PHARMA DEVILS QUALITY ASSURANCE DEPARTMENT	
STANDARD OPERATING PROCEDURE	
DEPARTMENT: QUALITY ASSURANCE	SOP No.: XXXXX
TITLE: CLEANING VALIDATION	
Effective Date:	Next Review Date:
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1.0 OBJECTIVE:

The purpose of this SOP is to lay down the procedure for Cleaning Validation studies to be followed for equipment/accessories used in manufacturing.

2.0 SCOPE:

This SOP is applicable for documented evidence and actual experimental data that the procedure being followed for cleaning of equipment and accessories is effective and removes all residues of previous product up to a predetermined acceptance level thereby avoiding the risk of cross contamination. This procedure is also applicable for deciding worst case products for performing cleaning validation at the manufacturing facility of **XXXXX**.

3.0 RESPONSIBILITY:

Authorized designee of QA shall be responsible cleaning validation protocol and compilation of cleaning validation report.

Authorized designee of Quality control shall be responsible to review the protocol and sampling as per the protocol.

Authorized Designee of Production and Engineering shall be responsible to review the protocol and assist in execution of Study.

Head QA shall be responsible to approve validation protocol & report.

4.0 PROCEDURE:

4.1 Definition: Cleaning Validation: Cleaning validation shall be performed to provide a documented evidence and actual experimental data that the procedure being followed for cleaning of equipment and accessories is effective and removes all residues of previous product up to a predetermined acceptance level thereby avoiding the risk of cross contamination. This procedure is also applicable for deciding worst case products for performing cleaning validation.

Worst case product: The product selected from group of products that represents a great

risk carry over contamination to other products made in the same equipment by virtue of its solubility, toxicity, dose or a combination of these factors.

4.2 Cleaning Validation Approach:

4.2.1 Method of Calculating Acceptance criteria for residue of Active Ingredient:

4.2.1.1 Criteria no. 1 (Dose criteria): The principle for the requirement is that the standard Therapeutic Daily Dose (TDD) of the next product may be contaminated by no more than a certain proportion (1/1000 part i.e. NMT 0.001 dose) of the TDD of the product investigated in the cleaning validation ("worst product"). This method only applies when the therapeutic daily dose is known. Scientific rationale for above statement is that pharmaceuticals are often considered to be non active at 0.1 of their normally prescribed dosage (1/10th) and the facility is solid dosage manufacturing unit.

4.2.1.2 Criteria no. 2 (ppm criteria): NMT 10 ppm of previous product shall appear in next product. 10 PPM criteria shall be followed until the identification of the worst case product. Scientific rationale of above statement is based on regulations for food industry which provides for maximum permissible limit of certain levels of hazardous substances.

4.2.1.3 Criteria no. 3 (Visually clean criteria): No quantity of residue should be visible on the equipment after cleaning procedure is performed. Scientific rationale of above statement is that the active ingredients in most of the product are visible at approximately 100 µg per 4sq. inch of surface area. Below that level, the residues are not visible human eye considered as acceptable in products that enter human food chain.

4.2.1.4 Criteria no. 4 (Based on Toxicological Data): In cases in which a therapeutic dose is not known (e.g. for detergents/cleaning agents) toxicity data shall be used for calculating MACO.

4.2.1.5 Criteria no. 5 (Health Based Data): In this case, the Maximum Allowable Carryover (MACO) should be based upon Permitted Daily Exposure (PDE). In the health based data criteria, the principle of MACO calculation is based on acceptable carry-over of your previous product, based upon the PDE, into your next product.

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4.2.2 **10 PPM** criteria shall be followed for cleaning validation until the finalization of product matrix and identification of worst case molecule. If the same product is being manufactured in the respective area then the cleaning shall also be verified based on the 10 ppm criteria.

4.2.3 Cleaning validation shall be carried out on the three batches of the identified worst case to evaluate the effectiveness of cleaning procedure.

4.2.4 Bracketing Approach shall be followed identify the worst product from the product matrix and the equipment train.

4.2.5 Grouping of Product/Product Matrix: The product matrix shall be prepared to identify the worst molecule (marker) on which the cleaning validation shall be performed In cases where a highly toxic and less soluble compound is contained in a product, it shall be chosen as marker, although additional markers shall be chosen if they are less soluble than the marker selected based on toxicity.

