DECODING PHARMA

QUALITY ASSURANCE DEPARTMENT

STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
Title: Process Validation	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

1.0 OBJECTIVE:

To lay down a Procedure for Process Validation.

2.0 SCOPE:

This SOP is applicable to all products manufactured at ……

3.0 RESPONSIBILITY:

QA (Officer/Executive): Preparation, Distribution (to Respective Department), Revision, Retrieval and Destruction of this SOP.

QA Manager: Review, Approval, Training and effective implementation of this SOP in all the applicable areas.

Production & QC: Effective implementation of the Procedure

4.0 ACCOUNTABILITY:

Head QA: Approval of this SOP & ensure Training and effective Implementation of SOP.

5.0 DEFINITION:

Process Validation is documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics".

6.0 PROCEDURE:

6.1 TYPES OF PROCESS VALIDATION:

6.1.1 PROSPECTIVE PROCESS VALIDATION:

- "Validation carried out during development stage or before the Commercial Production"

6.1.2 CONCURRENT PROCESS VALIDATION:

- "Validation carried out during routine production of products intended for sale".

6.2 PROCESS VALIDATION PROTOCOL:

- A document stating how validation will be conducted, including Test Parameters, product characteristics, manufacturing equipment, and decision points on what constitutes acceptable test results.

6.3 VALIDATION BATCH:

- Validation Batch is a Batch Manufactured and tested to verify the Critical Parameters & Manufacturing Process controls are adequate.

6.4 IN-PROCESS SAMPLING:

- Process of collecting a representative sample by selecting units deliberately from various identified locations within a Lot or Batch, or from various phases or periods of a process to obtain a sample dosage unit that specifically targets locations throughout the Compression / Filling Operation that have a higher risk of producing failing results in the Finished Product Uniformity of content.

6.5 APPROACH TO PROCESS VALIDATION:

6.5.1 Two Basic approaches to process validation are- one based on validation carried out during development stage or before the Commercial Production (Prospective Validation), and second based on validation carried out during routine production of products intended for sale (Concurrent Validation).

6.5.2 Whenever possible, Prospective Validation is preferred. Retrospective Validation is no longer encouraged and is, in any case, not applicable to the manufacturing of Sterile Products.

6.5.3 Both Prospective and Concurrent Validation, may include:

- Extensive Product Testing, which may involve extensive sample testing (with the estimation of confidence limits for individual results) and the demonstration of intra- and inter-batch homogeneity;
- Challenge/Worst Case Tests, which determine the Robustness of the Process;
- Control of Process Parameters being monitored during normal production runs to obtain additional information on the reliability of the process.

STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
Title: Process Validation	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

6.6 VALIDATION/RE-VALIDATION SHALL BE CARRIED OUT IN FOLLOWING CASES:

- Introduction of New Product
- Periodic Validation
- Change in the Batch Size of the Product
- Change(s) in the actual process that may affect quality or its validation status.
- Change(s) in the product design which affects the process i.e. Change in Critical Process Parameters, Optimization Batch (es) shall be planned to evaluate such parameters and their impact on process and product quality.
- Change in Critical Equipment's.
- Appearance of negative trend of product quality.
- Change initiated due to Market Complaints, Deviations on Shop Floor, Annual Product Review and Stability Studies etc.
- Physical characters (Particle Size, Bulk Density, Moisture Content etc) or Excipients having potential impact on process.
- Transfer of process from one facility to another.
- Change in the application of the process.
- Change in Critical Formulation Component i.e. Raw Material Quantity.
- Change in manufacturer or vendor of Active Pharmaceutical Ingredient (vendor under development).

6.6.1 The need for revalidation should be evaluated and documented. This evaluation should include historical results from Quality Indicators, Product Changes, Process Changes, Changes in External Requirements (regulations or standards) and other such circumstances.

6.7 PREPARATION OF A NEW PROCESS VALIDATION PROTOCOL AND REPORT:

6.7.1 The Process Validation Protocol and Report shall be written in English Language only by using Microsoft Word typing.

