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## 1.0 PURPOSE:

To lay down a procedure for preparation, review, approval, control and maintenance of Master Formula for Intermediate and API (Active Pharmaceutical ingredient) manufactured at Discovery Laboratories Pvt Ltd.

## 2.0 SCOPE:

- 2.1 This SOP (Standard Operating Procedure) is applicable to all Intermediates and APIs manufactured at Discovery Laboratories Pvt Ltd.
- 2.2 Master Formula prepare after the effective date of the SOP shall follow the procedure outlined in this version. As such existing Master Formula shall not require to be modified, unless the Master Formula requires to be revised for any changes.


## 3.0 RESPONSIBILITY:

- 3.1 Production representative shall be responsible to prepare master formula and for subsequent updations/ revisions of it.
- 3.2 R&D, Production, Quality Control & Quality Assurance shall be responsible to review Master Formula.
- 3.3 Head-QA or designee shall be responsible to approve Master Formula and for effective implementation & compliance to this SOP.

## 4.0 DEFINITIONS:

- 4.1 **Master Formula:** A document or set of documents specifying the starting materials with their quantities, with a description of the procedures and precautions required to produce a specified quantity of a product as well as the processing instructions, including the in-process controls. The scope of the Master Formula shall not include physical operations such as milling, sifting, micronization, compacting etc and packaging operations, which shall be controlled through respective approved master BPRs (Batch Production Records).

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- 4.2 **Critical:** Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the product meets its specification.
- 4.3 **In-Process Control (or Process Control):** Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.
- 4.4 **Batch:** A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits.
- 4.5 **Batch Size:** It is expressed in Kg based on the standard input quantity of key raw material on whose basis the yield is calculated for a batch.
- 4.6 **Theoretical Yield:** The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production. Theoretical yield would be calculated based on reaction stoichiometry by considering molecular weights.
- 4.7 **Expected Yield:** The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data. Expected yield must be established with appropriate range.
- 4.8 **Actual Yield:** The quantity of material or the percentage of theoretical yield that is actually produced in a batch. Actual yield shall be calculated and reported after drying stage of production. It shall exclude all physical operations such as milling, sifting, micronization, compacting etc.

## 5.0 **PROCEDURE:**

### 5.1 **Preparation, Review & Approval of Master Formula:**

- 5.1.1 Master formula for each intermediate and API shall be prepared by using the current version of format QA036-FM162.

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5.1.2 Master formula shall be prepared for new product and stage wise to the site after successful completion of initial validation batches.

5.1.3 Master formula shall be prepared by considering batch size and input quantities of raw materials, along with mole ratio/ multiplication factor with respect to key raw material, used during the manufacturing of validation batch.

5.1.4 Separate master formula shall be prepared for:

5.1.4.1 Different routes/ processes of same product.

5.1.4.2 Different mole ratios or multiplication factors for raw materials of same product.

5.1.5 The prepared master formula shall be reviewed by R&D, Production, QC & QA and shall be approved by plant QA-Head or designee.

5.1.6 Approved master formula shall be controlled by QA as per document control SOP.

## 5.2 **Contents of Master Formula:**

The master formula shall contain:

5.2.1 **Header details:** The header part in all pages of master formula shall contain the following contents.

5.2.1.1 Company logo.

5.2.1.2 Title of the document.

5.2.1.3 Name of product and manufacturing stage (Intermediate/ API) of it for which the master formula is prepared.

5.2.1.4 MF No.: This number shall be allotted as per the below procedure.


**“MF– XXX-N-YYY/ZZ”**

Where,

MF- stands for Master Formula

XXX- denotes Product stage code.

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N – Stage code.

YYY- chronological sequence number of MF of particular product stage code which starts from 001 to 999

ZZ – denotes Revision Number which starts from 00 to 99

e.g.: MF-DAH-I-001/00 is MFR for DAH stage-I product.

5.2.1.5 Effective date of document.

5.2.1.6 ‘Supersedes’ i.e. the ref. no. of document which is superseded by this current version.

#### 5.2.2 Footer details:

Footer contains format number and page number on every page.


