# PROCESS VALIDATION PROTOCOL

# PRODUCT NAME

# LENALIDOMIDE CAPSULES 10 MG

# STANDARD BATCH SIZE

# 100000 CAPSULES

# PROTOCOL NO.

# LD/PVP/004-00

## Table of Contents

## 1. Approval Sheet

**Protocol Prepared By**

| Name | Designation | Signature | Date |
|---|---|---|---|
| Sachin Kuma | Sr. Officer QA | | 03/04/2024 |

**Protocol Checked By**

| Name | Designation | Signature | Date |
|---|---|---|---|
| Cajesh Kum. | Sr. Executive. | | 03/04/2024 |
| Ajay Bhatia | Sr. Officer QC | | 03/04/2024 |

**Protocol Approved By**

| Name | Designation | Signature | Date |
|---|---|---|---|
| N.P Mushran. | Head QA. | | 03/04/2024 |

**2. Introduction:**

Three consecutive batches taken for process validation of **Lenalidomide Capsules 10 mg**. If failure in any circumstances further three batches validated till result of all three batches consistent and complying the acceptance criteria.

**3. Objective:**

The document evidence to provide a high degree of assurance that the manufacturing process of **Lenalidomide Capsules 10 mg** will produce the product meeting its predetermined specification and quality attributes.

**4. Scope:**

This validation carried out for **Lenalidomide Capsules 10 mg** by monitoring all critical parameters during manufacturing that have impact on product quality.

**5. Revalidation:**

The manufacturing process is subjected to revalidation when following changes occur.

1. When change in quantity and change in Excipients
2. Change in master formula.
3. Change in manufacturing process.
4. Change in equipment and machinery.
5. Change in vendor of Raw material.

**6. Validation team:**

Following validation team is responsible for carried out process validation.

| Sr. No. | Designation | Department | Responsibility |
|---|---|---|---|
| 1. | IPQA | Quality Assurance | Sampling of sample as per sampling plan |
| 2. | Maintenance Head | Maintenance | For smooth working of utilities |
| 3. | Sr. Executive QA | Quality Assurance | To prepare process validation protocol and Report |
| 4. | Production Manager | Production Manager | Overall responsible for checking & implementation of process validation |
| 5. | QC Executive/ Manager | Quality Control | To analyze all the sample drawn at different stages during process validation |
| 6. | QA Head | Quality Assurance | Overall responsible for compliance of Process Validation |
| 7 | Quality Head | Quality Assurance | Responsible for approval of Process Validation Protocol & report |

**7. Product & Batch Detail:**

Process Validation of **Lenalidomide Capsules 10 mg** shall be carried out on any three consecutive batches. The details are as under:

**Product/ Generic Name** : Lenalidomide Capsules 10 mg

**Strength** : 10 mg per capsules

**Product Code** : LD/003

**Batch Size** : 500 Capsules

**Dosage Form** : Hard gelatin capsule for oral use only

**Overage** : 2 %

**Composition** : Each hard gelatin capsule contains:

Lenalidomide 10 mg
Excipients q.s
Approved colour used in empty capsule shell

**Packing Detail** : white to off white colour granular powder filled in size "2" hard gelatin capsule having yellow body & yellow cap. Such 30 capsule packed in 30 ml HDPE bottle

**Storage Condition** : Store between 15˚C to 30˚C. Protect from light & moisture.

**Batch Detail for validation**

3 consecutive batches are selected

| Sr. No. | Batch No. | Batch Size | Batch Manufacturing Date | Mfg. Date | Exp. Date |
|---|---|---|---|---|---|
| 1. | OC0079 | 100000 Capsules | 03/04/2024 | 04/2024 | 03/2027 |
| 2. | OC0080 | 100000 Capsules | 05/04/2024 | 04/2024 | 03/2027 |
| 3. | OC0081 | 100000 Capsules | 07/04/2024 | 04/2024 | 03/2027 |