6.7.2 Process Validation Protocol and Report shall be initiated by QA Department. The person directly involved in the Process Validation Activity shall initiate the New Process Validation Protocol and Report / Revision of Process Validation Protocol and Report.

6.7.3 Initiator shall check the completeness of draft Process Validation Protocol and Report and send the hardcopy to the different Departmental Heads (Head-Production, Quality Control & Engineering) for review.

6.7.4 Draft Process Validation Protocol and Report hardcopy shall be send to customer for review (if required).

6.7.5 On receipt of the comments (if any), the same shall be reviewed and incorporated in the Process Validation Protocol and Report after discussion with Head-QA.

6.7.6 The draft Process Validation Protocol and Report after completion of checking and incorporation of comments or suggestions as agreed, shall be destroyed, this shall be done in concerned Originating Department.

6.7.7 Master Copies of all Process Validation Protocol and Report shall be printed in QA Department only.

6.7.8 No manual correction shall be made in Approved Copy (Master / Controlled Copy).

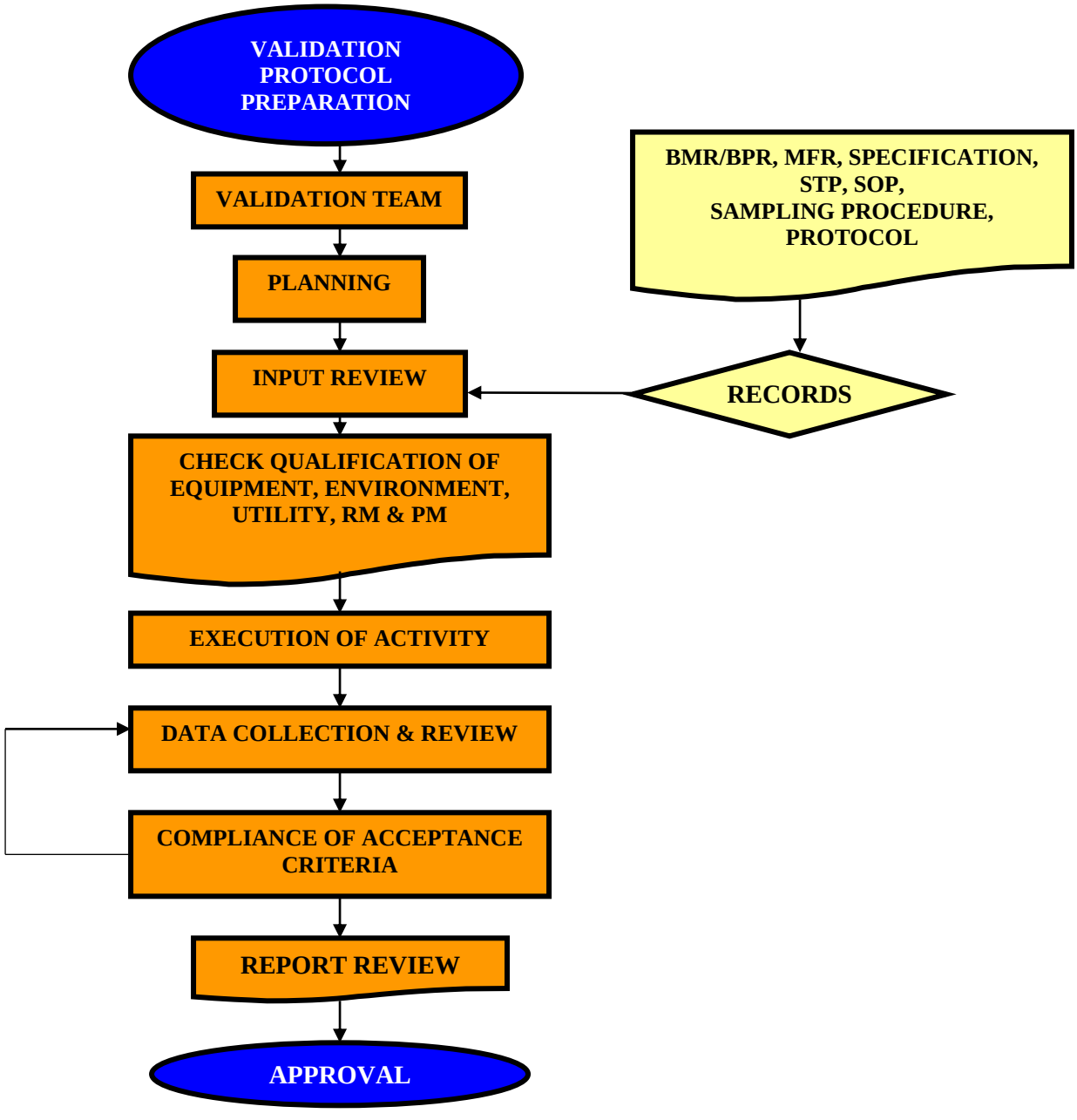
6.7.9 Procedure for Preparation, Validation/Qualification Protocol and Report is given in SOP.

