# PROTOCOL FOR DETERMINATION

# OF

# VISUAL RESIDUE LIMIT

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## 1. OVERVIEW:

### 1.1 Introduction:

The determination of visual residue limit shall be performed on a range of different material surfaces defined in the **SOP Determination of Visual residue limit.**

During this study a surface of test material (coupon) shall be spiked with Blank, Positive and Test solution. The Minimum amount of the residue detected by the Master and all observers shall be considered as Visual Residue Limit for that API.

### 1.2 Objective:

The objective of this protocol is to determine the visual residue limit on a range of different material surfaces typically found in pharmaceutical manufacturing.

### 1.3 Scope:

This document is applicable for determination of visual residue limit for different material surfaces being used in the product contact surfaces in the facility.

### 1.4 Responsibility:

To conduct the visual residue limit study for test coupons team shall be formed. The team shall contain the members from the Quality Control, Engineering, Production and Quality Assurance Departments. The Validation team is described through the following responsibility:

| | |
|---|---|
| Quality Assurance | To prepare the protocol & report |
| | To provide the training |
| | To execute & supervise the study |
| Quality Control, Engineering, Production and Quality Assurance | To review the protocol |
| | To conduct the study |
| | To collect and analyze samples |
| Corporate Quality Assurance | To review validation protocol |
| | To review validation report |
| QA Head | To approve validation protocol |
| | To approve validation report |

## 2. EXECUTION TEAM:

Following personnel shall be responsible for the execution of qualification study;

| | | |
|---|---|---|
| Quality Control | : | To collect the sample and conduct the study as per protocol. |
| Engineering | : | To provide utility for testing. |
| Quality Assurance | : | To review & monitor the study and compile and prepare VRL study report. |

## 3. TRAINING RECORDS:

**3.1 Purpose:**

The purpose of the training is to familiarize the trainees with the requirement of visual residue limit study.

**3.2 Scope:**

This training is applicable to the all concerned persons which are involved in the visual residue limit study.

**3.3 Topics:**

The following topics shall be covered during training:

3.3.1 Purpose & procedure of visual residue limit study.

3.3.2 Identifying the responsibility of involved person.

3.3.3 Documentation practices to be followed.

3.3.4 General precautions / guidelines to be followed during visual residue limit study.

## 4. REQUIREMENT FOR PERFORM THE STUDY:

Following items shall be required for the execution of visual residue limit study:

**4.1** The coupons of different product contact materials (SS316, Teflon, Acrylic, Silicon etc.) should be available in the laboratory.

**4.2** Representative of Typical manufacturing area with ambient lighting of >400 Lux.

**4.3** Test sample solution of worst case for the study product (as mentioned in Table-1).

**Table -1**

| S.No. | API | Solubility |
|---|---|---|
| 1. | Imipenem | Sparingly soluble in water |
| 2. | Meropenem | Sparingly soluble in water |
| 3. | Ertapenem Monosodium | Freely soluble in water |

**4.4** Selection of Masters and Observers as per **Format – 1 "List of masters and observers required for inspection of visual residue."**

## 5. SYSTEM / EQUIPMENT DESCRIPTION:

Nil

## 6. QUALIFICATION PROCEDURE OR METHODOLOGY:

### 6.1 General Recording Instructions:

6.1.1 Read the contents of the document thoroughly before proceeding for execution of the activity (in case of doubts / contradictions / contact the reviewers/ approver of the document for clarifications).

6.1.2 Recording of all the observations and data shall be as per SOP **Good Documentation Practices.**

6.1.3 Recording will be done on format of the approved protocol.

### 6.2 General Safety Instruction for Execution:

Safety shall be one of the key considerations during the execution of this document. The following guidelines shall be observed during the execution stage:

6.2.1 All personnel involved with the execution shall identify hazards associated with performance of testing and precautions to be taken.

6.2.2 All personnel involved with the execution shall check that utilities are safely isolated when energizing or de-energizing.

6.2.3 All personnel involved in the execution shall inform the company management any hazard, to themselves or others, associated with the materials, equipment, method of working and the precautions to be taken.

### 6.3 Procedure for Visual Residue Limit Study:

6.3.1 The determination of visual residue limit study shall be executed by simulating the actual conditions by applying the artificial soiling of coupons for dirtying them.

