ION LABS QUALITY FIRST	Standard Operating Procedure **Qualitative Standards**	**SOP Number** **D-109**	**Revision** **6**
		Effective Date 05/14/19	**Page** **Page 1 of 8**

Written by/ Date	**Reviewed by/ Date**	**Approved by/ Date**
04/05/19	04-17-19	04/17/19
Title: Analytical Development Manager	**Title: QC Laboratory Supervisor**	**Title: QC Laboratory Director**

1.0 Purpose

The purpose of this SOP is to provide guidelines for qualifying qualitative reference standards for dietary supplements and pharmaceuticals, finished product blend standards, documenting inventory of standards, and construction of libraries.

2.0 Scope

This procedure applies to all pure chemical standards, complex-defined chemical standards, botanicals and their extracts used in the qualitative analysis of raw materials. This procedure also applies to finished product blends for use as standards. The use of qualitative standards for the analytical tools FTIR, HPLC spectral analysis, TLC, and MS will be defined.

3.0 Responsibility

3.1 It is the responsibility of QC analysts to follow this procedure.

3.2 It is the responsibility of the QC Laboratory Management to maintain and keep current this procedure. The QC Laboratory Management is also responsible for ensuring compliance to the procedure.

4.0 Definitions

4.1 **USP** - United States Pharmacopeia

4.2 **FCC** - Federal Chemical Codex

4.3 **ACS** - American Chemical Society

4.4 **NIST** - National Institute of Standards and Technology

4.5 **CofA** - Certificate of Analysis

4.6 **FTIR** - Fourier Transform Infrared Spectroscopy

4.7 **HPLC** - High Pressure Liquid Chromatography

4.8 **MS** - Mass Spectroscopy

4.9 **RTmax** - Retention time at maximum peak height using λmax.

4.10 **NLT** - Not Less Than

4.11 **TLC** - Thin Layer Chromatography

4.12 **RMID** - Raw Material Identification

4.13 **QC** - Quality Control

5.0 References

5.1 D-109-F1, Form, Qualitative Reference Standard Log

5.2 D-109-F2, Form, Finished Product Blend Reference Standard Log

5.3 D-107, SOP, USP Reference Standards

5.4 D-106, SOP, Analytical Standards

6.0 Hierarchy of Qualitative Standards

6.1 Hierarchy of use- Fine Chemicals and complex-defined chemical standards.

6.1.1 For dietary supplements, a first tier standard is an appropriate pure chemical or complex-defined chemical standard traceable to a recognized source and accompanied by a CofA.

Examples of recognized sources: USP, ACS, NIST, etc.

6.1.2 A second tier standard is an appropriately purified form of the analyte obtained through an approved chemical vendor and is accompanied by a CofA.

6.1.3 A third tier standard is an appropriately purified form of the analyte obtained from a raw material vendor and is accompanied by a CofA.

6.1.4 For pharmaceutical standards only USP traceable standards will be used. Pharmaceutical standards will be identified and logged as per instructions for D-107-F1 Analytical Standard Log.

6.2 Hierarchy of use- Botanicals

6.2.1 First tier botanical standard is a certified reference standard obtained from American Herbal Pharmacopoeia, Chromadex, Alkemist Labs or United States

Pharmacopeia and is accompanied by a CofA.

6.2.2 A second tier standard is a reference material obtained from a recognized source other than first tier and is accompanied by a CofA.

Examples of recognized sources: Sigma, Spectrum, etc.

6.2.3 A third tier botanical reference standard is a raw material of similar composition (extraction format) obtained from a raw material vendor. The material must be obtained from a vendor that is not used by Ion Labs as a source of the raw material for production unless the material is either patented, the raw material manufacturing process is proprietary, requires enzymatic digestion or they are the sole manufacturer of the raw material. A lot of material not used in Ion Labs production is required if using a standard from the same vendor used in production. Raw materials that contain certain excipients or flow agents such as maltodextrin are not to be used for FTIR identification. When FTIR identification is acceptable, preference is given to a composite scan of multiple raw material sample lots. The sub hierarchy for vendor samples is:

6.2.3.1 A composite average of up to three different vendors that are not used for purchasing the specific raw material for finished product. This requirement applies to general raw materials that can be supplied from multiple vendors.