6.7.10 Storage of Process Validation Protocol and Report (Master Copy):

All Master Copy of Approved Process Validation Protocol and Report shall be stored in QA Department.

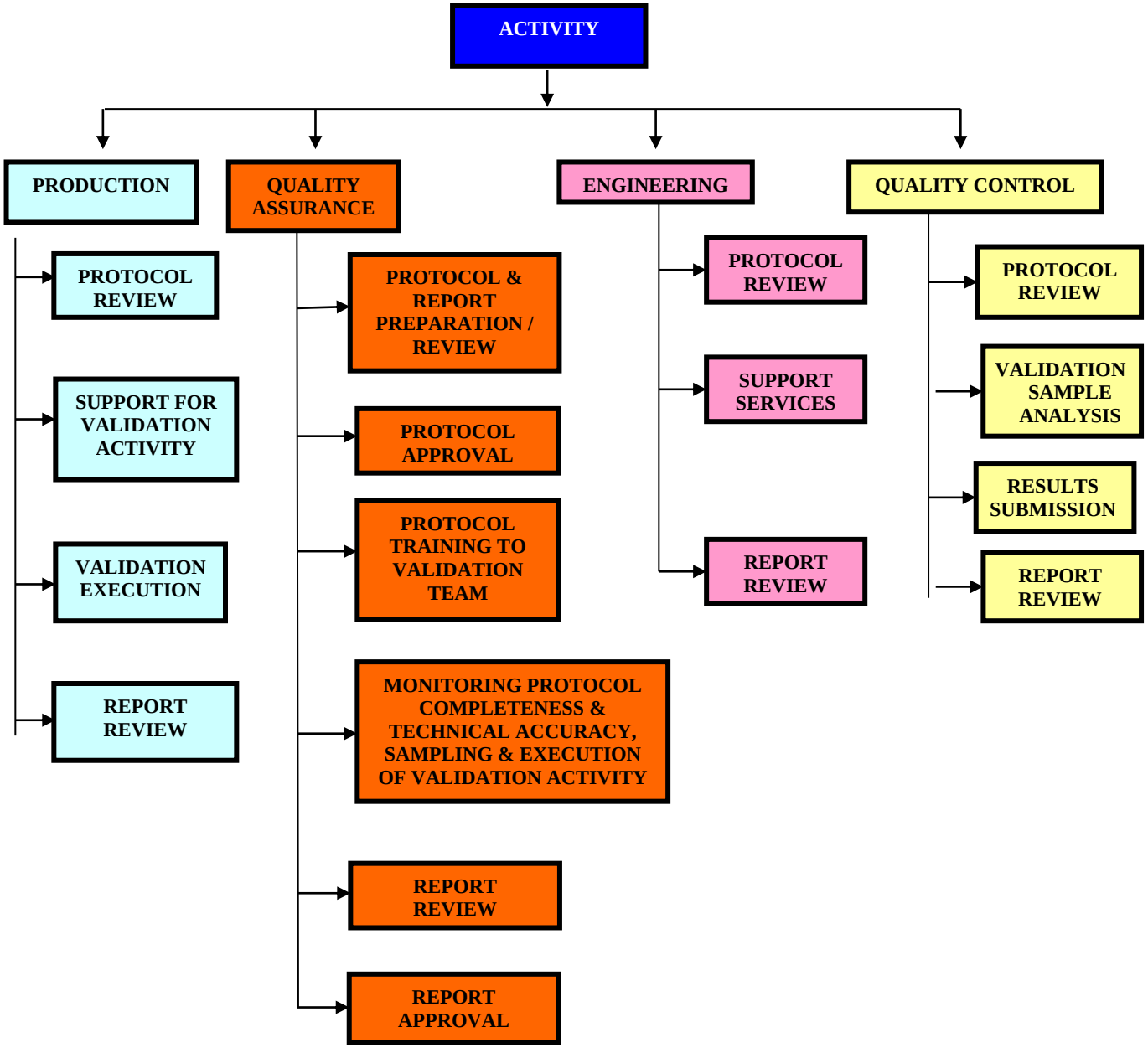
STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
Title: Process Validation	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