6.3.2 Study shall be performed for existing worst case active pharmaceutical ingredient.

6.3.3 Study shall be perform on material surface area is greater than 5% of the total product contact surface.

6.3.4 A starting coverage of 400µg/$dm^2$ or approximately 4µg/$cm^2$ shall be used or shall be decided based on the characteristics of API.

6.3.5 The spike solution concentration shall be in increasing order on every coupon in a stepwise fashion.

6.3.6 The study shall involve preparation of coupons as Blank, Positive & Test coupon having same material of construction as that of the product contact.

6.3.7 The minimum concentration of the residue detected by the master and all observers shall be considered as visual residual limit for the API.

6.3.8 **Preparation of Stock solution (400ppm):**

Weigh and transfer 100mg of required API into a 250ml volumetric flask, add 100ml of water for injection (WFI) and sonicate to dissolve. Make up to the volume with water for injection (WFI) and mix.

6.3.9 **Preparation of spiking solution:**

6.3.9.1 **50 ppm Solution:** Take 2.5ml of above stock solution in 20ml volumetric flask; add 5ml of water for injection (WFI) and mix. Make up to the volume with water for injection (WFI) and mix. Take 1 ml of this solution in to the coupon.

6.3.9.2 **100 ppm Solution:** Take 5.0ml of above stock solution in 20ml volumetric flask; add 5ml of water for injection (WFI) and mix. Make up to the volume with water for injection (WFI) and mix. Take 1 ml of this solution in to the coupon.

6.3.9.3 **200 ppm Solution:** Take 10.0ml of above stock solution in 20ml volumetric flask; add 5ml of water for injection (WFI) and mix. Make up to the volume with water for injection (WFI) and mix. Take 1 ml of this solution in to the coupon.

6.3.9.4 **300 ppm Solution:** Take 15.0ml of above stock solution in 20ml volumetric flask; add 5ml of water for injection (WFI) and mix. Make up to the volume with water for injection (WFI) and mix. Take 1 ml of this solution in to the coupon.

**Note: In same manner prepare required concentration as per above mention.**

6.3.9.5 If the Solution spiked residues on the coupons is not visible to master and observers then the spike solution concentration shall be in increased on every coupon.

6.3.9.6 The solution of each concentration shall be applied evenly on to 10 x 10 $cm^2$ flat coupons of the various materials of construction.

6.3.10 **Preparation of the coupons:**

6.3.10.1 **Blank coupons:**

Blank shall be prepared with spiking the solution of dissolving medium (without API) and air dry naturally. Blank shall be prepared for each type surface.

6.3.10.2 **Positive coupons:**

Spike the same concentration of test solution on plate; dry the plate in the oven at temperature of about 40° C.

6.3.10.3 **Test coupons:**

A starting coverage of 400 µg/$dm^2$ shall be used (Fourman and Mullen described a VRL at approximately 4 µg/$cm^2$) or shall be decided based on the characteristics of API. The solutions of each concentration shall be applied evenly onto to 10x10$cm^2$ coupons of the various materials of construction. Each plate (coupons) shall be left to air dry naturally before visual examination.

6.3.10.4 Solution of API to be tested shall be preferably prepared by dissolving in solvents (if compatible), the solvent shall leave no residue and dries to a more even coverage, with minimal sample rings.

6.3.11 **Testing Procedure:**

6.3.11.1 After drying of coupons, master shall inspect the each coupon (Blank, Positive and Test) independently from a distance of 6, 20, 30 and 50 inches and shall also view the same coupons from an angle of approximately 30° and 60° from the surface and record the observations in the respective **Format - 2** "Recording the visual inspection observation on different coupons)".

☞ *Visual inspection observation shall be reported for all the above mentioned observing distance with its view angle.*

6.3.11.2 Finally each observer shall inspect each plate (Coupon) independently as per the procedure.

6.3.11.3 Visual inspection shall be carried out with ambient lighting of >400 Lux to minimize any variability due to lighting conditions.

6.3.11.4 Similarly, if the API is too dense, the study shall be repeated to decrease the concentration of API on every coupon in a stepwise fashion until it is visually undetected.

6.3.11.5 The observations of Test coupons shall be compared with Blank and Positive Coupons. Results from the inspections of the coupons shall be summarized in the study report.

☞ *During the course of inspection the coupons shall be protected from any possible air current.*

6.3.12 **Disqualification of observer from visual inspection:**

6.3.11.1 If the residue cannot be detected by any of observer, but it is detected by the Master, the observation shall be recorded and re-training shall be conducted.