4.2.6 The 'Worst molecule ' shall be indentified on the basis of following factors:

- Physical characteristic i.e. Solubility
- Toxicity
- Therapeutic Dose of the Product
- Maximum Daily Dose of the Product.
- Batch Size of the Product.
- Concentration of Active Ingredient

4.2.7 On the basis of product matrix Active pharmaceutical substance having low solubility in cleaning media and having more toxicity shall be considered for cleaning validation.

4.2.8 If the solubility and toxicity of two or more molecules are identical then the molecule having more difficulty in cleaning shall be considered for cleaning validation.

4.2.9 In case the multiple batch size of the worst product is being manufactured then the batch in which the API load is more shall be considered in cleaning validation.

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4.2.10 In the setting of acceptance criteria for swab, based on the dose based criteria the minimum daily dose of the product, maximum daily dose of the product, minimum batch size of the product among the all products mentioned in the product matrix shall be selected.

4.2.11 In the setting of acceptance criteria for swab based on the 10 PPM criteria the minimum batch size of the product among the all products mentioned in the product matrix shall be selected.

4.2.12 In the equipment train/matrix the all the equipments shall be considered from which all the products mentioned in the product matrix shall be manufactured in evaluating the total equipment surface area.

4.2.13 Maximum surface area among all the identical equipments (working on same principal) shall be considered in evaluating the total equipment surface area.

4.2.14 The product matrix and equipment train/matrix shall be evaluated after the introduction of new molecule and equipment. If the introduction of new equipment and product shall affect the maximum allowable carry over limit/product then the cleaning validation shall be again performed to evaluate the suitability of existing cleaning procedure. The evaluation shall be carried out based on the SOP of New Product Introduction SOP.

4.2.15 If the cleaning agent is used in the cleaning process then their absence shall be evaluated in the cleaning validation and to assure the effectiveness of cleaning.

4.2.16 Recovery of identified worst molecule shall be carried out on the different material of construction and the recovery results shall be included in the calculation of cleaning validation sample results. Authorized designee of Quality Control shall include the recovery factors during calculation of cleaning validation sample results.

4.2.17 In case the worst case molecule has not going to manufacture for a period and it is evaluated based on 10 ppm criteria then the second worst case shall be considered in the cleaning validation and the cleaning data of the worst case shall be evaluated against the specified limit.

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4.3 Authorized designee of quality assurance shall ensure that the prerequisites for cleaning validation as listed below are available (but not limited to) prior to initiate cleaning validation.

4.3.1 Approved cleaning validation protocol.

4.3.2 Validated analytical method for estimation of previous product in the rinse/swab.

4.3.3 Sampling plan and Sampling Kit.

4.3.4 Cleaning procedure of Equipment. If the Quantity has been quantified in the equipment cleaning SOP then the same shall be challenged in the validation study and deviation from the mentioned quantity shall be recorded if any and if required SOP of the respective equipment shall be revised to introduce the validated quantity. If the quantity has not been mentioned in the SOP then the same shall be mentioned in the respective equipment cleaning SOP.

4.3.5 Swab (Micro and chemical) and rinse collection procedure availability.

4.3.6 Swab and rinse collection location availability.

4.3.7 Criteria and Procedure of Visual verification of Cleaning.

4.3.8 Availibity of the analytical testing procedure of swab/rinse and microbiological testing of cleaning samples to quantify the amount of the residue present in each swab and

4.4 Setting Acceptance Criteria:

4.4.1 Dose Criteria;

As per this criteria not more 0.001 dose of any product shall appear in the maximum daily dose of the next product. The following equation shall be used for the calculation of MACO (Maximum Allowable Carry Over):

Maximum Allowable Carry Over (mg per batch) =TD x SF x BS x 10^6 / MDD

Where,

TD: Single therapeutic dose (smallest strength of product manufactured, in product matrix)
SF: Safety Factor (0.001)
BS: Minimum Batch Size (Kg.) of the product in product matrix
MDD: Maximum Daily Dose; milligram of dosage units of the product per day(in product matrix)
10^6: conversion factor for Kg to mg.

4.4.2 10 PPM (0.001% of the minimum batch size) Criteria;

As per this criterion, not more than 10 ppm of any product will appear in another product. The following equation is used to calculate the limit:

Maximum Allowable Carry Over (mg per batch) = 10×10^{-6} **(mg/mg) X BS in mg**

BS: lowest batch size of the product in mg.

4.4.3 LD_{50} Criteria; In cases where no other data is available (e.g. ADE, OEL) and only LD_{50} data is available (e.g. detergents), the following equation is used to calculate the limit.