6.8 PROCESS VALIDATION FLOW:



STANDARD OPERATING PROCEDURE	
Department: Quality Assurance	**SOP No.:**
Title: Process Validation	**Effective Date:**
Supersedes: Nil	**Review Date:**
Issue Date:	**Page No.:**

6.9 RESPONSIBILITY & ACTIVITY FLOW FOR PROCESS VALIDATION:



6.10 PROTOCOL DEVELOPMENT:

6.10.1 Identification of the process to be validated.

6.10.2 Identification of Product(s) to be manufactured using this process.

6.10.3 Objective and measurable criteria for a successful validation.

6.10.4 Length and duration of the validation.

6.10.5 Shifts, Operators, Equipment to be used in the process.

6.10.6 Identification of utilities for the Process Equipment and quality of the Utilities.

6.10.7 Identification of Operators and required Operator Qualification.

6.10.8 Complete description of the Process.

6.10.9 Relevant specifications that relate to the Product, Components, Manufacturing Materials, etc.

6.10.10 Any special controls or conditions to be placed on preceding processes during the Validation.

6.10.11 Process parameters to be monitored and methods for controlling and monitoring.

6.10.12 Product characteristics to be monitored and method for monitoring.

6.10.13 Any subjective criteria used to evaluate the product.

6.10.14 Definition of what constitutes Non-conformance for both measurable and subjective criteria.

6.10.15 Statistical methods for data collection and analysis.

6.10.16 Consideration of maintenance and repairs of Manufacturing Equipment.

6.10.17 Criteria for Revalidation.

6.11 LAYOUT OF PROCESS VALIDATION PROTOCOL AND REPORT:

All Process Validation Protocol and Report shall contain Header, Footer and Body. Format of **Process Validation Protocol and Report** is given in SOP.

6.11.1 All pages shall contain Format No. in a Footer part.

6.11.2 All the points in the Process Validation Protocol and Report shall be numbered sequentially and sub paragraph of the Process Validation Protocol and Report be also numbered sequentially with an Incremental Number derived from the Heading Number.

6.11.3 Written Process Validation Protocol shall specify the procedures (and tests) to be conducted and the data to be collected.

6.11.4 The Protocol should specify a sufficient number of replicate process runs to demonstrate Reproducibility and provide an Accurate Measure of Variability among Successive Runs.

6.11.5 The test conditions for these runs should encompass Upper and Lower Processing Limits and Circumstances, including those within Standard Operating Procedures, which pose the greatest chance of Process or Product Failure compared to ideal conditions.

6.11.6 Key Process Variables should be monitored and documented.

6.11.7 Analysis of the data collected from monitoring will establish the variability of process parameters for individual runs and will establish whether or not the equipment and process controls are adequate to assure that product specifications are met.

6.11.8 Trend in the process should be monitored to ensure the process remains within the established parameters. When monitoring data on quality characteristics demonstrates a negative trend, the cause should be investigated, corrective action may be taken and revalidation considered.

6.11.9 Any change in the Process and/or Product including changes in Procedures, Equipment, and Personnel etc should be evaluated to determine the affects of those changes and the extent of Revalidation considered.

