# CLEANING VALIDATION PROTOCOL OF LEVONORGESTREL TABLET 1.5 MG

**Revision Index**

| Revision No. | Effective Date | Reason for Revision |
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| 00 | | First issue |
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| **Document Name:** Cleaning Validation Protocol for Levonorgestrel Tablet 1.5 mg | | |
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| **Revision No:** 00 | **Document Number:** | **Effective Date:** |

**Table of Contents**


| Sr. No. | Contents |
|---|---|
| 1. | Approval signatures |
| 2. | Objective |
| 3. | Scope |
| 4. | Responsibilities |
| 5. | Validation team |
| 6. | Verification of completion of method validation |
| 7. | Training details |
| 8. | Type of cleaning |
| 9. | Equipment details |
| 10. | Product details |
| 11. | Selection of worst case |
| 12. | Cleaning validation strategy |
| 13. | Sampling methods |
| 14. | Sampling locations of equipment |
| 15. | Experimental plan |
| 16. | Sampling procedure |
| 17. | Sampling frequency |
| 18. | Establishment of limit |
| 19. | Recovery study |
| 20. | Clean equipment hold time study |
| 21. | Dirty equipment hold time study |
| 22. | Analytical method |
| 23. | Validation of analytical method |
| 24. | Acceptance criteria |
| 25. | List of deviations |
| 26. | Action to be taken in case of failure |
| 27. | Revalidation criteria |
| 28. | Abbreviation |
| 29. | Enclosed documents |
| 30. | Reference |

## 1.0 APPROVAL SIGNATURES:

| **PREPARED BY** | | | |
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| **DEPARTMENT** | **NAME** | **DESIGNATION** | **SIGNATURE /DATE** |
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## 2.0 OBJECTIVE:

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

## 3.0 SCOPE:

This document is applicable to the equipments used in the Sex Hormone OSD formulation facility of ……., to ensure the validation of equipments cleaning procedure for the removal of contaminants associated with previously product residue, cleaning agents reside as well as control of potential microbial contamination. Cleaning validation shall be carried out initially for at least three, consecutive runs of product and the data obtained will be compared with pre-established acceptance criteria. Clean equipment hold time and dirty equipment hold time study will be performed as per defined procedure.

## 4.0 RESPONSIBILITIES:

Responsibilities of different department/ personnel involved in different activities related to the cleaning validation are defined below:

| Department | Responsibilities |
|---|---|
| **Quality Assurance** | To prepare Cleaning Validation Protocol.<br>To co-ordinate for the preparation of documents & execution of cleaning activities with appropriate individuals and departments.<br>To withdraw swab samples as per sampling plan.<br>To monitor the cleaning validation activity.<br>To review and approve the Protocol to ensure compliance with regulatory and cGMP rules prior to execution.<br>To approve the resolution and the execution of discrepancies.<br>To review and approve the cleaning validation report. |
| **Production** | To ensure availability of personnel to assist in the execution of cleaning validation protocol.<br>To ensure availability of equipments duly qualified for cleaning validation activity. |
| **Engineering** | To ensure availability of facilities and utilities duly qualified for cleaning validation activity. To provide equipment product contact surface area. |
| **Analytical Research & Development** | To provide analytical method and recovery study details to evaluate the efficiency of sampling method. |
| **Quality Control & Microbiology** | To prepare analytical method validation protocol.<br>To carry out the analysis of cleaning validation samples in accordance with protocol. |
| **Regulatory** | To ensure that all processes are carried out in compliance with the regulatory requirements. |

## 5.0 VALIDATION TEAM:

The following personnel will be involved in cleaning validation study.

| Name | Department | Designation |
|---|---|---|
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## 6.0 VERIFICATION OF COMPLETION OF METHOD VALIDATION:

| Sr. No. | Name of Method | Document Number | Effective Date |
|---|---|---|---|
| 1. | | | |
| 2. | | | |
| 3. | | | |
| 4. | | | |
| 5. | | | |
| 6. | | | |

## 7.0 TRAINING DETAILS:

All the operators involved in cleaning operation of equipments shall be appropriately trained as per current version of respective SOP's.
Personnel involved in sampling and testing of samples shall be appropriately trained as per current version of SOP No. ……. Refer **Annexure - 1** for training records.