5.2.3 **Document approval sheet:** Document approval sheet shall be on 1<sup>st</sup> page of master formula.

5.2.4 **Table of contents:** Table of contents shall be on 2<sup>nd</sup> page of master formula.

5.2.5 From 3<sup>rd</sup> page onwards the body part shall contains, but not limited to, the following contents.

5.2.5.1 **Product description:** This section shall include the details of product (Intermediate/ API) such as name of product, manufacturing stage, type of product, chemical name, molecular formula, molecular weight, CAS registry no., physical appearance and storage conditions.

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5.2.5.2 **Formula details:** Input quantities of raw materials used during the manufacturing of initial validation batch of product shall be listed along with mole ratios/ multiplication factors for raw materials with respect to key raw material. These details shall include material name/ code, unit of measurement, standard quantity, mole ratio and multiplication factor. Mention shall be made of any substance that may disappear in the course of processing.


5.2.5.3 **Yield details:** This section shall include the batch yield details such as standard batch size (input quantity of raw material basis for yield calculation), theoretical yield and expected yield in both weight & percentage. The name of key raw material on whose the yield calculation is done shall be addressed here.

5.2.5.4 **Synthetic scheme:** This section shall include the chemistry along with the brief process description.

5.2.5.5 **Production equipment details:** This section shall include the details of major production equipments (like reactor, centrifuges, dryers and etc.) which are used during the manufacturing of the product such as equipment name, model/ type, location and SOP reference for operation and cleaning of the same.

5.2.5.6 **Process flow:** This section shall include the flow of process in representation of operations with details of materials with chemical names, type of equipments, parameters and in-process checks. This process flow sheet shall be approved and enclosed as Annexure-1 for respective master formula.

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**5.2.5.7 Production operation instructions:** This section shall include all the detailed production operation instructions, up to yield reporting, which contain:

- Detailed stepwise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures).
- The instructions for any in-process controls with their limits.
- Details regarding drying and/ or others as applicable.
- The precautions to be taken for the hazardous reaction shall be mentioned in the master formula.
- Any special precautions to be observed.

**5.2.5.8 Critical process parameters control:** This section shall include the appropriate critical process parameters with appropriate justifications.

**5.2.5.9 Retest/ expiry period:**

5.2.5.9.1 For existing product, the details of retest / expiry period shall be addressed.

5.2.5.9.2 For new products following full development study, this should include:


5.2.5.9.2.1 Proposed Retest period based on stability commitment or filing documents.

5.2.5.9.2.2 For other markets, retest / expiry period proposed based on initial stability batches./ expiry period

5.2.5.9.3 This data can be addressed as addendum after

5.2.5.9.3.1 The initial evaluation of the stability of validation batches.

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5.2.5.9.3.2 The final evaluation of the stability of validation batches.

5.2.5.10 **Standard reprocessing method:** This section shall include the details of standard reprocessing methods if applicable. These details shall be either addressed in original master formula or attached as an addendum to it.

5.2.5.11 **Revision history:** This section shall include the revision history of the particular master formula which contains the details such as revision no., reasons for revision, change control no. as applicable.

### 5.3 Control of Master Formula:

5.3.1 Approved master formula shall be controlled by QA.

### 5.4 Revision/ Updation of Master Formula:

#### 5.4.1 Revision:

5.4.1.1 Master formula shall be reviewed if any changes, such as changes/modifications in synthetic scheme, mole ratios/ multiplication factors for raw materials, type of production equipments, process, critical process parameters etc., are required to be made in current version, then it shall be revised through change control by incorporating the proposed changes. This new version shall be prepared, reviewed, approved and controlled same as described in point 5.1 to 5.2.

5.4.1.2 The obsolete version shall be retained with QA.

## 6.0 FORMATS / ANNEXURE(S):


6.1 Master Formula Record : QA036-FM162.

6.2 Process flow chart : Annexure-1

## 7.0 CHANGE HISTORY:

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QA001-FM139-01

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Revision No.	Effective Date	Details of Revision	Ref. CCF No.
00	02.06.2017	New SOP introduced.	---

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