6.11.10 Various changes may occur in Raw materials and/or Processes, which are undetected, or considered at the time to be inconsequential. These changes may cumulatively affect the validation status of the process. Periodic Revalidation should be considered for these types of processes.

6.12 PROCESS VALIDATION TEAM:

Members of the Validation Team shall include representatives from:

- Quality Assurance
- Production
- Quality Control
- Engineering

6.13 PROCESS VALIDATION FOR LIQUID INJECTIONS IN AMPOULES:

6.13.1 Critical Process Variables:

Following are the Critical Process Variables which are to be validated during Process Validation but not limited to:

- **Washing and Sterilization of Sterile Garments:** Washing Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Cleaning and Sterilization of Equipments:** Washing Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Preparation of Bulk Solution:** Mixing Time, Mixing Speed, Process Time & Capacity of the Mixing Vessel etc.
- **Filtration of Bulk Solution:** Pre & Post Integrity of Filters, Process Time etc.
- **Ampoule Sterilization and Depyrogenation:** Process Time, Conveyor Speed, Conveyor Start Temperature, Sterilization Time, Sterilization Temperature Range Sterilization Hold Time etc.
- **Empty Ampoules:** Sterility, BET, Physical Observation etc.
- **Filling and Sealing:** Differential Pressure in Sterile Area, Temperature, Relative Humidity Process Time, Machine Speed, Fill Volume, Hopper/Tank Level Qualification, Pressure reading of Nitrogen, Sealing Inspection, Clarity, Leak Test etc.
- **Visual Inspection of Filled Ampoules:** Physical Defects i.e. Deformation, Black or White Particles, Volume Variation, Clarity, Fibers etc.
- **Packing:** Packing Style, Quality and Quantity of Packing etc.

6.13.2 Sampling and Analysis Plan:

Following are the Sampling and Analysis Plan during Process Validation but not limited to:

- **Preparation of Bulk Solution:** Description, pH, Identification Assay, Weight/ml, Bioburden etc.
- **Filtration of Bulk Solution:** Sterility etc.
- **Ampoule Sterilization and Depyrogenation:** Conveyor Start Temperature Conveyor Speed Sterilization Hold Time etc
- **Empty Ampoules:** Sterility, BET, Physical Observation etc.
- **Filling and Sealing:** Extractable Volume, Description, Identification, Particulate Matter, pH Assay, Sterility, BET etc.

- **Packing:** As per Finished Product Specification

6.13.3 Sample Quantity:

Quantity of the Samples shall be withdrawn as per the quantity mentioned in the respective Process Validation Protocol.

6.13.4 Sampling Location:

Samples shall be withdrawn as per the locations mentioned in the respective Process Validation Protocol.

6.14 PROCESS VALIDATION FOR LIQUID INJECTIONS IN VIALS:

6.14.1 Critical Process Variables:

Following are the Critical Process Variables which are to be validated during Process Validation but not limited to:

- **Washing and Sterilization of Sterile Garments:** Washing Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Cleaning and Sterilization of Equipments:** Washing Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Preparation of Bulk Solution:** Mixing Time, Mixing Speed, Process Time & Capacity of the Mixing Vessel etc.
- **Filtration of Bulk Solution:** Pre & Post Integrity of Filters, Process Time etc.
- **Washing & Sterilization of Rubber Bungs:** Process Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Sterilization of Aluminium Seals:** Process Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Washing & Sterilization of Vials:** Process Time, Speed of Washing Machine, Pressure of Water and Compressed Air, Conveyor Speed, Conveyor Start Temperature, Sterilization Time, Sterilization Temperature Range Sterilization Hold Time etc.
- **Filling and Sealing:** Differential Pressure in Sterile Area, Temperature, Relative Humidity Process Time, Machine Speed, Hopper/Tank Level Qualification, Fill Volume, Pressure reading of Nitrogen, Sealing Inspection, Clarity, Leak Test etc.

- **Visual Inspection of Filled Vials:** Physical Defects i.e. Deformation, Black or White Particles, Volume Variation, Clarity, Fibers etc.
- **Packing:** Packing Style, Quality and Quantity of Packing including coding Quality etc.

