be performed only when visual inspection of the equipment under study is found satisfactory.

- Unsatisfactory Visual examination, Swab or Rinse sample results attributed to the cleaning procedure shall require that the following steps be taken:
  - The failing cleaning procedure shall be revised.
  - Investigation shall be performed and documented in the validation summary- report.
  - The revised cleaning procedure shall be validated.

- Unsatisfactory visual inspection result shall require re-cleaning the equipment using the existing cleaning procedure. Proper cleaning must be verified prior to use of the equipment for manufacturing. Swab or Rinse samples may be used to verify the re-cleaning.
- Equipment which, after the cleaning, has passed visual inspection, but has subsequently failed to meet the analytical or microbiological acceptance criteria for swab or rinse sample shall require re-cleaning using the existing cleaning procedure.

- Data gathered in verifying the re-cleaning cannot be used for the validation of the cleaning procedure. If the failed equipment was used in the manufacturing of products, the effect of the unsatisfactory analytical or microbiological result must be investigated prior to release of the affected products.

- Production department in consultation with Quality Assurance shall initiate an investigation as to the causes of the unsatisfactory results.

- Sampling and analytical methods shall depend on the nature of residue and manufacturing equipment. The cleaning validation protocols shall specify the sampling techniques and locations.

- Rinse sample (where applicable) can be applied to equipment that can hold solvent/water, and is used between successive rinse steps to evaluate the effectiveness of the rinsing steps.

- Swabbing is the preferred sampling technique since it is used for establishing the levels of residues of moderately soluble or insoluble active ingredients, cleaning agents and microbial bio-burden.

- Swabbing of product contact surface of manufacturing equipment and utensils must include "difficult to clean" area.

- Operator and supervisor's experience as to the most difficult to clean locations shall be taken into account.

- Most equipment will be swabbed for 3-5 location, depending on the equipment size, accessibility, and complexity.

- Equipment with a small surface area, such as De-duster, will be swabbed for 1-3 locations.

- Instructions for swabbing will be specified in each validation protocol for each piece of equipment.

- The time of cleaning can vary from the validated time depending upon the no. of people involved in cleaning procedure.

The procedure will specify the following:

- Type of swab.
- Type and amount of solvent used to extract the residual material.
- Swabbing technique.
- Dimension of equipment surface area to be swabbed (e.g. 5 cm x 5 cm).
- Holding time and conditions for swab samples prior to testing.

Samples will be stored in appropriate containers tightly sealed and identified with the following information:

- Equipment identification/Location.
- Product name and strength.
- Batch number.
- Sampled by, time and date of sampling.

8.0 ACCEPTANCE CRITERIA:

The following criteria shall be applied for the acceptance of a cleaning validation run:

- The equipment surfaces should be clean externally & internally when examined visually.
- The most stringent value (least) calculated amongst the dose criterion and 10-ppm criterion shall be considered as the acceptable limit for the contaminant level in the next product.

In case of non-compliance with the values as calculated for the contaminant limits, an investigation into the cause of non-compliance should be conducted. Consideration such as improving the cleaning procedures and revalidation should be considered.

8.1 Calculation of the Residue acceptance limits:

Calculation of the Residue acceptance limits for cleaning validation limits shall be based on the following assumptions:

- The contaminant is evenly distributed across the entire common surface area.
- 100% of the contaminant is transferred to the next product.
- There is even distribution of the contaminant throughout the next product.

Following three criteria shall be employed for calculation of the acceptance limits for the residue in the next product. The least value derived from the three shall be considered as the acceptance limit for cleaning the previous product.

- **Visually Clean Criterion:**

No quantity of residue shall be visible on the equipment after cleaning has been performed.

Rationale:

Published Spiking studies have demonstrated that the active ingredients in most products are visible at approximately 100 microgram per 5 x 5cm of area when distributed uniformly.

- **10 ppm Criterion:**

Not more than 10 ppm of any product to appear in another product.

Rationale:

This concept of using maximum allowable parts per million levels is based on the regulations that apply to food products, where-in residue levels equal to or less than 10 ppm are considered as acceptable in the next product.

The limit (ppm/swab) calculation is as follows:

Limit [ppm/swab] = R x (K/L) x M

R 10 mg of active ingredient of previous product/kg in next product.
K Batch size of product B in Kg.
L Equipment surface area in common between the previous product and next product expressed in square centimeters.
M Sampled surface area (5 x 5cm).

