TITLE: QUALIFICATION, HANDLING, STORAGE AND USAGE OF REFERENCE STANDARDS AND WORKING STANDARDS

1.0 PURPOSE:

To lay down the procedure for qualification, handling, storage and usage of reference/ working standards used in the quality control department.

2.0 SCOPE:

The scope of this sop is applicable for qualification of reference/ working standards used in Quality control department at Discovery.

3.0 RESPONSIBILITY:

3.1 Analyst-QC is responsible to follow this SOP.

3.2 Head-QC/Designee is responsible for ensuring implementation of this SOP.

3.3 Head-QA/Designee is responsible for monitoring overall compliance of this SOP.

4.0 DEFINITIONS:

4.1 **Reference standard:** A substance that has been shown by an extensive set of analytical tests to be an authentic material that should be of high purity. These standards are procured from Pharmacopoeial sources like USP / EP / BP/JP /IP etc. In case of Non Pharmacopoeial products, the reference standards can be prepared in-house with the help of R&D.

The reference standards are also known as primary standards. The reference standards can be used in laboratories for determination of qualitative and quantitative analysis, and also used to qualify the working standard.

4.2 **Certified reference material:** The reference materials procured with certificate of analysis (traceable to National Institute of Standards and Technology (NIST)) from authentic sources like Sigma-Aldrich, Merck, Rankem, etc…. can be used in laboratory for quantitative/ Qualitative analysis purposes. The potency/purity provided on certificate shall be used directly in respective calculation.

These reference materials can also be used to calibrate the equipments like MR, KF, HPLC and GC etc.

4.3 **Working standard:** The working standards are qualified against reference standards and shall be used for routine quantitative / qualitative analysis purposes. These are also known as secondary reference standard.

5.0 PROCEDURE :

5.1 **Qualification of in-house reference standards:**

5.1.1 For Pharmacopoeial products, the reference standards can be procured from Pharmacopoeial sources like USP / EP / BP/JP /IP etc… or shall be prepared from in-house reference standards for both Pharmacopoeial and Non Pharmacopoeial products.

5.1.2 The in-house reference standards can be prepared either by synthesis in R&D or from any vendor or from any of the high pure plant batch.

5.1.3 The chemical structure identification shall be established and conformed by NMR, MASS and IR etc (NMR, MASS identification shall be done for first time only).

5.1.4 Qualification of in-house reference standard is performed by conducting full testing in duplicate as per respective approved procedure.

5.1.5 The potency of in-house reference standard shall be determined by using mass balance method.

Potency = 100 – (Total impurities by HPLC/GC + Water content / LOD + Residue on ignition / Sulphated ash + Residual solvents by GC).

5.1.6 The analytical data shall be recorded in the qualification protocol as per the format no. QC005-FM078.

5.1.7 A COA shall be prepared as per the format no. QC005-FM036.

5.1.8 The batch numbering shall be followed for the reference standard as defined below

Batch No: **XXXZRSYYNNN**

Where:

XXX indicates : Product Code

Z Indicates : Stage

RS indicates : Reference standard

YY indicates : Year code [2017 shall be reflected as 17]

NNN indicates : Serial number starting from 001 w.r.t. product.

e.g.: DAH-IRS16001

5.1.9 Validity period for reference standard shall be three years from the effective date.

A list of reference standards shall be maintained as per the format no.QC005-FM035.

5.1.10 For reference standard, 2-4 gms shall be packed in a vial for analysis and the remaining will be packed in double LDPE bags, further packed in triple laminated cover and will be stored at ambient or 2-8°C or freezer as per applicability of the product.

5.2 **Qualification of working standard:**

5.2.1 A latest and high pure approved batch shall be selected for the qualification of working standard.

5.2.2 The identified approved batch of the product shall undergo full testing as per the respective Specification and Standard Testing procedure (STP).

5.2.3 If reference standard is not available, then the potency shall be calculated by mass balance method.

5.2.4 Description test shall be performed as per respective testing procedure.

5.2.5 The Identification test shall be performed against official pharmacopoeia reference standards or against the in-house reference standard or against previous working

standard. Or shall be compared against IR reference spectra provided in pharmacopoeias or authentic IR library source.

5.2.6 Water Content / Loss on drying test shall be performed in duplicate as per respective testing procedure.

5.2.7 Chromatographic purity by HPLC/GC or Related substances by HPLC/GC shall be performed in duplicate as per respective testing procedure in the below sequence.

Sequence :

5.2.7.1 Blank/ Diluent inj-01

5.2.7.2 Blank / Diluent inj-01 if required.

5.2.7.3 Standard preparation inj-01

5.2.7.4 Sample preparation-1 inj-01

5.2.7.5 Sample preparation-2 inj-01

5.2.8 Calculate the average of two preparations, if and only if, the obtained results of two preparations are within the specification limit.

5.2.9 The purity/potency of working standard shall be defined as follows by mass balance method.

Potency = 100 – (Total impurities by HPLC/GC + Water content / LOD + Residue on ignition / Sulphated ash + Residual solvents by GC).

5.2.10 In case of non availability of approved product, the existing working standard validity shall be extended by re-testing the parameters; description, water/LOD and Chromatographic purity (by area normalization method) tests shall be verified as per the respective Specification and STP, the potency shall be calculated by mass balance method. The retested results of chromatographic purity should be with-in the specification.

5.2.11 If reference standard are available, then the assay (potency) of selected approved batch shall be determined as per below sequence.