## 8.0 TYPE OF CLEANING:

Cleaning of equipment is classified as follows:

❖ **Type – A: Batch – to – Batch cleaning (For controlled area equipments only)**
Type –A cleaning shall be performed in following cases:

- During campaign production in between one batch to another batch of same product.
- Changeover for lower strength to higher strength (provided that colour/flavour is same) of the same product.
- After maintenance of non-product contact parts.

*Current version of SOP shall be followed during cleaning.

❖ **Type – B - Product to Product Change over ( For controlled area equipments only)**
Type –B cleaning shall be performed in following cases:

- During changeover of different products with different active ingredients, color, and flavor.
- Changeover for higher strength to lower strength of the different product.
- After maintenance of product contact parts.

*Current version of SOP shall be followed during cleaning.

Cleaning validation shall be applicable for critical cleaning such as cleaning between manufacturing of one product and another, of surfaces that come into contact with products, drug products and API.

Amongst from Type- A and Type-B cleaning, Type B cleaning is one that is employed during product change over, and it will be considered for cleaning validation.
In Type B cleaning procedure, potable water is used for cleaning and purified water BP is used for final rinsing of product contact parts.

The objective of the product change over cleaning is to demonstrate the capability of the cleaning method to remove the product residue and cleaning agents until acceptable levels, and keep the bio-burden within the acceptance criteria, avoiding the contamination of the next product produced in the same line. The equipment shall be cleaned as per respective cleaning SOPs.

The necessity for cleaning validation shall be decided based on a respective risk analysis.

## 9.0 EQUIPMENT DETAILS:

The Equipments list, Equipment ID number, Product contact surface area and cleaning SOP details are given in the **Annexure - 2.**

## 10.0 PRODUCT DETAILS:

The product details such as active ingredients, solubility, strength, batch size, Lowest Recommended Daily Dose (LRDD) and Maximum Recommended Daily Dose (MRDD**)** of the products manufactured in sex hormone facility are given in **Annexure -3.**

## 11.0 SELECTION OF WORST CASE:

Based on the solubility of active material in water, strength and difficult to clean after manufacturing activities, the worst-case product shall be selected as per **Annexure-3.**

Using the therapeutic dose as the basis of limits calculations is appropriate for situations where the material is an active ingredient and therapeutic dosage levels are known. There are other situations, however, where the material is not medically used and there are no known therapeutic dose data available. In these cases, it is necessary to base the limit calculations on the toxicity of the material.

Cleaning procedures for products and processes which are very similar do not need to be individually validated. A validation study of the 'worst case' may be considered acceptable.

When a representative product is chosen, this should be one that is most difficult to clean.

**Selecting the worst-case product:**

For multiproduct equipments, a cleaning validation study shall be performed for worst case product manufactured in any manufacturing sequence. In order to reduce the analytical work load involved in testing all the permutation of sequences, product and equipments shall be grouped in families and worst case shall be selected in each family.

The route of administration of a product may affect the level at which the product is found to be allergenic, toxic or potent.

Selection of worst case related to the product shall be the one that can represent all other products manufactured in the pieces of equipment, using the same cleaning procedure. The solubility of the active ingredients of product in water, or another solvent used for the equipment cleaning, is a critical factor for the ease of cleaning. More insoluble is active ingredient more difficult to get rid of it. Therefore the worst case shall be represented by the product with the insoluble active ingredient.

Based on the worst-case product selection as per **Annexure-3**, set of equipments used for wet granulation process of Levonorgestrel tablets 1.5 mg of Group A is considered for cleaning validation study.

**Selecting the worst case related to equipments:**

The matrix and worst-case approach shall be followed to limit the number of pieces of equipments in the area to be validated for cleaning. Assuming that product contact surfaces are made up of stainless steel and that the similarities exit in the equipments, design, operating principle and size, and in cleaning procedure, a rationale for grouping pieces of equipments and selecting one representative piece for cleaning validation study shall be developed.

The manufacturing equipments shall be grouped to make the cleaning validation study manageable and criteria for equipment grouping are listed below:

1) Identical, interchangeable pieces of equipments with same cleaning procedure can be grouped together.
2) Equipment with same operation principle and same cleaning procedure, but with different product contact surface area, can group if they can be interchanged.
   Since the larger batch is processed in larger equipment group with larger product contact surface area represents the worst case, on which validation study shall be allowed.
3) Also identify potential critical sites or areas where residues are likely to accumulate.
4) An equipment train is generally recognized as a grouping of equipment or systems which function as a unit during the production of a product.
5) The complexity of cleaning validation is directly proportional to complexity of the equipment train.