- **Safety Factor:** It should be realized that a safety factor is an arbitrary factor. [**Note:** some will assert that in a safety factor of 0.001, 0.1 due to one factor, 0.1 to another factor, and 0.1 to a third factor. In such a case, the arbitrary nature of the factor is just transferred to each of those three factors.]

- **Dose Criterion:**
(i). **For Oral:** Not more than 0.001 dose of any product shall appear in the maximum daily dose of next product.

(ii). **For Parenteral:** Not more than 0.0001 dose of any product shall appear in the maximum daily dose of next product.

(iii). **For Topical:** Not more than 0.01 dose of any product shall appear in the maximum daily dose of next product.

- The limit (ppm/swab) calculation shall be as follows:

$$\text{Limit [ppm/swab]} = \frac{I \times K \times M \times 1000 \times 1000}{SF \times J \times L}$$

The description the terms are as given:
SF Safety Factor.
I Minimum daily dose of active in Product A calculated as (active/unit) x (units/dose) x (min. doses/day)
J Maximum daily dose of product B calculated as (Unit Qty.*) x (units/dose) x (max. doses/day) [* = mg or ml depending upon the formulation].
K Minimum batch size of product B in Kg.
L Equipment surface area in common between the previous product and next product expressed n square centimeters.
M Sampled surface area (5 x 5cm).

8.2 Microbial evaluation criteria:

Microbiological monitoring as a part of cleaning validation serves as a tool to confirm the adequacy of cleaning procedures & the same will be established as part of validation programme.
The limits defined below are guidance values only:

- For oral dosage forms not more than 100 CFU/swab (5 x 5cm).
- For parenteral dosage forms not more than 10 CFU/swab (5 x 5cm) before sterilization.
- For cleaned equipment hold time Not more than 1 log increase from the initial swab result.
- For All Pathogens Absent

The cleaning procedure shall be considered validated when the acceptance criteria, as specified in the protocol, have been met.

The failure of individual sampling points will not necessarily mean that the cleaning method is inadequate. Each deviation will be investigated and based on the investigation, corrective actions will be taken that may require further follow up or further validation.

8.3 Visual Inspection:

After the cleaning of equipment, visual inspection shall be performed prior to other sampling. Therefore, visual inspection will be part of the cleaning validation acceptance criteria for all equipment and utensils. The clean dry equipment must contain no visible residue.

8.4 Active Residue:

Calculation of active residue after cleaning shall be based on product contact surface area. This approach is based on the Acceptable Daily Intake (ADI).
ADI is defined as the amount of the drug product (mg/day), that a person can be exposed as a contaminant in another pharmaceutical product without experiencing any adverse health or pharmacological effects.

Based on the above, the calculation for carry over are based on the assumption that only a fraction (1/1000 for oral dosage) of the smallest daily dose of product “A” can be carried over to a maximum allowed daily dose of product “B” manufactured in the same equipment.

The factor of 1000 was obtained based on; oral drug products are pharmacologically inactive and safe at 1/1000 of their normally prescribed dosage.

The following formula will be used for determining the residue level. For oral drug products the factor is 1000 and for Injectable, it is 10,000.

MAR = STD x SBS/SF x MDD

Where,

MAR = Maximum Allowable Residue

STD = Smallest therapeutic dose of any product manufactured in equipment train (Product-A).

SBS = Smallest batch size of the any product manufactured in equipment train (Product-B).

SF = Safety factor i.e. 1000 for Oral Dosage Forms and 10,000 for Parenterals.

MDD = Maximum daily dose of any product manufactured in equipment train (Product-B).

8.5 Establishment of Acceptance Limits:

A. The calculations shall be based on the smallest batch size & maximum daily dose of the product to be manufactured and the equipment surface area.

B. Maximum Allowable Residue (MAR) for Product A in the subsequent products after a changeover will be calculated using the following formula:

$$MAR = \frac{\text{Smallest Strength of Product A} \times \text{Smallest Batch Size of Product B}}{\text{Safety Factor} \times \text{Maximum Daily Dose of Product B (Weight)}}$$

(Safety Factor is 100 for Topical, 1000 for Oral Dosage and 10,000 for Parenteral)

C. Calculate the Maximum Allowable Residue (MAR) of Product A against all other product.

D. Among the limits established for the Product A with respect to subsequent product, the least value will be considered as the Acceptance limit for that product.