## 8. Equipment and machinery List

| Sr. No. | Name of equipment / instruments | ID No. |
|---|---|---|
| 1. | Granulation Isolator | KPL/CT/001 |
| 2. | Automatic Capsule Filling Machine with line machine | KPL/CT/003 |
| 3. | Blister Packing | KPL/CT/004 |
| 4. | Octagonal Blender | KPL/CT/008 |
| 5. | Octagonal Blender | KPL/CT/009 |
| 6. | Starch Paste Kettle | KPL/CT/010 |
| 7. | Vibro shifter | KPL/CT/011 |
| 8. | Rapid Mixer Granulator | KPL/CT/012 |
| 9. | Fluid bed dryer | KPL/CT/013 |
| 10. | Cone mill | KPL/CT/014 |
| 11. | Colloid mill | KPL/CT/015 |
| 12. | Metal detector | KPL/CT/016 |
| 13. | Electronic Weighing Balance | KPL/CT/017 |
| 14. | Electronic Weighing Balance | KPL/CT/018 |
| 15. | Electronic Weighing Balance | KPL/CT/019 |
| 16. | Electronic Weighing Balance | KPL/CT/022 |
| 17. | Fogger | KPL/CT/023 |
| 18. | Leak Test | KPL/CT/024 |
| 19. | Electronic Weighing Balance | KPL/CT/026 |
| 20. | Electronic Weighing Balance | KPL/CT/027 |

**9. Batch Weighing Sheet:**

**Batch Size:** 500 Capsules

| Sr. No | Name of Ingredient | Spec. | Qty per capsule (in mg) | Overage (%) | Qty for batch 1.0 Lac (in Kg) |
|---|---|---|---|---|---|
| 1 | Lenalidomide | IHS | 10.000 | 2% | 1.0400 kg |
| 2 | Croscarmellose Sodium | BP | 12.500 | Nil | 1.250 kg |
| 3 | Microcrystalline cellulose-102 | BP | 80.000 | Nil | 8.000 kg |
| 4 | Lactose | BP | 173.550 | Nil | 17.3550 kg |
| 5 | PVK K-30 | BP | 2.850 | Nil | 0.285 kg |
| 6 | Isopropyl Alcohol IPA | BP | 50.000 | Nil | 5.000 kg |
| 7 | Talcum | BP | 2.850 | Nil | 0.285 kg |
| 8 | Magnesium Stearate | BP | 2.850 | Nil | 0.285 kg |
| 9 | Empty hard gelatin Capsule shell size # 2 having yellow body and yellow Cap. | IHS | 1NOS | Nil | 102000 Nos. |

**Average Fill Content of Capsules:** 285 mg ±10 %

**Average Fill Content of 20 Capsules:** 5.7 gm ± 2 %

**Average Weight of Capsule:** 347 mg ± 10 %
(Filled Weight + Empty Capsule)

**10. Approved Raw and Packing Material:**

The raw or packing material uses in manufacturing process are from approved vendor.