Refer **Annexure-4** for Equipment grouping.

Equipment grouping is based on the type of manufacturing process used during activity, i.e. wet granulation process (Group A) and dry mixing (Group B) as per **Annexure-4.**

## 12.0 CLEANING VALIDATION STRATEGY:

SOP for equipment cleaning procedure must be in place. Refer **Annexure-2** for cleaning SOP numbers.

Equipments cleaning procedure must be strictly followed as per respective SOP of equipment cleaning.

Procedure for sampling and sampling locations from all cleaned equipments shall be identified.

Personnel involved in the cleaning activities shall be trained. Refer **Annexure-1.**

Recovery studies shall be performed to determine the recovery factor which shall be considered while calculating the acceptable limit for residue.

Validation studies shall be executed according to protocol any deviation from the protocol shall be recorded as per SOP No…….

Operational issues such as the number of products manufactured, the use of campaigns and utilization of equipment and the complexity of the equipment shall be considered during cleaning validation program.

The period and conditions for storage of unclean equipment before cleaning, and the time between cleaning and equipment reuse, should be validated and recorded.

Equipment should be stored in a dry condition after cleaning.

The acceptance limit shall be the most stringent value obtained by any of the 3 criteria i.e. visual cleanliness, 10 ppm criteria and dose criteria.

For calculation of contamination limit in case of 10 ppm criteria and dose criteria, refer **Annexure-5.**

## 13.0 SAMPLING METHODS:

**Selection of Methodology:**

For demonstrating effectiveness of cleaning method, cleaning efficiency can be determined by swab sampling or rinse method.

**Rinse Sampling:**

Rinse water technique is acceptable for the surface, which are inaccessible or for the equipment parts which are not usually removed during the cleaning process. Rinse water sampling shall be performed as per SOP No……..

**Swab sampling:**

Area hardest to clean and which are reasonably accessible can be evaluated for effectiveness of cleaning by swab technique. Additionally, residue that are dried out or are insoluble can be sampled by physical removal. Swab sampling shall be performed as per SOP No…….

**Preparation of swab for chemical analysis:**

Following method is adopted for getting uniform quality of swab of absorbent cotton, which does not make interference during analysis of previous residual active drug.

Approx, 2 gm absorbent cotton shall be taken in 100 ml ethanol in glass beaker, the quality of cotton and ethanol shall be increased proportionately if requirement of swab is more.

Put beaker in ultra- sonic bath for 15 min.

Discard the ethanol from the beaker and remove the ethanol from the cotton by squeezing it then add another fresh 100 ml ethanol in the beaker.

Again repeat the same procedure four times. Thus, we can get cotton for swab, which does not produce more interference during analysis and give reliable absorbency at low detection level. Make the swab sample of approximately 0.2 gm by weight or use readymade Hi-clean swab with polypropylene stick from sampling kit box. After taking the swab sample dip the swab stick in swab solution: 5 ml of acetonitrile & water in ration 1:1 & send to Q.C for analysis.

**Preparation of swab for Microbial contamination:**

For microbial contamination, collect sterile viscous swab dipped in normal saline solution from microbiology departments or use sterile Hiclean swab with polypropylene stick (gamma irradiated) for swabbing.

## 14.0 SAMPLING LOCATIONS OF EQUIPMENT:

The critical points defined, based on the visual inspection considering mainly the possibility of accumulation of residue and the difficulty of cleaning. The critical sampling locations for equipments are mentioned in the **Annexure-6.**

## 15.0 EXPERIMENTAL PLAN:

Equipments shall be cleaned after completion of production run. Equipment shall be cleaned as per current version of respective SOPs using potable water and purified water BP shall be used for final rinsing of product contact parts of equipments. Swab samples shall be taken from the hard to clean surfaces of the equipments immediately after cleaning is completed as per locations mentioned in **Annexure-6.**

Record the results for visual cleanliness of equipments as per **Annexure-7.**

The swab sample shall be analysed for residual drug content based on the previous product manufacturing in that equipments to demonstrate that the cleaning method is effective removing contamination of previous product and achieve desired level of cleanliness.

## 16.0 SAMPLING PROCEDURE:

**Swab sampling procedure for product contamination:**

Production department shall perform cleaning of equipments as per respective SOP's.

After equipment cleaning, QA personnel shall visually inspect the equipments for its cleanliness.