5.2.11.1 The injection sequence shall be as follows-

5.2.11.2 Blank (diluent) – One injection.

5.2.11.3 System suitability solution – One injection (if only required)

5.2.11.4 Reference standard solution – Five/Six injections as per respective STP.

5.2.11.5 Sample preparation 1 – Two injections.

5.2.11.6 Sample preparation 2 – Two injections.

5.2.11.7 System suitability solution – One injection (if only required).

5.2.12 If system suitability analyst are different than the assay standard and sample preparation, an additional blank shall be injected after system suitability injection to avoid any possible carry over.

Calculate the results as follows.

Assay 1: Sample preparation 1 Vs standard solution.

Assay 2: Sample preparation 2 Vs standard solution.

5.2.13 The variation between the two assay results shall not be more than ± 0.5 % w/w and it shall not be more than ± 1.0% with respect to the initial release result.

5.2.14 The working standard number shall be assigned as follows;

Batch No: XXXZWSYYNNN

Where,

XXX indicates : Product Code

Z indicates : Stage

WS indicates : Working standard

YY indicates : Year code [2016 shall be reflected as 16]

NNN indicates : Serial number starting from 001 w.r.t. product.

e.g.; DAH-IWS16001

5.2.15 The analytical data shall be recorded in the qualification protocol as per the format no QC005-FM078.

5.2.16 A COA shall be prepared as per the format: QC005-FM036.

5.2.17 Validity period for working standard shall be one year from the effective date.

5.2.18 List of working standard shall be prepared as per format no.: QC005-FM035.

5.3 **Packing and Labeling:**

5.3.1 The standards after qualification shall be dispensed in clean fresh pre labeled amber color vials with the help of fresh butter paper in a cleaned area.

5.3.2 Ensue that no other material is available in the surroundings prior to start the dispensing activity.

5.3.3 The fresh vials shall be checked visually for cleanliness and further physically for absence of any extraneous matter by reverse tapping of the opened vials on a fresh and clean butter paper.

5.3.4 Wear suitable PPE during preparation of standard vials.

5.3.5 For working standard about 2 gms of standard shall be packed in 15 vials. The vials from 1 to 12 are meant for monthly usage while the 13-15 vials were kept as stock vials. The working standards if requested by customers can be provided from the stock vials.

5.3.6 Labels shall be prepared and pasted on standard vials from 1 to 12 as per format no.: QC005-FM037, while for stock vials as the format no.: QC005-FM038.

5.4 **Storage:**

5.4.1 The labeled and packed standard vials shall be placed in plastic containers and stored in a desiccators or refrigerator at 2 to 8ºC / freezer as per the prescribed storage conditions of corresponding products.

5.4.2 Validity period for working standards shall be one year from the effective date and the effective date shall be within one week from the date of completion of analysis.

5.5 **Distribution of standards:**

5.5.1 After the qualification pre defined monthly vial shall be issued for regular analysis. After the vial validity the vial should be disposed and shall be replaced with a new vial as per the validity dates labeled on the individual vial.

5.5.2 The issuance and disposal details shall be recorded in the standard issue and disposal record of format no: QC005-FM079

5.5.3 In case of damage to an existing opened vial, 2 gms shall be issued from the stock vial, and the details shall be recorded in the standard issue and disposal record (QC005-FM079).

5.6 **Precautions while usage of standards:**

5.6.1 After taking out the standards from refrigerator wipe the outer surface of vial with tissue paper and the same shall be kept in a desiccators for about 10 minutes to attain room temperature before weighing to avoid any exposure to moisture.

5.6.2 The working standard vials shall be opened, closed and placed back to their designated place within minimum time to avoid exposure to the moisture.

5.6.3 The working standard vials shall be allowed to attain room temperature before weighing.

5.6.4 If more than one standard need to be weighed, open only one standard vial at the time of use to avoid exposure and contamination risk.

5.6.5 Complete the activity of one standard and close the vial properly before weighing the second standard.

5.6.6 The required quantity of standard material shall be dispensed carefully.

5.6.7 The excess dispensed material should not be added back into the vial.

5.6.8 The stock of Reference standard / Working standard shall be in lock and key.

5.6.9 The storage of working standard shall be in line with the labeled storage conditions.

5.7 **GC standards (Standards required for GC analysis):**

5.7.1 Certified material procured from authentic sources like Sigma-Aldrich, Fluka, Merck etc shall be used as standards for GC analysis.

5.7.2 Manufacturer's certificate of analysis of the certified material shall be preserved and the potency/purity mentioned on the certificate shall be used for quantitative analysis.

6.0 FORMATS / ANNEXURE(S):

6.1 List of standards : QC005-FM035

6.2 Certificate Of Analysis : QC005-FM036

6.3 Standard : QC005-FM037

6.4 Standard label for stack : QC005-FM038

6.5 Standard Qualification Protocol : QC005-FM078

6.6 Standard issue and disposal record : QC005-FM079

7.0 CHANGE HISTORY:

Revision No.	Effective Date	Details of Revision	Ref. CCF No.
00	01.06.2007	New SOP "working standard preparation' analysis and labeling working standard	--
01	01.08.2009	In this SOP formats change with more clear and clarity	--
02	01.10.2010	Working standards storage change one to two bottles	--
03	01.03.2014	1. Formats are the part of SOP. So prepared separately. 2. Incorporate TLC standards preparation	--
04	01.01.2017	1. SOP format changed make in line with SOP-QA-001-04. 2. Standard label contents were modified. 3. Standard label for stock included 4. Altogether procedure has been rephrased for better clarity.	QC-CRF-025/16
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