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1.0 PURPOSE:

To lay down the procedure for Describing the approach to Process Validation.

2.0 SCOPE:

This procedure applies to the all intermediates and drug substances (APIs) manufactured at Discovery Laboratories Pvt. Ltd.

3.0 RESPONSIBILITY:

3.1 Production department shall be responsibilities to:

3.1.1 Preparation of Validation protocol and Report

3.1.2 Execute the activity as part of team

3.1.3 Complete necessary documentation

3.1.4 Reviewed the validation protocol and report

3.1.5 Ensure the completion of the activity&collection of samples as per Sampling plan and send to QCas per the Protocol.

3.2 Quality Control department shall be responsibilities to:

3.2.1 Conduct testing of all samples and to verify the results against the acceptance criteria.

3.2.2 For Drying, Blending, Sifting Milling Validation, Samples shall be drawn by Quality Control

3.3 Engineering department shall be responsibilities to:

3.3.1 Complete qualification activities before starting the process validation.

3.3.2 Ensure calibration of related equipment's timely.


3.4 Ware house department shall be issued the raw materials as per production request.

3.5 QA department shall be responsibilities to:

3.5.1 Prepare and update the validation master plan timely.

3.5.2 Review and approve the all the related documents, protocols and reports, and co-ordinate all Depts. in the process validation study

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3.5.3 Allot the document no. for validation activities and record in respective log.

3.5.4 Provide necessary support to production department wherever necessary.

3.5.5 Head-QA shall be responsible to ensure the effective implementation and Compliance to this SOP.

3.5.6 Ensure Training to be provided to the Concerned Persons before Starting Validation Activity

4.0 DEFINITIONS:

4.1 Process Validation:

Is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

4.2 Prospective Process Validation:

Prospective validation is establishing documented evidence that a system does what it purports to do prior to the commercial distribution of a new API or an API made by a new or modified process.

4.3 Concurrent Process Validation:

Concurrent validation is establishing documented evidence that a system does what it purports to do based on information generated during the actual implementation of the system.


4.4 Retrospective Process Validation:

Retrospective validation is establishing documented evidence that a system does what it purports to do based on a review and analysis of historic information.

4.5 Validation Protocol:

A written plan stating that how validation shall be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing

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equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

4.6 Validation Report:

A summary of the validation results shall be captured in Process validation report against the acceptance criteria with overall conclusion of the validation activity of the particular product.

5.0 PROCEDURE:

5.1 Approach to Process Validation:

5.1.1 There are three approaches to Process validation

5.1.1.1 Prospective process validation

5.1.1.2 Concurrent process validation

5.1.1.3 Retrospective process validation

5.1.2 As an in-house policy, prospective validation is the most preferred approach for validation of new or revised manufacturing processes.


5.1.3 Concurrent validation shall be conducted when data from replicate production runs are unavailable, batches are produced infrequently or batches are produced by a validated process that has been modified.

5.1.4 Retrospective validation shall be carried out for well established processes that have been used without significant changes to product quality due to changes in raw materials, equipments, systems, facilities, or the manufacturing process.

5.1.5 Batches selected for retrospective validation shall be representative of all batches made during the review period, including any batches that failed to meet specifications, and shall be sufficient in number to demonstrate process consistency.

5.1.6 Process validation activity and its documentation shall be done stage wise or combined.


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5.2 Process validation program:


- 5.2.1 Process validation shall be conducted for products after the manufacturing process is finalized on completion of Trial batches / new process transferred from Research and Development / any major change made in the existing process based on the change assessment.
- 5.2.2 A minimum of three consecutive production batches shall be considered for prospective or concurrent validation. For retrospective validation, data from ten to thirty consecutive batches shall be considered to assure process consistency but fewer batches can be taken if justified.
- 5.2.3 Before the execution of process validation, the Batch Production Record (BPR) shall be finalized. All specifications and testing methods related to raw materials, in-process checks, intermediates shall be finalized.
- 5.2.4 All raw materials used in the process validation shall be tested and released as per approved specifications.
- 5.2.5 Training of the concerned personnel involved in the validation activity shall be completed before the execution of validation.
- 5.2.6 The acceptance criteria for yield, each critical and quality parameters, raw material, intermediate and finished product shall be defined in the protocol and the same shall be reviewed and reported.
- 5.2.7 Each specific manufacturing process shall be monitored closely using the critical process parameters mentioned in development report. During the execution of the validation activity, critical process parameters, in- process controls, yield ratios and quality attributes of the Intermediates shall be verified against predefined acceptance criteria.

