

Standard Operating Procedure

Title: Management of Reference Substances

Department	Laboratory	Document no	LAB-020
Prepared by:		Date:	Supersedes:
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Document Owner

Laboratory Manager

Affected Parties

All Laboratory staffs

Purpose

To describe a procedure for ordering, referencing, storing, use and general register maintenance for Reference Substances.

Scope

It is the responsibility of the Laboratory staff using the Reference Substance to:

- Ensure its availability and use within expiry.
- Follow the relevant procedures in this SOP.

It is the responsibility of the Laboratory staff assigned to "Reference Substances Maintenance" to:

- Order Primary Reference Substances.
- Order Breakdown Product/Impurity Reference Substances.
- Order any Secondary Raw Material Reference Substance Type 2 attained from within the internal and external sites.
- Order Primary Reagent Reference Solutions.
- Log and reference all Reference Substances received.
- Follow the procedures in this SOP.

Definitions

Primary Reference Substance (PRS)	A Reference Substance or chemical Reference Substance manufactured and tested to compliance by a certified source.
Primary Reagent Reference Solution (PRRS)	A reference reagent/solution or chemical reference reagent/solution manufactured and tested to compliance by a reputable source.
Secondary Raw Material Reference Substance (SRMRS)	A Reference Substance, whose purity has been established against a Primary Reference Substance. Used primarily in routine analysis.
Breakdown/ Degradation Product (BDP)	The material substance resulting from the decomposition of the Reference Substance. A breakdown product manufactured and tested to compliance by a certified or reputable source is also a Primary Reference Substance.
Impurity	Contaminants found with active substance. These contaminants may be incompletely removed precursor materials or other impurities from the manufacturing process. An impurity of high purity manufactured and tested to compliance by a certified source is also a Primary Reference Substance. Note: To avoid confusion between impurities and breakdown products, impurities will be referred to as breakdown products when referencing Reference Substances.

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Procedure

1. Primary and Impurity Reference Substance

1.1. Certified and reputable Primary and Impurity reference substances sources

1.1.1. Primary and Impurity Reference Substances as indicated under definitions, are substances manufactured and tested to compliance by a certified source. The certified sources from which these quality Reference Substances can be obtained from are, British Pharmacopoeia (BP), United States Pharmacopoeia.

1.1.2. Analytical reagents can be used as Primary Reference Substances under special circumstances, particularly if the substances are not obtainable through the above Certified sources. Where this is the case a Reputable Supplier should be used and a Certificate of Analysis for the substance should be obtained.

1.2. Ordering of Primary and Impurity Reference Substances

To arrange for an order of a Primary and Impurity Reference Substance to be ordered by the assigned Laboratory Staff doing Reference Substance maintenance, simply contact them with the complete details of:

- Reference Substance needed
- The Pharmacopoeia to buy from
- The Pharmacopoeia catalogue number
- The number of bottles needed (include weight per bottle, e.g. 2 x 25mg bottles)
- The urgency requirement

It is appropriate for the assigned Laboratory staff doing Reference Substances maintenance to advise Laboratory staff that an order has been placed and indicate an estimated time of receipt.

The following should then be sent to the Pharmacopoeia (**Note:** Send by registered mail.):

- Letter addressed to the department indicating enclosed items and indicating an order is being placed,
- Copy of Purchase Order Number,
- Copy of Licence to Import,
- Payment details where applicable,

If the pharmacopoeias requested a statement of use for the Reference Substance being ordered, so it is appropriate to include in letter a statement for appropriate use.

Note: Follow local regulatory guidelines for importing reference substances.

1.3. Registration of the Primary and Impurity Reference Substances

1.3.1. When the reference substance is received, sign it off as received on the Laboratory "Order book".

1.3.2. Assign a reference substance reference code and enter information as appropriate onto the "Reference Substances log" (see section 6).