6.14.2 Sampling and Analysis Plan:

Following are the Sampling and Analysis Plan during Process Validation but not limited to:

- **Preparation of Bulk Solution:** Description, pH, Identification Assay, Weight / ml, Bioburden etc.
- **Filtration of Bulk Solution:** Sterility etc.
- **Washing & Sterilization of Rubber Bungs:** Sterility, Visible Observation, Bacterial Endotoxin Test, Moisture Content etc.
- **Sterilization of Aluminium Seals:** Sterility, Visible Observation, Bacterial Endotoxin Test, Bioburden etc.
- **Washing & Sterilization of Vials:** Clarity, Visible Observation, Sterility, Bacterial Endotoxin Test etc.
- **Filling and Sealing:** Description, Sterility Test, Bacterial Endotoxin Test, Particulate Matter, pH, Water Content, Assay, Identification, Extract Volume, Volume Variation etc.
- **Packing:** As per Finished Product Specification

6.14.3 Sample Quantity:

Quantity of the Samples shall be withdrawn as per the quantity mentioned in the respective Process Validation Protocol.

6.14.4 Sampling Location:

Samples shall be withdrawn as per the locations mentioned in the respective Process Validation Protocol.

6.15 PROCESS VALIDATION FOR THREE PIECE (EYE / EAR DROPS):

6.15.1 Critical Process Variables:

Following are the Critical Process Variables which are to be validated during Process Validation but not limited to:

- **Washing and Sterilization of Sterile Garments:** Washing Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Cleaning and Sterilization of Equipments:** Washing Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Preparation of Bulk Solution:** Mixing Time, Mixing Speed, Process Time & Capacity of the Mixing Vessel etc.
- **Filtration of Bulk Solution:** Pre & Post Integrity of Filters, Process Time etc.
- **Formation of Empty LDPE Vials:** Weight of Empty Vials, Presence of Foreign Particles, Design of Empty Vials, Wall Thickness, Parison Temperature etc.
- **Filling and Sealing:** Process Time, Machine Speed, Hopper / Tank Level Qualification, Extruder Temperature, Hydraulic Oil Level, Hydraulic Oil Temperature & Pressure, Chilled Water Temperature & Pressure, Air Pressure etc.
- **Sterilization of Filled and Sealed Vials:** Process Time, Sterilization Hold Time, Sterilization Temperature Range, Pressure Range during Sterilization etc.
- **Leak Testing of the Filled Vials:** Process Time, Vacuum Hold Time, Applied Vacuum etc.
- **Visual Inspection of Filled Vials:** Physical Defects i.e. Deformation, Tip Cut, Collar Cut, Rough Surfaces, Scratches, Black or White Particles, Volume Variation etc.
- **Packing:** Packing Style, Quality and Quantity of Packing including Coding Quality etc.

6.15.2 Sampling and Analysis Plan:

Following are the Sampling and Analysis Plan during Process Validation but not limited to:

- **Preparation of Bulk Solution:** Description, pH, Identification Assay, Weight / ml, Bioburden etc.
- **Filtration of Bulk Solution:** Sterility etc.
- **Filling and Sealing:** Description, Sterility Test, Bacterial Endotoxin Test, Particulate Matter, pH, Water Content, Assay, Identification, Extract Volume, and Volume Variation etc.
- **After Terminal Sterilization:** Sterility
- **Packing:** As per Finished Product Specification.

6.15.3 Sample Quantity:

Quantity of the Samples shall be withdrawn as per the quantity mentioned in the Respective Process Validation Protocol.

6.15.4 Sampling Location:

Samples shall be withdrawn as per the locations mentioned in the respective Process Validation Protocol.