6.3.11.2 After the retraining, re-inspection of same plates shall be performed. If the observer is unable to detect residue they should be disqualified from qualified visual inspector list.

6.3.11.3 Residue detected by the master must be detected by the observers also.

## 7. ACCEPTANCE CRITERIA:

**7.1** The Minimum amount of the residue detected by the Master and all observers shall be considered as Visual Residue Limit for that API.

**7.2** The residue on the coupons should be visually identified by all inspectors in the all conditions.

## 8. REVALIDATION CRITERIA:

**8.1** All the personnel shall be qualified before awarding as the Master and Observer inspector.

**8.2** If the residue cannot be detected by any of observer, but is detected by the Master, the observation shall be recorded and re-training shall be conducted.

## 9. OBSERVED DEVIATION (IF ANY):

**9.1** The deviation/ discrepancy shall be addressed as per the **SOP**: Reporting and Monitoring of Process Non-Conformance in the Automated Quality Management System Software.

## 10. QUALIFICATION/STUDY REPORT:

**10.1** The validation report shall consist of a summary document, in narrative form, which shall briefly describe the activity performed along with the observations recorded in relevant attachments.

## 11. ABBREVIATIONS/GLOSSARY:

| | | | |
|---|---|---|---|
| **11.1** | QA | : | Quality Assurance |
| **11.2** | NA | : | Not Applicable |
| **11.3** | SOP | : | Standard Operating Procedure |
| **11.4** | CQA | : | Corporate Quality Assurance |
| **11.5** | CP | : | Common Procedure |
| **11.6** | VRL | : | Visual Residue Limit |
| **11.7** | API | : | Active Pharmaceutical Ingredients. |
| **11.8** | PPM | : | Parts Per Million |
| **11.9** | WFI | : | Water For Injection |
| **11.10** | SS | : | Stainless Steel |

## 12. LIST OF FORMATS :

| Format No. | Format Title |
|---|---|
| **1** | List of masters and observers required for inspection of visual residue. |
| **2** | Recording the visual inspection observation on different coupons. |

### 12.1 Format – 1: List of Masters and Observers Required for Inspection of Visual Residue

**a) LIST OF MASTERS:**

| S.No. | Master Name | Designation | Department | Sign& date |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |
| | | | | |

**b) LIST OF OBSERVERS:**

| S.No. | Observer Name | Designation | Department | Sign& date |
|---|---|---|---|---|
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

Approved By (Name & Sign/Date):

**(QA Head or Designee)**

**12.2 Format – 2:**

**Recording the visual inspection observation on different coupons**

**Product details** :

**Coupon Details** :

**Spiking solution used**:

**Lux Meter ID:** **Observation in Lux:** **(Limit: >400Lux)**

**Master & Observer Details**:

| Master | Name | Designation | Department | Sign& date |
|---|---|---|---|---|
| Master-1 | | | | |

| Observer | Name | Designation | Department | Sign& date |
|---|---|---|---|---|
| Observer-1 | | | | |
| Observer-2 | | | | |
| Observer-3 | | | | |
| Observer-4 | | | | |

**Recording the observation:**

| Distance (In Inches) | Angle (°) | Master | Observer-1 | Observer-2 | Observer-3 | Observer-4 |
|---|---|---|---|---|---|---|
| 6 | 30 | | | | | |
| 20 | | | | | | |
| 30 | | | | | | |
| 50 | | | | | | |
| 6 | 60 | | | | | |
| 20 | | | | | | |
| 30 | | | | | | |
| 50 | | | | | | |

**Remarks:**

| | |
|---|---|
| **Checked by (Sign / Date)** | **Reviewed by (Sign / Date)** |

## 13. REFERENCE DOOCUMENT (IF ANY):

**13.1** SOP: Determination of Visual Residue Limit.

**13.2** QUALITY POLICY: Cleaning Validation.

**13.3** SOP: Preparation of Validation and Qualification Protocol and Its Control

**13.4** SOP: Management of Validation/Qualification documents in DMS.

**13.5** SOP: Management of Formats in DMS.

## 14. REVISION HISTORY:

| Superseded Protocol | | S. No. | Step No. | Changes Made |
|---|---|---|---|---|
| Protocol No. / Version No. | Effective Date | | | |
| NA | NA | Change Control No.: …….. | | |
| | | 1 | NA | New Protocol |