1.3.3. Compile the data in the "Primary and Impurity Substance Summary Sheet" form **Form-330** with the relevant information to reflect Reference Substances log Book entries. File the manufacturer's "Certificate of Analysis" in the appropriate Laboratory office cabinet.

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- 2.2.1. When the PRRS is received, sign it off as received on the Laboratory "Order book".
- 2.2.2. Assign a reference substance reference code and enter information as appropriate onto the "Reference Substances log Book" (see section 6).
- 2.2.3. Compile the data to the form **Form-345** with the relevant information to reflect "Reference Substance Log Book" entries. File the manufacturer's "Certificate of Analysis" in the appropriate Laboratory office cabinet
- 2.2.4. **Note:** It is not important to place "masking tape" around the lid of the bottle. These bottles are supplied with an unbroken seal, and the analyst should remember to write down "Date bottle opened" and advise the assigned laboratory person to update information on Summary Sheet and on Reference Substances Log.
- 2.2.5. These Reagent bottles are generally very big, so leave on them their own label, which is appropriate for toxicity information, and place a "Primary Reagent Reference Solutions" label (**Form-360**) on the bottle, which has been filled in with the appropriate known information.
- 2.2.6. When all information on the label has been filled in, normally by the time the "Date bottle opened" is known, place a layer of sticky tape over the label to protect the label.
- 2.2.7. Place bottle in "Main Lab Desiccator" storage location together with other PRRS.

2.3. Coding the Primary Reagent Reference Solutions

The PRRS are coded to be included in the Reference Substances Log Book. The reference code for PRRS is generated using the following format:

- PRRS\Sod\XXXX\1
- The first section indicates that the substance is a Primary Reference Reagent Solution.
- The second section indicates the first three letters of the reagent solution name. The example above, "Sod" is for Sodium.
- The third section indicates the manufacturer's Batch number for the reagent solution collected from the C of A.
- The fourth section indicates the container/unit number.

3. Secondary Raw Material Reference Substance (SRMRS)

3.1. Secondary Raw Material Reference Substance Source

The Secondary Raw Material Reference Substance (SRMRS) can be prepared by sampling the purchased Raw Materials active substance, test these against a Primary Reference Substance (PRS) to establish its purity and then use these in routine analysis. These "Raw material" active substances are originally used for manufacturing products, received with manufacturer's Certificate of Analysis and tested to conform to specifications by Laboratory on arrival.

3.2. Ordering Raw Materials for Secondary Raw Material Reference Substance

Raw materials to be used as Secondary Raw Material Reference Substance are sampled by sampling personnel in warehouse Sampling Booth at the time of arrival according to section 4 of **SOP WAR-045**.

- Where a further sample of the raw material is needed from the bulk raw material, it can be ordered through the Warehouse system. The assigned Laboratory staff should do this by compiling a Sample Request form (**Form-010**) (see **SOP WAR-045**) and sending to warehouse sampling personnel.

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- The first section indicates that the substance is a Secondary Raw Material Reference Substance.
- The second section indicates the first three letters of the Active family of the Secondary Raw Material Reference Substance.
- The third section indicates the Laboratory Batch number of the original "Raw material".
- The fourth section indicates the last 2 numbers of the year the sample was taken from the "Raw material" bulk to be used as a Secondary Raw Material Reference Substance.
- The fifth section indicates the number bottle sampled.