E. Acceptance limit shall be calculated for all the products as per the above procedure.

F. Similarly calculate the Maximum Allowable Residue (MAR) of all the other products in against other products and update the product matrix.

G. List out the equipment used for the each product including their product contact surface area.

H. Calculate the Acceptance limit of each equipment according to the respective equipment surface area; and acceptance limit for the product per swab using following formulae:

Acceptance Limit for Equipment (µg/eq.) = MAR (mg) x Equipment Surface Area / Total Surface Area

Acceptance Limit for per Swab (µg) = Acceptance Limit for Equipment x Swab Surface Area / Equipment Surface Area

I. Perform the calculations with respect to each product.

8.6 Cleaning Agent:

Cleaning agent used, scientifically justified and based on:

- The solubility of the materials to be removed;
- The design and construction of the equipment and surface materials to be cleaned;
- The safety of the cleaning agent;
- The ease of removal and detection;
- The product attributes;
- The minimum temperature and volume of cleaning agent and rinse solution; and
- The manufacturer's recommendations.

The residue limit for product contact surface area/part for cleaning agents is calculated based on their toxicity data. For determination of cleaning agents residue level worst-case scenario will be considered for each equipment.

The following formula will be used for determining the residue level:

$$\text{MACO} = \frac{\text{NOEL x SBS}}{\text{MDD}} = \frac{\text{NOEL x 70 x SBS}}{\text{SF X MDD}}$$

Where,

MACO= Maximum allowable carryover
SBS = Smallest batch size of the any product manufactured in equipment train (Product- B)
NOEL = No Observed Effect Level (i.e. LD_{50} x 70/SF).
SF = Safety factor (1000)
MDD = Maximum daily dose of any product manufactured in equipment train (Product-B).

8.7 Microbial Test:

Swab samples to be collected from product contact surface area immediately after completion of cleaning activities and after specified hold time period for total aerobic microbial count.

The limits for the microbiological bio-burden criteria for product contact surface are presented below.

Product Equipment Contact surface	Microbiological bio-burden, cfu/25cm^2		Corrective Action
	Total plate count	Mold and Yeast	
Alert Level	Less than or equal to 50	Less than or equal to 35	▯ No action required
Action Level	Less than or equal to 100	Less than or equal to 50	▯ Investigate possible causes. ▯ Perform re-cleaning. ▯ Perform extra microbial testing
Limit	Less than or equal to 200	Less than or equal to 100	▯ Investigate possible causes. ▯ Perform re-cleaning and re-Sampling. ▯ Finished product testing for microbial contamination with Speciation if positive.

8.8 Hold Time Study:

To establish the effectiveness of cleaning equipment will be kept idle for 72 hrs. in dirty condition. To establish the expiry of cleaning in view of microbiology, equipment shall be kept idle after cleaning for 72 hrs. and microbiological swab shall be taken and analyzed. This will be considered as worst case and microbial load should remain well within limit.

8.8.1 Estimation of Hold Time for Equipments:

- **Establishing Dirty Equipment Hold Time:**

The nature of previous product residue on the equipment surface may change over a period of time. Those changes include drying of residue and/or microbial proliferation. Such changes may make the residue more difficult to remove by the cleaning process.
The cleaning process should be able to adequately clean the equipment under worst cases of normal operating conditions, a demonstration of effectiveness under the worst case dirty equipment hold time shall be done by conducting product changeover cleaning after holding equipment dirty for specified time. This shall be carried out on critical equipment only.

In case it is not be possible to conduct hold time study along with the batches taken for cleaning validation study because of the production schedule, hold time studies shall be carried out as and

when the equipment are available for this study.

- **Establishing Cleaned Equipment Hold Time:**
  The objective for establishing time limit between equipment cleaning and reuse is to ensure that the equipment remains clean till the next use. This needs demonstration that there is no microbial proliferation in cleaned equipment during storage.

  For establishing the time limit, initial swab samples for cleaned surface shall be taken. Thereafter, the equipment shall be protected as prescribed in the SOP and stored in its designated area. Periodic samples of product contact surface for microbiological contamination shall be taken. Based on the data generated acceptable time limit shall be established.

