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RWANDA FDA Rwanda Food and Drugs Authority	**Title:** Procurement and control of reference substances and reference materials	

RWANDA FDA QUALITY CONTROL LABORATORY CONTROLLED DOCUMENT Toll free : 9707

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INSTRUCTIONS

1.Controlled issues of this SOP may **not** be copied
2. **All** amendments are written on the page provided
3. **Only** authorized, numbered, stamped copies of this SOP as described in the SOP for document control
4. This SOP shall **not** be used outside the Rwanda FDA Quality Control Laboratory without the authority of the authorizing personnel.

1. Table of Content

2. Purpose

To lay down a procedure for procurement of reference substance and reference material handling, transport, storage of reference standards and working standards in order to prevent contamination and deterioration and in order to protect their integrity.

3. Scope

This procedure is applicable for all the reference substances and reference materials used in QCL.

4. Policy

4.1. The ISO/IEC 17025:2017 Clause 6.4.1.: Laboratory shall have access to equipment (including, but not limited to, measuring instruments, software, measurement standards and reference materials.

4.2. WHO Good Practices for Pharmaceutical Quality Control laboratories WHO Technical report Series No 957, 2010, Annex 1, section 2" Reference substances and reference material"

5. Definitions and Abbreviations

5.1 The definitions and abbreviations provided in the QMS/SOP/001 document of Rwanda FDA and QCL/MAN/001 shall be applied.

5.2 **Primary standard**: A standard shown to have suitable properties for the intended use; the demonstration of suitability being made without comparison to an existing standard;[3]

5.3 Standard that is designated or widely acknowledged as having the highest metrological qualities and whose value is accepted without reference to other standards of the same quantity, within a specified context.

5.4 **Secondary standard:** A standard established by comparison with a primary standard;

5.5 **Reference material (RM):** Material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process;

5.6 **Certified reference material (CRM):** Reference material characterised by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability;

5.7 **Reference substance (or standard):** An authenticated, uniform small amount of material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use; In this case a Reference standard may be a CRM, a reference material, a primary standard, a secondary standard and reference cultures.

5.8 **Log:** Record showing how the reference standards were used at different times;
5.9 **T**: tray
5.10 **I.P.**: Indian Pharmacopoeia
5.11 **B.P.**: British Pharmacopoeia
5.12 **U.S.P.**: United State Pharmacopoeia
5.13 **E.P**: European Pharmacopoeia
5.14 **Ref.**: Reference
5.15 **Std.**: Standard
5.16 **RS**: Reference Substance
5.17 **RI**: Reference Impurity
5.18 **EDQM:** European Directorate for Quality of Medicines

6. Responsibility

6.1 Division Manager shall ensure the availability and procurement of reference standard well in advance;
6.2 Laboratory officers shall prepare technical specifications for all reference substances and materials needed;
6.3 Designated QMS is responsible of implementation and maintenance of this SOP and archives superseded or obsolete documents.
6.4 All Quality Control Laboratory staff are responsible for verifying that the official version of this document is used,
6.5 Laboratory Officers are responsible to ensure adequate implementation of this SOP in their respective working area.

7. Distribution

7.1 Designated Quality Management Sytem staff of Rwanda FDA
7.2 Designated Quality Management Sytem staff of QCL
7.3 Director of Units
7.4 All laboratory officer and Technicians

8. Safety Precautions

8.1. All drug analysts are required to read and understand the material safety data sheets for all reference standards used while performing laboratory tests;

8.2. Always wear gloves and a laboratory coat and/or apron while transporting reference standard to storage facility, to weighing room and sample preparation room; this practice prevent cross contamination of the reference material;

8.3. Always use the available face masks and splash guards when necessary; this practice prevent cross contamination of the reference material;

9.0 Procedure

9.1. Director of Unit assign laboratory officer to prepare technical specifications of all reference substances and reference materials needed by laboratory and the procurement of reference is also done according to the law n° 62/2018 of 25/08/2018 governing public procurement.

9.2. QCL procure the reference standard of known metrological traceability like USP, B.P, EP, NIST etc. from approved supplier.

9.3. On receipt of the reference standard, check all the details on the label, certificate of analysis or on the website of manufacture like EDQM, USP and enter the respective detail in the format of records for reference substance and reference materials;

9.4. Assign the Ref. number for Ref. std. and impurity standard as follows:

RIA_{01} for Ref. Impurity standard and RSA_{01} for Ref. standard respectively.

9.4.1. A unique identification number, is assigned to each batch of reference substance;

9.4.2. A new identification number is assigned to each new batch;

9.4.3. This number is marked on each vial/container of the reference substance;

9.4.4. The identification number is quoted on the analytical worksheet every time the reference substance is used;

9.4.5. The reference substance Log (QCL/FMT/003), see appendix IV, is always filled before taking and after returning the reference substance/material.

9.4.6. In the case of pharmacopoeia reference substances, a batch number and/or the batch validity statement should be attached or written to the worksheet;

9.4.7. The register for control of reference substances and reference materials (**QCL/REG/006**) should be maintained and contains the following information:

(a) the identification number of the substance or material;
(b) a precise description of the substance or material;
(c) the source;
(d) the date of receipt;
(e) the batch designation or other identification code;
(f) the intended use of the substance or material (e.g. as an infrared reference substance or as an impurity reference substance for thin-layer chromatography);
(g) the location of storage in the laboratory, and any special storage conditions;
(h) Any further necessary information (e.g. the results of visual inspections);
(i) Expiry date or retest date;

(j) Certificate (batch validity statement) of a pharmacopoeial reference substance and a certified reference material which indicates its use, the assigned content, if applicable, and its status (validity); and

(k) In the case of secondary reference substances prepared and supplied by the manufacturer, the certificate of analysis.