QA person shall take wet swab without touching head of swab from sampling kit and rub over 10 cm X 10 cm area initially vertical fashion without changing the face of swab as shown in the **figure-1** and then turn the swab to other swab and apply it on the area horizontal fashion as shown in the **figure- 1,** covering all the area from hard to clean surface of the equipment as identified in **Annexure – 6.**

Put the swab in glass test tube containing diluents (5 ml of Acetonitrile & water in ratio 1:1) and send to QC for analysis with labelling as per sample locations.

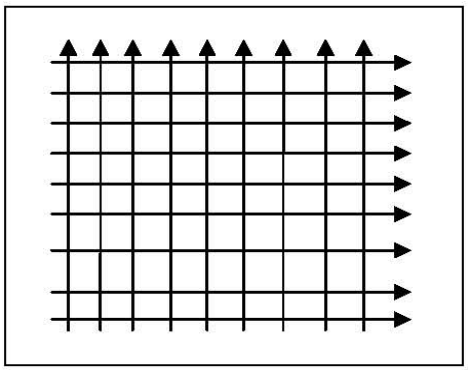
If required, use cleaned stencilled piece of PVC having surface area of 10 cm X 10 cm.

Find out the level of contamination that is present in the swab.

Record the results for residue for previous product per swab of 10 cm X 10 cm as per **Annexure-8.**

Swab is to be taken as shown in the below diagram.

**Figure-1**



**Swab procedure for Microbial contamination:**

Microbiologist shall swab shall an area of 5 cm X 5cm with vertical and horizontal strokes using sterile swab residue rinsed in saline solution as shown in the **figure-1.**

If required, use cleaned stencilled piece of PVC having surface area of 5 cm X 5 cm.

Sample shall be taken from hard to clean surface of the equipments as identified in **Annexure-6.**

The swab shall be transferred to a test tube containing 10 ml sterile saline solution.

Label the tube with location and equipment name and send to the microbiology lab for further testing.

Microbiologist shall perform the analysis as per SOP No. …….

Record the microbial results as per **Annexure-9.**

The acceptable limit for microbial count is NMT 100 CFU/Plate (contact plates having diameter 90 mm). This limit is based on recommendation for areas class D from WHO TRS 961 annexure 6, Table-3. (Recommended limits for microbial contamination).

In case of growing, the type of organism present is determined and the absence of pollution indicator organisms such as, Escherichia coli, *S.abony* (Salmonella), *S.aureus* and *Pseudomonas aeroginosa* shall be demonstrated from all locations monitored. It is necessary, as well, to ensure that high levels of other microbial flora do not mask these organisms.

**Rinse sampling procedure (if applicable).**

Rinse samples shall be taken after final cleaning of the equipments as per their cleaning SOP No…. and once the equipment qualify visual inspection test.

Rinse the whole internal product contact with surface with measured quantity of purified water.

Rinse sample is collected in cleaned 100 ml glass bottle or test tube with stopper from outlet of the equipment.

After collecting rinse sample, put the identification tag on sample bottle or test tube with stopper and send to QC for chemical residue.

## 17.0 SAMPLING FREQUENCY:

Cleaning validation shall be carried out initially for at least three, consecutive run of product and equipments selected by worst case study and report shall be prepared based on result obtained accordingly.

Monitoring of the cleaning validation has to be performed as a part of periodic monitoring.

## 18.0 ESTABLISHMENT OF LIMIT:

Carry–over of product residue should meet define criteria, for example the most stringent of the following three criteria:

**Visual cleanliness:**

Immediately after cleaning, visual inspection of equipments and accessories must be done. The points for visual inspection are described in the **Annexure-7.** Critical points for the visual inspection are based on the possibility of accumulation of residue and the difficulty of cleaning.

No quantity of residue should be visible on the equipments after cleaning procedures are performed.

Spiking studies should determine the concentration at which most active ingredients are visible, but this criterion may not be suitable for high potency, low dose drugs.

**Maximum 10 ppm contamination of the product:**

Maximum 10 ppm level residue contamination of the previous active pharmaceutical in the product is widely accepted in the pharmaceutical industries.

Therefore, the limit of residual contamination or MAR (Maximum Allowable residue) in a swab is calculating using the following formula.

$$\text{MAR / Swab} = \frac{10 \times \text{Min. Batch Size of next product B (kg)} \times \text{Swab surface area (cm}^2\text{)}}{1 \times \text{Total surface area of equipment (cm}^2\text{)}}$$

Example: Following hypothetical case demonstrate calculation of MAR.