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- 5.2.8 The supporting utilities like water, equipment qualifications and calibration of measuring instruments, which affect quality shall be qualified and shall be within valid calibration cycle before undertaking a process validation study.
- 5.2.9 The equipment and its accessories qualification / calibration details shall be verified and all should be within due date of qualification / calibration before start the process validations and the details shall be captured in the validation report to ensure the validation status of respective equipments used for manufacturing.
- 5.2.10 All the Trial / Process Validation batches shall be released to the market only after approval of process validation report and the relevant documents should be closed.
- 5.2.11 For all new products, after successful completion of validation atleast one month hold time study shall be made available to release the material. In case of any specific requirements of customer the material can be dispatched before completion of hold time study program with justification.
- 5.2.12 If the Trial batch process is similar with the validation batch process and the batch material meets respective quality parameters, the material can be dispatched to regulatory / DMF submitted markets. However prior intimation / approval shall be taken from customer / regulatory authority for dispatch of material.
- 5.2.13 Trial batches shall be dispatched to other than regulatory / DMF submitted markets. However prior intimation / approval shall be taken from customer for dispatch of material.
- 5.2.14 If the validation batch at any particular stage fails for reasons related to process, Process Development Department shall be consulted for investigation and necessary process optimization. If required, Trial batch(s) shall be taken and subsequently, three consecutive batches shall be considered for validation.

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5.2.15 If an assignable cause is not found for the failure during the validation run, subsequently three consecutive batches shall be considered for validation.

5.2.16 If a batch at any particular stage fails during validation for reasons unrelated to process requirement (e.g. power failure, equipment breakdown etc.), that batch shall be removed from the validation study and the subsequent consecutive batch(s) shall be considered for validation.

5.2.17 Validation activity shall be carried out according to approved process validation protocol. The entire validation activity shall be monitored by Production and QA personnel with the support of Research and Development, if required.

5.2.18 Appropriate sampling procedures shall be in place for the sampling of in-process, intermediates and referred in the process validation protocol.

5.2.19 The processes of physical modifications to the batches like milling shall be validated. For batches, which have to be blended for dispatch, the blending process shall be validated.

5.2.20 Holding time study shall be conducted for Intermediates stages for three validation batches or based on the recommendations made in the change assessment.

5.2.21 In the manufacturing process where the use of recovered solvents is recommended, at least one batch shall be manufactured using recovered solvents as a part of validation.

5.2.22 The validation protocol and report shall be numbered as follows:

For Protocol **PV/PC/XX-Z/YNNNN**,

For report **PV/R/XX-Z/YNNNN**


Where,

‘PV’ : Stands for Process Validation

‘PC’ : Stands for Protocol

‘R’ : Stands for Report

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‘XX’ : Stands for Product Code

‘Z’ : Stands for Stage code

‘YY’ : Stands for last two digits of the calendar year.

‘NNN’ : Stands for serial number of the protocol for the product in the year starts from 001.

e.g.-1: PV/PC/AMT-1/19001 validation protocol for AMT stage-1 is prepared in the year 2019. The corresponding report will be PV/R/AMT-1/19001.

e.g.-2: PV/PC/AMT-2/19001 validation protocol for AMT stage-2 is prepared in the year 2019. If the corresponding report is to be prepared in next calendar year (2019) the report will be PV/R/AMT-2/19001 only.

5.2.23 The validation protocol and report numbers along with other details shall be written in process validation log register (QA019-FM074) product wise.


5.2.24 Validation protocol shall be prepared by user department with brief process description, selection of batches, critical quality attributes, equipment usage details , acceptance criteria, testing methods, sampling plan, data to be collected etc...and the same shall be verified by and approved by Quality assurance.

5.2.25 Process validation protocol shall be issued to the Production department, Quality control department and other concerned department and controlled as per the ‘Document distribution and retrieval record’.

5.2.26 After completion of validation activity, compile the validation report that is in accordance to the validation protocol, summarize the results and draw appropriate conclusions on validation status of respective product / stage.

5.2.27 The validation report shall be appropriately reviewed by Heads of respective departments/Designee and approved by Head-QA/Designee.

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5.2.28 Any deviations, changes or failures during the validation study shall be handled as per the respective SOPs.

5.3 **Revalidation:** The process shall be revalidated for any of the following reasons, but not limited to:

5.3.1 Changes to the manufacturing process

5.3.2 Change in manufacturing block / site

5.3.3 Change in the source of API starting materials (intermediates) as appropriate

5.3.4 Change in batch size

5.3.5 Change in any physical modification process parameters

5.3.6 Any other change that would affect the product quality

5.4 **Periodic review:** All validated systems shall be periodically reviewed to verify that they operate in a validated state. This shall be done annually as a part of annual product quality review provided there are no significant changes made to the validated process or systems.


6.0 FORMATS/ANNEXURE(S):

6.1 Process Validation Log register : QA019-FM074

7.0 CHANGE HISTORY:

Revision No.	Effective Date	Details of Revision	Ref. CCF No.
00	01.06.2007	New SOP is introduced.	---
01	01.07.2009	SOP format changed and reviewed for more clarity.	---
02	15.06.2014	Revised as per current SOP & more clear and clarity.	---
03	01.09.2014	Responsibilities for all departments clearly.	---
04	12.11.2017	1. SOP Format changed make to inline with SOP-QA-001-05. 2. Process validation definitions are included. 3. Process Validation program and Revalidation procedure has been elaborated for better clarity.	CCF/GEN/ 17028

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Revision No.	Effective Date	Details of Revision	Ref. CCF No.
		4. Process validation protocol and Report numbering included. 5. Periodic review procedure included for validated procedures. 6. Process Validation Log Register modified. 7. Altogether procedure has been rephrased for better clarity.	
05	20.06.2019	The instruction for verification and recording of equipment qualification / calibration details is incorporated.	CCF/GEN/19023

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