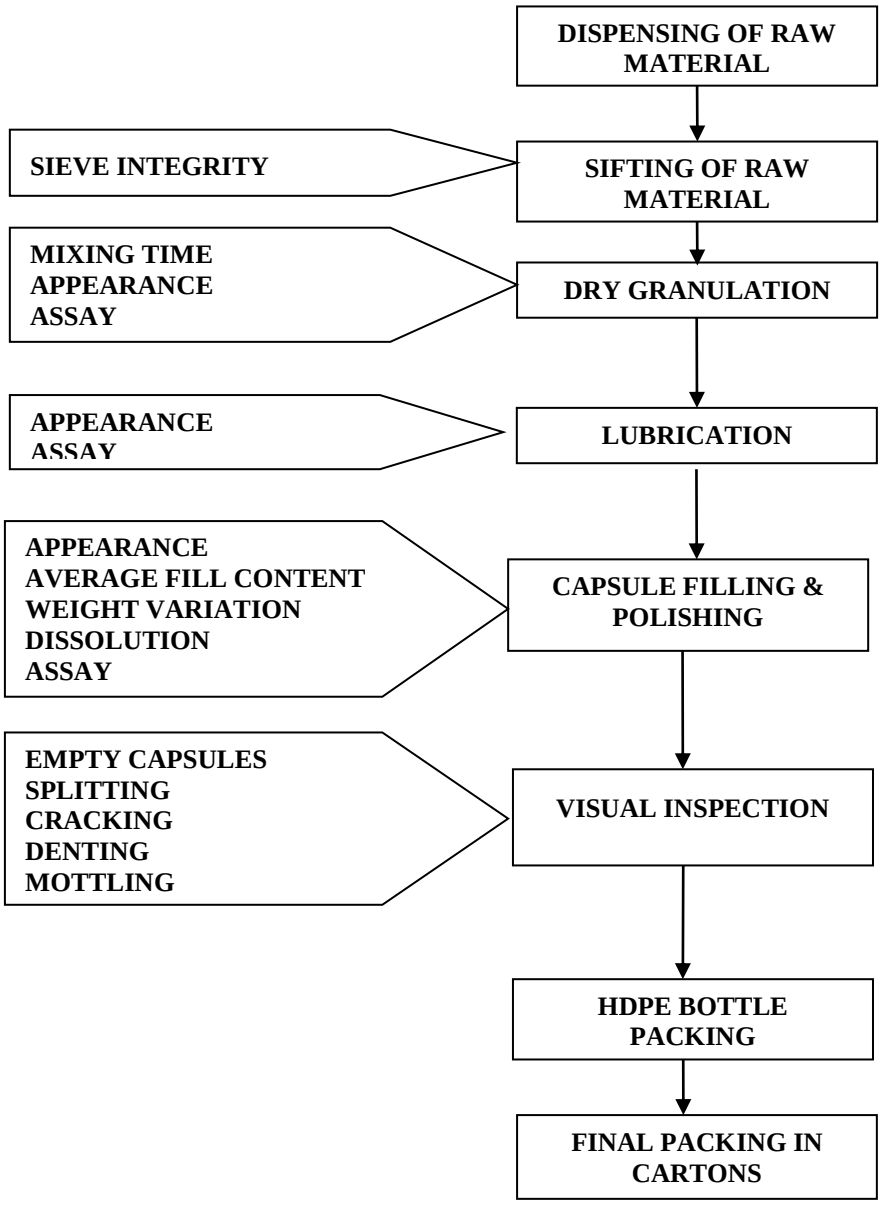
**Raw Material:**

| Raw Material | Spec. | Vendor |
|---|---|---|
| Lenalidomide | IHS | Adley Lab Limited |
| Croscarmellose Sodium | BP | Avon Pharma Chemicals |
| Microcrystalline cellulose- 102 | BP | Himanshu Traders |
| Lactose | BP | Avon Pharma Chemicals |
| PVP K-30 | BP | Anand Lathiya |
| Isopropyl Alcohol IPA | BP | Avon Pharma Chemicals |
| Talcum | BP | Neelkanth Minechem |
| Magnesium Stearate | BP | Zacfa Chemicals |

**Packing Material:**

| Packing Material | Spec. | Vendor |
|---|---|---|
| 30 ml Flat HDPE Bottle | IHS | Preet Plastics, INDIA |
| Printed Sticker Label | IHS | Arihant Labels |
| Printed Laminated Carton | IHS | Sain Packaging Pvt. Ltd. |

## 11. PROCESS FLOW DIAGRAM



**12. Manufacturing Process**

Check the Equipment for Cleanliness prior to use before manufacturing process and check the status label displayed. Take line clearance from IPQA for cleanliness

**12.1 Sifting:**

Sifting process carried out to obtain granules of uniform size and to remove extrinsic particles and this having impact on flow and filling and other physical properties of Capsules.

Sift the raw material as per the sieves size mentioned below

| Sr. No | Raw Material | Sieve Size |
|---|---|---|
| 1. | Lenalidomide | 60 # |
| 2. | Croscarmellose Sodium | 60 # |
| 3. | Microcrystalline cellulose-102 | 40 # |
| 4. | Lactose | 40 # |
| 5. | PVK K-30 | 40 # |
| 6. | Isopropyl Alcohol IPA | 40 # |
| 7. | Talcum | 40 # |
| 8. | Magnesium Stearate | 40 # |

Check the integrity and cleanliness of sieves before and after sifting process.

| Sr. No | Sieve No | Check Sieve Integrity before Sifting | Checked by | | Check Sieve Integrity after Sifting | Checked by | |
|---|---|---|---|---|---|---|---|
| | | | Production | QA | | Production | QA |
| 1. | 40 # | | | | | | |
| 2. | 60 # | | | | | | |

**12.2 Dry Mixing:**

1. Transfer Lenalidomide, Microcrystalline Cellulose into blender and mix for 10 min.

2. Transfer the Croscarmellose Sodium, Lactose and PVPK-30 & Talcum in step 1. And mix for specified time and visually examined the ingredients; it should be uniformally mixed and dense

| Sr. No | Mixing Time (minutes) |
|---|---|
| 1. | 5 Minutes |
| 2. | 10 minutes |
| 3. | 15 minutes |

IPQA personal shall draw 1.0 gm of Samples each at different mixing time and send to Quality Control Department for Analysis

**12.3 Lubrication:**

Unload the previously mixed granules in Double cone blender and add magnesium Stearate. Mix the whole blend for specified time & visually examine the blend; the blend should be properly mixed and uniformally dense.

| Sr. No | Mixing Time (minutes) |
|---|---|
| 1. | 3 minutes |
| 2. | 5 minutes |

IPQA personal shall draw 1.0 gm of Samples each at different mixing time and send to Quality Control Department for Analysis.

Unload the blend sample in a double lined polythene bag placed in HDPE drum, close the polythene tightly and transfer the bulk to Capsule filling area.