NOEL = $LD_{50} \times BW/2000$
Where,
LD_{50}: Lethal Dose 50 in mg/kg animal. The identification of the animal (mouse, rat etc.) and the way of entry (oral etc.) is important (mg/kg)
BW: Is the weight of an average adult (e.g. 70 kg)
2000: 2000 is an empirical constant
Maximum Allowable Carry Over (mg per batch) =NOEL x BS x 10^6 / MDD x SF

Where,

NOEL: No Observed Effect Level (mg/day)
SF: Safety Factor (0.001)
BS: Minimum Batch Size (Kg.) of the product in product matrix
MDD: Maximum Daily Dose; milligram of dosage units of the product per day (in product matrix)
10^6: conversion factor for Kg to mg.

4.4.4 Health Based Criteria (PDE);

PDE: NOEL X BW/F1XF2XF3XF4XF5
Where,
NOEL: No Observed Effect Level (mg/day)
PDE: Permitted Daily Exposure
BW: Is the weight of an average adult (e.g. 70 kg)
F1 = (2-12) a factor for extrapolation between species
F2 = (1-10) to account for variability between individuals
F3= (1-10) variable factor to account for toxicity study
F4= (1-10) factor applied for causes of toxicity
F5= (1-10) factor may be applied if NOAEL is not established
Maximum Allowable Carry Over (mg per batch) =PDE x BS x 10^6 / MDD
Where,
PDE: Permitted Daily Exposure
BS: Minimum Batch Size (Kg.) of the product in product matrix
MDD: Maximum Daily Dose; milligram of dosage units of the product per day (in product matrix)
10^6: conversion factor for Kg to mg.

4.5 Setting Swab Limit: The swab limits shall be established for dose based, 10 ppm, LD_{50} and PDE criteria. In calculating the swab limits MACO obtained based on each criteria shall be used for calculation of swab limits for each criteria (dose based, 10 ppm, LD_{50} and PDE criteria). The Swab limit shall be calculated based on the below mentioned criteria.

Swab Limit (drug in mg per swabbed area) = MACO X SWAB AREA (cm^2)**/TS** (cm^2)

Where, TS: Total product contact surface area

4.6 Setting Rinse Limit: **T**he rinse limits shall be established for dose based, 10 ppm, LD_{50} and PDE criteria. In calculating the rinse limits MACO obtained based on each criteria shall be used for calculation of rinse limits for each criteria (dose based, 10 ppm, LD_{50} and PDE criteria). The rinse limit shall be calculated based on the below mentioned criteria.

Rinse Limit (Drug in mg per liter) = MACO (mg)/ Total Volume of Rinse (liter)

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4.7 The least MACO/Swab and MACO/Rinse obtained from the calculations in each criteria shall be considered as acceptance criteria in cleaning validation studies.

4.8 Acceptance criteria for Microbial contamination:

4.8.1 Total Viable Count shall be NMT 100 CFU/swab. If the estimated value of probable contamination in the next product is within limits of acceptance criteria, then the procedure being followed for cleaning of the equipment shall consider validated otherwise investigation shall be carried out based on the Failure Investigation SOP.

4.9 Hold time of equipment:

The cleaned equipment/Dirty Equipment/Campaign product hold time study shall be carried out based on the criteria specified in the respective study protocol and the hold time period shall be evaluated and specified.

4.10 Revalidation:

Revalidation shall be carried out in following situations:

4.10.1 Equipment changes/modifications which affects the MACO value.

4.10.2 Changes in cleaning procedure

4.10.3 On appearance of new findings based on current knowledge.

4.10.4 Revalidation of cleaning procedure shall be carried out a frequency of 3 years, if worst case molecule remains same during defined period.

4.11 The content of cleaning validation protocol (but not limited to) and report (Specimen Copy) shall be as per Annexure-I;

5.0 TRAINING:

Trainer: Head – Quality Assurance

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Trainees: All Departmental / Sectional Heads

6.0 DISTRIBUTION:

Controlled Copy : Head of Department – Quality Assurance

Original Copy : Quality Assurance

7.0 ANNEXURE(S):

Annexure-I: Format of Cleaning Validation Protocol and Report.

8.0 REFERENCE(S):

EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.

9.0 REVISION HISTORY:

S.No.	Revision No.	Change Control Number	Details of Revision	Reasons(s) for Revision

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ANNEXURE I

SPECIMEN PROTOCOL FOR CLEANING VALIDATION

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