Previous Product: A

Next Product: B

Minimum Batch Size Product B is 30 Kg.

Total Surface area of equipments is 850,000 ($cm^2$)

Swab Surface area is 100 ($cm^2$)

Thus, maximum Residual concentration (MAR) of product A in a batch of product B

$$\text{MAR /Swab} = \frac{10 \times 30 \times 100}{1 \times 850{,}000} = 0.0353 \text{ mg /swab} = 35.3 \text{ µg /swab}$$

From the above calculation of worst case 35.3 µg /swab of residual contamination of active drug product can be considered as safe acceptance limit so, by criterion 35.3 µg /swab of residual contamination of active drug product can be finalised as the acceptance criterion for all production.

**Dose Criteria:**

Generally 1/10$^{th}$ of lowest recommended daily dose (LRDD) is considered pharmaceutically ineffective, a factor of 10 was applied to this to built in safety and another factor of 10 was applied to build in robustness in the method (to compensate process and testing variability). Thus 1/1000$^{th}$ of lowest recommended daily dose of previous product in maximum recommended daily dose (MRDD) of next product was accepted as safe limit for residual active drug contamination.

The acceptance criteria of residual active drug contamination shall be established as given below.

PPM is calculated by formula mentioned below.

$$\text{MAR (µg/swab)} = \frac{\text{LRDD of previous product (A) X SBS X SSA X 1000 X 1000 X 1000}}{\text{1000 X MRDD of next product (B) X TSA}}$$

Where:

LRDD: Lowest Recommended Daily Dose (mg)

MRDD: Maximum Recommended Daily Dose (mg)

SBS: Smallest Batch Size of next Product (kg)

SSA: Swab Surface Area ($cm^2$)

TSA: Total Surface area of equipments (product contact part) ($cm^2$)

**Example:** Following hypothetical case demonstrate calculation of MAR.

Previous Product: A

Next product: B

LRDD of product A is 1mg/day

MRDD of product B is 300 mg/day

Minimum batch size of product B is 3.0 kg

TSA if equipment is 850,000 $cm^2$

Swab Surface Area is 100 $cm^2$

Thus, Maximum Allowable Residual Concentration (MAR) of Product A in a batch of Product B

$$MAR\ (\mu g/swab) = \frac{1 \times 3{,}000{,}000 \times 100 \times 1000}{1{,}000 \times 300 \times 850{,}000} = 1.18\ \mu g/swab$$

Thus the limit of residual contamination is 1.18µg/swab.

For certain allergic ingredients, penicillin, cephalosporin or other potent steroid and cytotoxic, and limit should be below the limit of detection by best available analytical methods.

## 19.0 RECOVERY STUDY:

Recovery study for active pharmaceutical ingredients shall be conducted as per swab testing method at time of validation. Refer **Analytical Method Validation Document No. ……..** for recovery study details.

Recovery percentage should not be less than 75 % of sprayed concentration for all products.

## 20.0 CLEAN EQUIPMENT HOLD TIME STUDY:

**Objective:**

The objective for establishing time limit between equipment cleaning and reuse is to ensure that the equipment remain clean till the next use. Clean equipment hold time study sometimes called expiry period of cleaned equipment. This needs demonstration that microbial proliferation is within acceptable level in cleaned equipments during storage. Time limit depends on: -

- Level of protection provided to the equipment after cleaning.
- Environment control and work practices.
- Nature of product to be manufactured by using the subjected equipments.

**Procedure:**

This study shall be performed after the completion of the last cleaning validation cycle.

Clean the equipment as per respective cleaning SOP and cleaned equipments shall be kept at designated place and with required class of cleaning.

Zero time swab sample shall be taken as per surface swab sampling procedure specified in the **Annexure- 6.**

The equipment shall be closed and kept in prescribed environmental condition at designated place.

Swab samples shall be collected at 24 hrs, 48 hrs and 72 hrs intervals for bio-burden determination according to the sampling plan described in the **Annexure-6.**

**Swab sampling Procedure:**

Swab sample shall be collected from the pre determined measured surface area of the equipments as mentioned in **Annexure- 6** these areas shall not same as that used for chemical testing.

Microbiologist shall swab an area of 25 cm2 with straight strokes using sterile swab residue in saline solution.