**13. Filling & Polishing:**

Take line clearance from IPQA for cleanliness of area and equipment. Record the temperature and humidity of the Capsule Filling Area

Assemble the capsule filling machine and put the blend in the hopper and run the capsule filling machine at different speed and check the physical parameter. Discard the capsules obtained during trial run.

| Sr. No | Speed |
|---|---|
| 1. | Minimum Speed |
| 2. | Optimum Speed |
| 3. | Maximum Speed |

Inform IPQA personal for sampling of Filled capsules.

IPQA personnel shall draw sample of Filled Capsules at minimum speed, optimum speed & maximum speed and send to Quality Control Department for Analysis.

Load the filled capsule in the polishing machine to remove the debris of powder sticking with the capsule

**14. Visual Inspection**

Visual inspection helps to remove the physical defects of the capsules, thus ensure appearance quality of Capsules.

Inspect the filled and polished capsules for any defects.

| Sr. No | Physical Defects/Rejections |
|---|---|
| 1. | Empty Capsules |
| 2. | Splitting |
| 3. | Cracking |
| 4. | Denting |
| 5. | Mottling |

**15. Sampling Plan:**

| S. No. | Stage | Sampling time / Qty. | Test / Process parameters |
|---|---|---|---|
| 1 | Mixing | After Mixing of<br>5 minute<br>10 minute<br>15 minute<br>Sample quantity approx. 1.0 gm for each sample | Appearance<br>Assay |
| 2 | Lubrication | After Mixing of<br>3 minute<br>5 minute<br>Sample quantity approx. 1.0 gm for each sample | Appearance<br>Assay |
| 3 | Capsule Filling & Polishing | Speed:<br>Minimum Speed<br>Optimum Speed<br>Maximum Speed<br>Sample quantity approx. 20 capsule | Description / Appearance<br>Average Fill Weight of capsule<br>Uniformity of weight/Content<br>DT / Dissolution<br>Assay |
| 4. | Visual Inspection | At different speed of capsule filling machine | Empty Capsules<br>Splitting<br>Cracking<br>Denting<br>Mottling |
| 5. | Packing | Cleanliness of bottle<br>Extrinsic particles (Dust or black particles)<br>Leak test | Should be clean and dry<br>Should be free from extrinsic particles<br>Should be comply |

**16. Acceptance Criteria**

| Stage | Test / Process Parameter | Acceptance Criteria |
|---|---|---|
| Dry Mixing | Appearance | When observed visually material should appear uniform and dense. |
| | Assay | 90.0 % to 110 % |
| Lubrication | Appearance | When observed visually material should appear uniform and dense |
| | Assay | 90.0 % to 110 % |
| Filling & Polishing | Appearance | white to Off white colour granular powder filled in size "2" hard gelatin capsule having yellow body & yellow cap |
| | Average fill content | 285 mg ± 10 % (256.5 mg to 315.5 mg) |
| | Average weight of filled capsule | 347 mg ± 10 % (312.3 mg to 381.7 mg) |
| | Uniformity of dosage Units (By Weight Variation) | Not more than two of the individual weights deviate from the average weight by more than the 10 percent and none should deviate more than 20 % |
| | Dissolution | Not Less Than 75 % (Q) of Lenalidomide dissolved in 45 minutes |
| | Assay | 90 % to 110 % |
| Visual Inspection | Empty Capsules | Should be Nil, or not more than 1.5 % of total batch |
| | Splitting | |
| | Cracking | |
| | Denting | |
| | Mottling | |
| Packing | Cleanliness of bottle | Should be clean and dry |
| | Extrinsic particles (Dust or black particles) | Should be free from extrinsic particles |
| | Leak test | Should be comply |

**17. Deviation Report**:

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**18. Change Control**:

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**19. Abbreviation:**

| | | |
|---|---|---|
| PVP | : | Process Validation Protocol |
| IPQA | : | In-process Quality Assurance |
| USP | : | United State Pharmacopoeia |
| BP | : | British Pharmacopoeia |
| IHS | : | In House Specification |
| QA | : | Quality Assurance |
| mg | : | milligram |
| gm | : | gram |
| q.s | : | quantity sufficient |
| mm | : | millimeter |
| AC | : | Anticancer |
| Hr | : | Hour |
| S.S | : | Stainless Steel |
| HDPE | : | High density polyethylene |

**20. Post Approval**

**Protocol Checked By**

| Name | Designation | Signature | Date |
|---|---|---|---|
| | | | |
| | | | |

**Protocol Approved By**

| Name | Designation | Signature | Date |
|---|---|---|---|
| | | | |