3.5. Secondary Raw Material Reference Substance testing completion

- 3.5.1. Once testing on the Secondary Reference Substance is completed, enter results and information onto **Form-325**. Attach all calculation sheets including chromatographs to the sheet.
- 3.5.2. All tests are done according to control Testing Methods listed in the "Raw Material Specification and Test Report" for the corresponding material.
- 3.5.3. The sample bottle, test results and printed documents and the filled Summary sheet **Form-325** will be handed over to authorised Laboratory staff to check thoroughly the testing results and approve the Secondary Raw Material Reference Substance for use as such by signing the bottom section of the "Secondary Raw Material Reference Substance Summary Sheet" (**Form-325**) to confirm the "Checks required" as described below have been performed.
- 3.5.4. **Checks required:**
 - Check all calculations.
 - Check that the physical appearance is correct when compared against Raw Material Control Method or Pharmacopoeia.
 - HPLC testing has been performed under recommended guidelines i.e. number of samples prepared and injections performed conform, including % relative standard deviation, averages and all calculations results show to be within specified limits of accuracy. Check also that the standard preparations have been made to fit the linear range validation for the control method used in the testing. Also check chromatogram quality is acceptable.
 - The assay results must reflect the intended use concentration expression as well as the expression shown in the relevant pharmacopoeia for the substance and both should be shown.
 - Water Content or Loss on Drying results for the SRMRS have been done where appropriate and results also conform to specified limits of the pharmacopoeia.
 - Check that all fields of the "Secondary Raw Material Reference Substance Summary Sheet" have been completed by the Laboratory analyst who tested the SRMRS sample, including book references for results traceability.
 - **Note:** Where a sample is found to be outside any limits for either of the tests conducted an Out of Specification investigation should be conducted. See **SOP LAB-055**.
- 3.5.5. Enter information onto the "Reference Substances Log Book".
- 3.5.6. Remove the "In-process Secondary Raw Material Reference Substance" label off the bottle and replace it with a "Secondary Raw Material Reference Substance" label (**Form-350**).

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The following rules are also applied:

- 5.1. PRS - Pharmacopoeia RS- Primary Reference Substances are given a maximum shelf life of 18 months after opening. When the expiry date published by the pharmacopoeias is within this period, the pharmacopoeial expiry date will take precedence. Substances that are purchased for identity use, once opened, can be used until the PRS expiry date is published, unless special consideration requirements are applicable for the substance.
- 5.2. PRRS - the manufacturer's expiry date is the final use by date of any bottle of solution. When the bottle is opened and in use, a one-year expiry date from the date the bottle is opened is set for the solution, providing this date does not exceed the manufacturer's expiry date in which case this date must be adhered to.
- 5.3. SRMRS - These RS should be re-tested in-house yearly against PRS. The re-test date for these may be set at a maximum of 1 year from this testing date, but the substance may not be used beyond the Expiry/ Re-test date on their Certificate of Analysis or the documented stability profile time frame for the substance, where expiry or re-test details are not published by the manufacturer or would indicate substance can be used further.
- 5.4. NO EXPIRY - Where an Expiry/ Re-test date is not provided by the manufacturer of any RS, a maximum use by period of 3 years from the date of manufacture (or receipt when date of manufacture not available) of the RS can be applied for the RS, unless special expiry requirements must be adhered to. Reagent Substances used as PRS with no expiry can be extended to a 5-year use by period from the date of manufacture or date bottle received as in general analytical use if used for identity purposes only. It is appropriate to contact manufacturer's to endeavour to obtain an Expiry/ re-test date for substances.

6. The Reference Substances Log Book

- 6.1. The log book is divided into several "sections" identifying the separate "types" of Reference Substance and relevant information.
 - 6.1.1. **Notes section** - This section provides the space to point out relevant general information regarding the spreadsheet including notes on how to make changes and find your way around it.
 - 6.1.2. **Primary and Impurity RS section** - This section is for information on Primary and Impurity Reference Substances.
 - 6.1.3. **Primary Reagent Reference Solutions (PRRS) section** - This section is for information on Primary Reagent Reference Solutions.
 - 6.1.4. **Secondary Raw Material Reference Substance section** - This section is for information on Secondary Raw Material Reference Substance..
 - 6.1.5. **Expiry Check PRS section** - This section provides communication of expiry dating checked by the authorised Lab. staff responsible for Reference Substances maintenance checked against pharmacopoeial catalogue.