The swab shall be kept in a test tube containing 10 ml saline solution.

The test tube is identified with location and equipment name and send to microbiology lab for microbial testing.

Record the result for hold time study of clean equipments as per **Annexure 9 & Annexure 10.**

## 21.0 DIRTY EQUIPMENT HOLD TIME STUDY:

All the product manufactured in the sex hormone OSD facility are potent. So, it is recommended that cleaning of equipment must be immediately done after completion of batches. Equipment should not be hold in dirty condition for safety reason as hormonal product are being potent & sensitive. Cleaned equipment study will be performed up to 72 hours and observation will be compiled in respective annexure-10.

## 22.0 ANALYTICAL METHOD:

Analytical method shall be validated to detect the lowest possible concentration of the drug so that the minimum limit of detection shall be less than the acceptance limit of that product in cleaning validation.

## 23.0 VALIDATION OF ANALYTICAL METHOD:

The analytical method shall be for the analytical performance parameter viz precision, specificity, solubility stability, Accuracy, linearity & range, limit of detection and limit of quantification, spike recovery study and responsibility. Reagent instruments and accessories require for analytical procedure and calculation shall be mentioned in protocol & report**.**

## 24.0 ACCEPTANCE CRITERIA:

| S.No. | Selection criteria | Acceptance criteria |
|---|---|---|
| 1. | Visual cleanliness | Equipments must be visibly free from particles on the surfaces. |
| 2. | Previous product residue contamination | 10 ppm criteria<br>Dose criteria |
| 3. | Microbial contamination | Pathogens should be absent.<br>Total aerobic bacterial count NMT 100 cfu/swab. (contact plates having diameter 90 mm)<br>Yeast, mould and pathogens shall be absent. |

## 25.0 LIST OF DEVIATIONS:

Any deviation occurring during the activity shall be recorded and assessed whether it has any GMP criticality. GMP non-critical deviations can be justified whereas GMP critical deviation may require investigation and corrective actions. Appropriate justification, investigation, corrective action and verification of effectiveness of corrective action shall be recorded as per SOP No……...

Refer **Annexure-11** for List of deviations.

## 26.0 ACTION TO BE TAKEN IN CASE OF FAILURE:

In case of failure to demonstrate values as calculated for the contamination limit, an investigation into the cause of failure should be conducted jointly by Production, Engineering, and Quality Assurance and Quality Control department.

After elevating the investigation consideration shall be given such as improving the cleaning procedure and revalidation should be considered as per the attached summary sheet.

## 27.0 REVALIDATION CRITERIA:

Revalidation of cleaning procedure shall be carried out in case of following conditions:

1) If solubility of new product being added is less than the previously considered worst case product.
2) If the new product carry over limit is above the previously determined residue carry over limit.
3) Introduction of new molecule.
4) Change in production equipments or any major modification of equipment, which has significant effect on the contact surface area.
5) Change in cleaning procedure, cleaning instructions (SOP) and/or cleaning agent.
6) Failure during routine monitoring.
7) Change in sampling, analytical or microbiological methods

## 28.0 ABBREVIATION:

| **Abbreviation** | **Definition** |
|---|---|
| QA | Quality assurance |
| QC | Quality control |
| OSD | Oral solid dosage form |
| ID | Identification |
| SOP | Standard operating procedure |
| ppm | Parts per million |
| CFU | Colony forming unit |
| mg | Milligrams |
| gm | Grams |
| ml | Millilitre |

## 29.0 ENCLOSED DOCUMENTS:

| Annexure | Title of annexure |
|---|---|
| 1. | Training record |
| 2. | Equipment details |
| 3. | Product details |
| 4. | Equipment grouping |
| 5. | Calculation of contamination limit |
| 6. | Swab sampling locations of equipments |
| 7. | Visual inspection results |
| 8. | Chemical & instrumental analytical results |
| 9. | Microbiological results |
| 10. | Clean equipment hold time results |
| 11. | List of deviations |
| 12. | Material safety data sheets |
| 13. | Summary Sheet |

## 30.0 REFERENCE:

WHO *Technical Report Series TRS 937, Annexure 4, Appendix3.*

WHO *Technical Report Series TRS 961 Annexure 6.*

FDA, Guide to Inspections of Validation of Cleaning Processes, 1993.

MHRA Guideline.

Pharmaceutical Inspection Convention, Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation and Cleaning Validation, PI 006-3 2007.

PDA Technical Report No.29.