6.2.3.2 A composite average of up to three samples from the same vendor using lots of material not to be used in finished products at Ion Labs.

6.2.4 Third tier standards also include samples that have been qualified by an external lab (i.e. raw materials that have been tested by Alchemist/Advanced Labs, Gibraltar, etc.)

6.3 Preparation of finished product blend standards

6.3.1 A sample of the finished product blend for the first pilot or production batch may be collected for each unique formula or formula modification for use as a general identity / blend uniformity reference standard for all subsequent lots.

6.3.2 A finished product blend may be prepared by R&D for a formulation. R&D may also make specific finished product blends required as a result of a deviation which alters the formulation in production or if a new raw material vendor is used that significantly changes the IR spectrum.

6.3.3 For instances where the finished product is tableted and has a correlation to the reference standard below 0.90 tableting will be performed on the standard using similar conditions to the finished product sample before comparing on FTIR.

6.3.4 In the event a standard cannot be established to verify blend uniformity and identity, other metrics are required to demonstrate blend uniformity and identification of the formula. For inclusive FTIR results, an OOS is not required if scientific justification is given as to why FTIR is not suitable in a particular instance or identification and blend uniformity are demonstrated using other test methods and techniques.

6.4 Hierarchy of use - Stability reference spectra

6.4.1 The stability reference spectra is the T=0 release spectra of the finished product that has not been recrystallized.

6.4.1.1 The use of recrystallization is not permitted during stability testing unless directed by an Out of Specification investigation or the Product Profile.

7.0 Libraries

7.1 Raw Material Qualitative Standard Library

7.1.1 For analytical standards that are used for qualitative assessment refer to SOP D-107 USP Primary Reference Standards, Section 6.2 for instructions on documenting and assigning a unique identifier for each USP Primary standard. See D-106 Analytical Standards, Section 6.2 for instructions on documenting and assigning a unique identifier for each Analytical Standard.

7.1.2 For pure chemicals, complex-defined chemical mixtures, and botanicals that are not used as quantitative standards the reference standard information will be logged and tracked in the Qualitative Standards log book.

7.1.3 On form D-109-F1 Qualitative Reference Standard Log, the following information will be included:

7.1.3.1 Standard Material Description

7.1.3.2 RMID#

7.1.3.3 CofA (Y/N)

7.1.3.4 Vendor / Source

7.1.3.5 Lot #

7.1.3.6 Quantity and Date received

7.1.3.7 Logged by/Date

7.2 The Qualitative Reference Standard Electronic Log will record at minimum the following information on the Reference Master Standard spreadsheet:

7.2.1 CofA available (Y/N)

7.2.2 Raw Material ID number (if available)

7.2.3 Name of chemical/botanical along with scientific name, extract ratio /% purity, plant part or other identifying information

7.2.4 Vendor/Source

7.2.5 Lot number

7.2.6 Date received or last audited

7.2.6.1 When a standard has expired or has been depleted the standard information on the Qualitative Reference Standard Electronic Log will be transferred to a new page under tab <Obsolete>.

7.2.6.2 A separate tab labeled <Cert. Ref. Stds.> will contain a subset of all the certified botanical reference standards.

7.2.6.3 A separate tab labeled <Fine Chemical Stds.> will contain a subset of all the fine chemical (non-raw material) standards.

7.2.6.4 On the first day of every month a copy of the current electronic log will be archived in a subfolder to the primary log. The copy should be identified by adding the date to the file name.

7.2.6.5 A CofA for each of the qualitative standards will be filed in a binder in alphabetical order. The RMID will be written on the top of each CofA. CofAs that are obsolete will be stored alphabetically in the back of the binder separated from the active CofAs.

7.2.6.6 The physical samples will be valid for no more than three years from date of receipt for botanicals and no more than five years from date of

receipt for fine chemicals. The receipt date should be written on the standard packaging. The vendor expiration supersedes the receipt date.