- **Hold time of Sterilized Equipment:**
  The equipment/accessories after sterilization shall be used for their intended purpose within the shift (8 hours); the same shall be stored under the LAF till they are being used.
  Due to the intricacy of the procedure for collection of swab samples from sterilized equipment surfaces without compromising the sterility factor; the hold time has been considered as a shift (8 hours).

Estimation of Hold time after cleaning and before its usage of the equipment:

- After cleaning of the equipment as per the respective cleaning procedure, swab samples are collected initially and after 72 hrs.
- Swab samples are tested for Microbial count, Fungus and Pathogens and the maximum Hold time after cleaning and before its usage of the equipment is evaluated after 72 hrs.

9.0 CLEANING VALIDATION PROTOCOL:

Cleaning validation protocol shall be developed for the 'Worst Case' product selected for cleaning validation programme. Since the activity is based on targeted molecule, protocol number shall be given with reference to targeted molecule name.
Protocol numbering system shall be as CVP/XX/YYYY-ZZ
Where,

CVP	Cleaning Validation Protocol
XX	Block (Ex.: GB for G-Block/IB for Injection Block/QB for Ointment Block)
YYYY	Four digit unique code representing serial no.
ZZ	Revision number

For cleaning validation report CVR shall be written in the place of CVP.

Each Protocol shall following information, but not limited to, are to be included in the cleaning validation protocol:

1) **Objective:**
   A brief description of the purpose of the validation study.

2) **Scope:**
   This section must include an extent of the cleaning validation protocol.

3) **Responsibilities:**
   This section includes the different responsibility for completing the cleaning validation programme.

4) **Protocol approval:**
   Signature of all the persons responsible for preparation, review, approval & authorization of cleaning validation protocol shall be mentioned here.

5) **Signature specimen:**
   Signature (specimen) of all the persons involved in the cleaning validation program mention here for proper identification of person for future reference.

6) **Protocol training record:**
   Training is to be provided to all personnel involved in the cleaning validation program for understanding and cGMP requirement.

7) **Equipment description and Cleaning procedure:**
   A brief description of the equipment used in the manufacturing of the selected product and the relevant SOP for equipment cleaning.

8) **Sampling plan and Sampling procedure:**
   - Number of satisfactory cleaning validation run shall be specified.
   - Type and number of sample during each validation run shall be specified.
   - In addition to visual inspection, the sampling plan shall include swab sampling of product contact surfaces.
   - The location of product contact surface samples (swab samples) shall be referenced on equipment drawing.
   - Sampling plan shall include swab for active residues and cleaning agent, rinse sample, wherever applicable and microbial limit test.

   Each protocol will include test forms, including the under given detail:

a) Equipment identification (Make, Model, Identification Number)
b) Product name and strength
c) Batch number
d) Name of person who performed the cleaning
e) Name of person who verified the cleaning
f) Name of person who performed sampling
g) Swab sample specific Location

9) Analytical and microbiological test method:

This section shall give references for the adopted analytical and microbiological test method to analyze the samples. The analytical method must be validated for the residue levels, or bio-burden as per the specification given in the protocol.

All test result must be calculated and reported to correspond with the predetermined acceptance criteria.

10) Acceptance Criteria:

The acceptance criteria for the cleaning validation shall be mentioned in the specific protocol and will be decided based on product matrix.

11) Deviation:

Any deviation taken during execution of the protocol shall be documented in this section. Justification for the deviation will be authorized by Quality Assurance Manager and Quality Assurance General Manager.

12) Summary report:

- After the completion of cleaning validation program for the selected product, a final report will be generated for each protocol.
- The report shall contain a summary and discussion of validation testing and result including relevant supporting document.
- Deviation to the cleaning validation protocol will be noted in the report.
- The summary report will be approved by GM Quality Assurance.

10.0 ANALYTICAL METHOD DEVELOPMENT AND VALIDATION:

- **Selection of the analytical method:**

Specific Analytical method shall be chosen to fulfill the basic requirement such that:
1. The sensitivity of the method shall be appropriate to the calculated carry over limit.

2. The method shall be practical and as much as possible shall use instrumentation existing in the facility.
3. The method shall be validated.
4. The analytical development shall include recovery study to challenge the sampling and testing method.