7. Summery of Changes

Version #	Revision History
LAB-020	New

End of Procedure

**Secondary Raw Material Reference Substance (SRMRS)
Summary Sheet**
(Ref. SOP LAB0-020)

In-house Reference Code					
Ref. Sub. Description Raw Material Code					
Laboratory Batch No		Storage Location			
Manufacturer		Supplier			
Manufacturer's Batch No		Storage Temperature Requirement			
Manufacturer's Assay & Assay Description.					
Date sample received by the Laboratory		Quantity received by Lab (originally)		Date bottle first opened	
Manufacturer's Expiry Date		Re-test date (set at 1 year from in-house testing date)			
Date tested/ re-tested in-house for Assay		Finished Goods control method used to test Assay			
Analyst testing Assay		Workbook reference of analyst testing Assay			
%Water Content (WC) or %Loss on Drying (LOD)		Raw Material Control Method used to test WC or LOD			
Analyst testing WC/LOD		Workbook reference of analyst testing WC/LOD			
Assay results & Description	Expressed as needed during use: (To appear on label of bottle after testing)				
	Expressed as in appropriate Pharmacopoeia:				
Breakdown Products Detected? Quantified?					
Physical appearance of SRMRS (see Raw Material control method)					
Analyst who performed assay / entered results from certificate of analysis (please circle)					
Name:		Signature:		Date:	
Please make sure the following are attached to this form:					
<ul style="list-style-type: none"> • Completed Form-340 to show calculations and resulting Chromatograms • Manufacturer's Certificate of Analysis • Copy of Raw Material Specification and Test Report showing in-house testing results. • All other summary sheets & testing results previously done on this bottle of reference substance 					
Pharmacopoeia Limits for SRMRS	BP USP EP (Please circle)	Assay Limit & Description		WC/LOD Limit	
This bottle of SRMRS has been APPROVED / REJECTED (please circle) by second Analyst for use as a Secondary Raw Material Reference Substance.					
Name:		Signature:		Date:	
Date bottle finished or discarded including reason (complete when known)					
Comments					

**Primary Reagent Reference Solutions (PRRS)
Summary Sheet**
(Ref. SOP LAB-020)

In- House Reference Number	
Reagent Reference Substance name	
Manufacturer	
Supplier	
Manufacturer's Batch number	
Manufacturer's Assay and Assay description	
Manufacturer's Re-test/ Expiry date	
Catalogue reference number	
Date Substance received	
Quantity received	
Storage temperature requirements	
Storage location	
Date bottle first opened	
Expiry date- set at 1 year from date opened	
PLEASE MAKE SURE THE FOLLOWING ARE ATTACHED TO THIS FORM: * MANUFACTURER'S CERTIFICATES OF ANALYSIS, WHERE SUPPLIED, FOR THE REFERENCE SUBSTANCE ABOVE.	
Date bottle finished or discarded (complete when known)	
Comments	

In- Process SRMRS Label

(Ref. SOP LAB-020.)

In-Process Secondary Raw Material Reference Substance

In-house Ref. Number.....
Reference Substance Name.....
Lab. Batch No.....Team.....
Date bottle opened.....Storage.....
Note: This substance must not be used as a reference substance in analysis until it is quantified against a primary Ref. Sub. And approved for use

In-Process Secondary Raw Material Reference Substance

In-house Ref. Number.....
Reference Substance Name.....
Lab. Batch No.....Team.....
Date bottle opened.....Storage.....
Note: This substance must not be used as a reference substance in analysis until it is quantified against a primary Ref. Sub. And approved for use

In-Process Secondary Raw Material Reference Substance

In-house Ref. Number.....
Reference Substance Name.....
Lab. Batch No.....Team.....
Date bottle opened.....Storage.....
Note: This substance must not be used as a reference substance in analysis until it is quantified against a primary Ref. Sub. And approved for use

In-Process Secondary Raw Material Reference Substance

In-house Ref. Number.....
Reference Substance Name.....
Lab. Batch No.....Team.....
Date bottle opened.....Storage.....
Note: This substance must not be used as a reference substance in analysis until it is quantified against a primary Ref. Sub. And approved for use