7.2.6.7 FTIR scans are kept electronically and hardcopies are made of the scans including the analysis for raw material and finished product testing packets. FTIR Standard scans can be used indefinitely.

7.3 HPLC spectral and MS libraries

7.3.1 Spectral and MS libraries are archived in separate folders within the filing system of the chromatography software by associated SOP # and analyte.

7.3.2 For chemical identification by UV/VIS chromatography a 3-D UV/VIS reference spectrum library is collected at the retention time of the analyte using an appropriate reference material diluted across the validated range of the assay. A separate reference library will be generated for each set of mobile conditions for a given analyte.

7.3.3 For mass spectral identification a sample can be injected directly into the detector and the material identified by molecular weight and verified using both positive and negative polarity.

7.3.4 For botanical identification using MS a molecular weight signature will be generated using appropriate reference standards. Raw materials will be tested against the MS reference library for identification by peak matching with a suitable number of peaks between sample and standard.

7.4 Finished product blend library

7.4.1 Finished product blends for dietary supplements will be given a unique identifier using the last two digits of the year – identifier (FPB) – and the formula number the standard relates to with a lower case letter to distinguish multiple reproductions of a blend. Active standards previous to this revision were given a unique identifier.

Examples of nomenclature: 13-FPB-6012a, 14-FPB-6152b, etc.

7.4.2 Form D-109-F2 Finished Product Blend Reference Standard Log will record the following information:

7.4.2.1 Unique identifier

7.4.2.2 Name of product

7.4.2.3 Formulation #

7.4.2.4 Date of creation

7.4.2.5 Date of expiration

Example of nomenclature: 13-FPB-6010c

7.4.3 All certified finished product blends for dietary supplements will be valid for 2 years from date of creation. They cannot be recertified. The FTIR reference scans can be used indefinitely.

7.4.4 Finished product blend standards will not be used for the identification of pharmaceutical preparations. Pharmaceutical preparations will be identified by the analytical characterization of the finished product to include identification of all active ingredients and their respective strengths.

8.0 Qualifying a Standard

8.1 For standards to be used for HPLC spectral analysis the pure chemical must test as a chromaphore with an absorbance spectrum in the UV/VIS spectrum and comply with section 6.1.

8.2 For standards to be used for FTIR they must meet the following qualification:

8.2.1 Fine chemicals NLT 0.90.

8.2.2 Botanicals NLT 0.80 or a 5 peak match.

8.3 For a standard to be used for TLC analysis it must comply with section 6.2.

8.4 Standards can also be qualified using an appropriate USP/FCC positive ID test.

8.5 For a standard to be used for MS analysis, it must comply with section 6.1.

9.0 Revision History

Revision	Date	Description of Changes	CCR #	By
1	02/21/13	New	-	-
2	11/07/13	Redefined standard hierarchy and criteria for selection. Added section on finished product blend certification. Added information for MS. Expanded nomenclature of standard identifiers. Created new finished blend log book.	13-1026	B. Johns
3	03/12/14	Added tableting of finished product reference standard. Added TLC standard qualification. Reformatted document for easier reading.	14-0187	B. Johns
4	12/01/14	Added criteria for pharmaceutical standards. Eliminated log D-109-F1 and replaced with an electronic log. Changed nomenclature for identification of standards. Updated responsibilities.	14-0964	B. Johns
5	12/22/15	Added use of blend material for finished product FTIR reference standard.	15-1276	B. Johns
6	04/08/19	Scheduled review: Added to third tier standard.	19-0236	J. Maignan

ION LABS QUALITY FIRST	RM Qualitative Reference Standard Log		
	Form: D-109-F1	CCR No. 19-0236	Revision: 6

Description	RMID #	CofA(Y/N)	Vendor/Source	Lot #	Quantity and Date Received	Logged By/Date

ION LABS QUALITY FIRST	Finished Product Blend Qualitative Reference Standard Log		
	Form: D-109-F2	CCR No. 19-0236	Revision: 4

ID #	Description	Formulation #	Date Created	Date Expired	Certified (Y/N)	Logged By/Date