- The development and validation of analytical procedure for the purpose of analyzing cleaning validation sample requires the selection of appropriate tests. The list of such tests, with their definition is given below:

1) Limit Of Quantitation:
The limit of Quantitation of an individual analytical procedure is the lowest amount of analyte in a sample, which can be quantitatively determined with suitable precision and accuracy.

2) Limit Of Detection:
The limit of detection of an individual analytical procedure is the lowest amount of analyte, which can be detected but not necessarily quantitated as an exact value.

3) Linearity:
The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration of analyte in the sample at LOQ level.

4) Recovery Study:
This study is to check the efficiency of swab or rinse sampling procedure from the surface (Contact surface like SS, Teflon rubber etc.). The study is performed by applying the known concentration of standard solution on surface at target and LOQ level. The recovery study will be performed by different analyst to demonstrate the robustness of the analytical procedure.

5) Stability of Solution:
The study of the stability of analytical solution is performed by preparing the sample solution at test concentration level.

6) Filter/Centrifuge Interference:
To study the filtration does affect the results of Assay method, carryout filter validation on Nylon filter.

11.0 REVALIDATION CRITERIA:

Revalidation of Cleaning procedure is required if any of the following occur:

- Modification of cleaning procedure.
- Modification of the surface area of product contact parts of equipments.
- Change in cleaning procedure.
- Change in analytical method for determination of residue.
- Failure during cleaning verification/validation.

12.0 CHANGE CONTROL:

Any changes to a parameter of a previously validated cleaning procedure must be evaluated by Quality Assurance department to determine if additional cleaning validation is required.
The following changes may affect the validated status of a cleaning procedure, but not limited to:

- New product
- Major product reformulation
- Equipment changes (size or type)
- Cleaning agent changes, or cleaning agent formulation changes
- Cleaning procedure changes
- Repeated cleaning failures.

13.0 DEFINITIONS:

- **Cleaning Validation:** Cleaning Validation is defined as "Establishing documented evidence that the cleaning process consistently provides a high degree of assurance that after cleaning, equipment and system are free from materials that would contaminate or adulterate subsequent product up to the predetermine acceptance criteria".

- **Equipment Train:** Equipment train is defined as "Group of equipment in sequence, utilized for manufacturing particular group of product, considering the batch size and capacity of equipment".

- **Limit of Detection:** The lowest amount of analyte in a sample which can be detected but not quantitated as an exact value. The Limit of Detection is mostly a parameter of limit tests.

- **Limit of Quantitation:** The lowest amount of analyte in a sample which can be quantitatively determined with defined precision and accuracy under the stated experimental conditions.

- **Validation Protocol:** A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment and decision points on what constitutes acceptable test results.

- **Validation Report:** Document reporting the validation activities, the validation data and the conclusions drawn.

- **Worst Case:** A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

14.0 REFERENCE:

- WHO supplementary guidelines - Cleaning Validation.
- ICH Q7 November 2000.
- EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use.

15.0 ABBREVIATION:

cfu	:	Colony Forming Units
cGMP	:	Current Good manufacturing Practice
cm	:	Centimeter
CQA	:	Corporate Quality Assurance
CV	:	Cleaning Validation
CVMP	:	Cleaning Validation Master Plan
EU	:	European
GM	:	General Manager
Hrs.	:	Hours
ICH	:	International Conference on Harmonization
LOQ	:	Limit of Quantitation
Ltd.	:	Limited
MDD	:	Maximum Daily Dose
NMT	:	Not More Than
Pvt.	:	Private
QA	:	Quality Assurance
SFG	:	Semi-Finished Goods

SOP	:	Standard Operating Procedure
Sq.	:	Square
Sr.	:	Senior
STD	:	Smallest Therapeutic Dose
STP	:	Standard Testing Procedure
WHO	:	World Health organization

16.0 REVISION HISTORY:

Revision No.	Change Control No.	Details of Changes	Reason for Change	Effective Date	Updated By
00					

ANNEXURE – I

Product Selection Criteria for Cleaning Validation …… Section (Tablet/Capsule etc.)

S.No.	Product Name	SFG No.	B. Size (Lac/ Kg)	Uncoated /Coated Product	Standard Therapeutic Dose	API Name	Strength (mg)	Avg. Wt. (mg)	% Content of API	Solubility in water	Remarks

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ANNEXURE - II

Equipment Selection Criteria for Cleaning Validation

Table-1: Comparison of Equipments …….. Area (Ex. Granulation/Compression/Coating/Filling/ Packing etc.)