6.16 PROCESS VALIDATION FOR DRY POWDER INJECTION:

6.16.1 Critical Process Variables:

Following are the Critical Process Variables which are to be validated during Process Validation but not limited to:

- **Washing and Sterilization of Sterile Garments:** Washing Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Cleaning and Sterilization of Equipments:** Washing Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Washing & Sterilization of Rubber Bungs:** Process Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Sterilization of Aluminium Seals:** Process Time, Sterilization Time, Sterilization Temperature Range, Sterilization Hold Time etc.
- **Washing & Sterilization of Vials:** Process Time, Speed of Washing Machine, Pressure of Water and Compressed Air, Conveyor Speed, Conveyor Start Temperature, Sterilization Time, Sterilization Temperature Range Sterilization Hold Time etc.
- **Filling and Sealing:** Differential Pressure in Sterile Area, Temperature, Relative Humidity Process Time, Machine Speed, Hopper Level Qualification, Fill Weight, Pressure reading of Nitrogen, Sealing Inspection, Clarity, Leak Test etc.
- **Visual Inspection of Filled Vials:** Physical Defects i.e. Deformation, Black or White Particles, Weight Variation, Clarity, Fibers etc.
- **Packing:** Packing Style, Quality and Quantity of Packing including Coding Quality etc.

6.16.2 Sampling and Analysis Plan:

Following are the Sampling and Analysis Plan during Process Validation but not limited to:

- **Washing & Sterilization of Rubber Bungs:** Sterility, Visible Observation, Bacterial Endotoxin Test, Moisture Content etc.
- **Sterilization of Aluminium Seals:** Sterility, Visible Observation, Bacterial Endotoxin Test, Bioburden etc.
- **Washing & Sterilization of Vials:** Clarity, Visible Observation, Sterility, Bacterial Endotoxin Test etc.
- **Filling and Sealing:** Description, Identification, Constituted Solution, Particulate Matter, Uniformity of Dosages Unit, pH, Water Content, Bacterial Endotoxin Test, Sterility Test, Assay and Related Substances etc.
- **Packing:** As per Finished Product Specification

6.16.3 Sample Quantity:

Quantity of the Samples shall be withdrawn as per the quantity mentioned in the respective Process Validation Protocol.

6.16.4 Sampling Location:

Samples shall be withdrawn as per the locations mentioned in the respective Process Validation Protocol.

6.17 BATCH SIZE FOR PROCESS VALIDATION BATCHES:

6.17.1 Process Validation shall be performed on batches of Fixed Batch Size or Minimum and Maximum Batch size can be taken for validation on the basis of equipment capacity.

6.18 PROCESS VALIDATION FOR NEW PRODUCT LAUNCHES:

Depending on the Product complexities and recommendation from F&D / Customer / Optimization Batches may not be required. In such cases, if 1st Validation Batch is manufactured without any change in Critical Process Parameters; it shall follow with next two Validation Batches. Otherwise 1st Validation Batch is considered as Optimization Batch followed by Three Validation Batches.

6.19 If any of the Process Validation Batch deviates to follow the recommended process parameters, the batch is not considered as Process Validation Batch and further Three Batches shall be considered as Process Validation Batch.

6.20 The Validation Batches may be commercialized on the basis of satisfactory Stability Data (Three / Six Month Accelerated Stability Study) for the product. However Stability Studies are continued and reviewed periodically.

7.0 ABBREVIATIONS:

BET	Bacterial End toxin Test
DQ	Design Qualification
F&D	Formulation & Development
LDPE	Low Density Poly Ethylene
LOD	Loss on Drying
Ltd.	Limited
PM	Packing Material
QA	Quality Assurance
QC	Quality Control
RH	Relative Humidity
RM	Raw Material
SS	Stainless Steel
STP	Standard Test Procedure

8.0 ANNEXURES:

Not applicable

9.0 DISTRIBUTION:

Controlled Copy No. 01	Head Quality Assurance
Controlled Copy No. 02	Head Quality Control
Controlled Copy No. 03	Head Production
Master Copy	Quality Assurance Department

10.0 REFERENCES:

- USFDA CDER: Guidance for Industry Process Validation: General Principles and Practices
- Schedule-M
- Validation Master Plan
- PIC's Guidelines
- SOP, Titled **"PREPARATION OF VALIDATION/QUALIFICATION PROTOCOL AND REPORT.**

11.0 REVISION HISTORY:

Revision No.	Change Control No.	Details of Changes	Reason of changes	Effective Date	Done By
00	Not Applicable	Not Applicable	New SOP		