Equipment	Area No. ….	Area No. ….	Area No. ….	Area No. ….	Area No. ….
	Capacity	Capacity	Capacity	Capacity	Capacity
Equipment Name					

Table-2: Area……..

S.No.	Equipment	Make	ID. No.	Capacity	Surface Area (cm^2)	#Surface Area (cm^2)

Table-3: Equipment Train selected as Worst case for Calculation of Acceptance Criteria:

S. No.	Equipment	Make	ID. No.	Capacity	Surface Area (cm^2)	#Surface Area (cm^2)

Extra 10% area added:

- To compensate any calculation incorrectness.
- To accommodate any minor changes in equipment design.
- To accommodate the usage of ancillary equipment.

As product is being manufactured in any of the one granulation area, total surface area of equipment train-1 is selected as worst case considering the highest surface area at the time of calculation of the acceptance criteria.

ANNEXURE - III

Calculation of Acceptance Criteria for Cleaning Validation (…… Section)

S.No.	Product Name	SFG No	API Name	B. Size	STD	LDD	Avg. wt. (mg)	MDD= LDD × Avg. wt.	Remarks

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ANNEXURE - IV

Evaluation of New Product for Cleaning Validation (…… Section)

For Cleaning Validation:

Product Name		
SFG No.		
Name of API		
Strength		
Batch Size (Kg)		
% Content of API		
Solubility in Water		
Change in Cleaning Procedure	**Yes**	**No**

For Acceptance Criteria:

Single Therapeutic Dose (in mg)	
Batch Size (Kg)	
Largest daily dose (in unit)	
Average weight (in mg)	
LDD × Avg. Wt. (in mg)	

Compare the above data with the data provided in the matrix and draw the conclusion whether above product falls under the existing matrix or required cleaning verification/validation or change in acceptance criteria is required.

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ANNEXURE - V

Evaluation of New Equipment for Cleaning Validation (…… Section)

Equipment Name		
Location		
Capacity		
Make		
Total surface area		
Total surface area with extra 10 %		
Equipment train	**New Introduction**	**Replacement**

Compare the above data with data provided in matrix and draw the conclusion whether above equipment falls under the existing matrix or required cleaning verification/validation or change in acceptance criteria is required.

Change in operating principles	**Yes**	**No**
Change in design		
Is surface Area of any train will be affected		
Change in cleaning procedure		
Total surface area of particular train in cm^2 (Existing)		
Total surface area of particular train in cm^2 (After considering area of new equipment)		

Conclusion:		
Validation required	**Yes**	**No**
Verification required	**Yes**	**No**
For Acceptance Criteria:		

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Change in Acceptance criteria required	Yes	No
Evaluated by:	Checked by:	Approved by:

ANNEXURE - VI

Calculation for Acceptance Criteria for Cleaning Validation

S.No.	Equipment Name	MAR (mg) (A)	Equipment Surface Area (cm^2) (B)	Total Surface Area (cm^2) (C)	Acceptance Limit (ALE) (µg/equipment) $\frac{A \times B}{C}$	Acceptance Limit per Swab (ALS) (µg/swab) $\frac{ALE \times Swab\ Surface\ Area^*}{B}$
1.		…..	….	…..	…..	….
2.			….		…..	
3.			….		…..	
4.			….		…..	
5.			….		…..	
Total			….		…...	

* Taking Swab Surface Area= 25 cm square

Considering,

Product-A XXXXXX **…….. (Batch size in nos.)…… Ex. Tablets/Capsules** manufactured before

Product- B YYYYYY **……. (Batch size in nos.)…… Ex. Tablets/Capsules.**

Single Therapeutic Dose of Product A (of the API in least quantity) **STD** = …… mg

Safety Factor, **SF** = Ex.: 1000 (for oral dosage forms)

Smallest Batch Size of Product B, **SBS** = ……..… Kg = …….. mg

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Maximum Daily Dose of Product B, **MDD** = …… mg
(considering maximum ……. mg a day for an adult)

Formula for Maximum Allowable Residue (MAR):

MAR = STD × SBS /SF × MDD

= …… × …….. /1000 × ……..

= ……. **mg**