9.4.8. To implement this, a format of records is used to contain all of the above information said in 9.4.7.

9.5. The reference standards must always be used for the purposes for which they are intended; and always be used within their validity period.

9.6. Reference standards shall be properly closed after use.

9.7. In case there is empty vial or container of reference substance/material, the container shall be discarded into suitable waste container.

9.8. **Transport**

9.8.1. In the transportation of reference standards; they should be transported in the original containers;

9.8.2. They should be transported and in suitable recommended conditions as indicated on their label.

9.9. **Records to be done when a reference standard is supplied**

9.9.1. The procured reference standards are of two main types, primary standards and secondary standards;

9.9.2. Whenever QCL receives a reference standard, this last is registered in the register "Control of reference substance and reference materials" (QCL/REG/006), see Appendix I

9.9.3. Then, when the reference substance/reference material is issued to specific laboratory for use this last records all received reference substance/materials in a format of list of reference substances and reference material **(QCL/FMT/002)**, appendix II.

9.10. **Giving codes to new chemical reference standard**

9.10.1. After receiving a new standard shall assign a specific code and register it; this means that all standards possessed by QCL are recorded systematically.

9.10.2. The code consists of three alphabetic letters, two numbers and hyphen.

9.10.3. Example_1: RSM_1-01 where RS means Reference Substance M means Standard whose initial letter is M, $_1$ is a number given to metronidazole when it was received and 01 means the first received batch of metronidazole. Note that RS can be replaced by RI to represent Reference Impurity.

9.10.4. Example_2

Name of standard	Initial Letter of the Name of std	No of name of std	No of the batch of std	Full code
Metronidazole RS	M	1	01	RSM_1-01
Metronidazole RS	M	1	02	RSM_1-02
Mebendazole RS	M	2	01	RSM_2-01
Paracetamole RS	P	1	10	RSP_1-10
Pyrazinamide RS	P	2	10	RSP_2-10

9.10.5. When a paracetamol standard has P_1-10, P shows the initial letter, No 1 means that among standards whose initial is P paracetamol was numbered the first; finally 10 stands for No of paracetamol std batch received. Now it is very clear that P_1-10 can't stand for Pyrazinamide.

9.10.6. They are stored into well labelled racks like (A-D) rack, (E-H) rack, (I-N) rack, (O-T) rack and (U-Z) rack. Therefore, Paracetamol is kept into (O-T) rack for easy of identification.

9.11. Format of reference substances and reference materials Log

Date	Name of standard	RS Code	Issued to:	Amount taken, mg	Time of return	REMARK(firstly open or finished or …)	SIGNATURE
Ex.:14.12.2020	Paracetamol RS	RSP_1-10	Felix T	15mg	10:00am	Ex.:firstly open	.....

The above table shows records that must be taken once a RS is used.

9.12. Labelled trays

9.12.1. Refrigerator or container in which reference substances or RI are stored is partitioned in five trays: T_1 allocating A-D, T_2 allocating E-L, T_3 allocating M-O, T_4 allocating P-U and T_5 allocating V-Z.

9.12.2. Note: the stated letters are initials of reference standard name.

9.13. **Storage of standards and Monitoring temperature/ laboratory**

9.13.1. In general, compendial standards should be used as soon as possible after receipt, i.e. it is recommended to order them when required for a test and not with the intention to store them;

9.13.2. If the latter is unavoidable they should only be stored as long as the batch is valid and under the recommended storage conditions;

9.13.3. We should keep in mind that RS which requires low temperature storage conditions (02 to 08 °C) these are stored in fridge, other reference substance with storage condition of ultralow temperature have to be stored into freezer;

9.13.4. Fewer may be stored in conditions of room temperature after checking details on their required storage conditions mentioned by manufacturer;

9.13.5. Any reference substance/material suited to room temperature condition during its storage must be kept under the same conditions.

9.13.6. Reference substances and Reference impurity are stored into different trays each one labelled in alphabetic order respectively to initial letters of the name of reference substance/impurities.

9.13.7. Therefore the Data for temperature monitoring are recorded every working day by the person in charge assigned by the LO by filling the form annexed on this document (QCL/FOM/017), see Appendix III.[3]

9.13.8. Reference materials whose storage condition require room temperature are kept in a room where the data regarding temperature and relative humidity are recorded every working day by the person in charge;

9.13.9. When Freezer is used, it should be securely locked and access restricted to designated personnel.

9.14. **Checking Stability And validity of standards**

9.14.1. In order to fulfil the ISO/IEC 17025:2017 requirements quality control Laboratory ensure that the reference standard conform with the specifications and the laboratory requirements before being used.

9.14.2. Check documentation accompanying the supplied reference standard; use online data where applicable especially for pharmacopoeia standard but non-compendial standards require deep checking described below;

9.14.3. Ckeck suitability of physico-chemical or biological critical quality especially attributes for the intended purpose including but not limited to identity by IR spectrum or by comparing immune-diffusion gels, or alternatively by HPLC/DAD i.e. comparison of spectra/chromatograms);

9.14.4. The quality checking with HPLC, the spectrum of non-compendial standard is compared to that one generated by pharmacopoeia standard(USP, Eur.P,...)

9.14.5. For researching validity of compendia standards use online EDQM and USP Catalogue where applicable and use the standard only when you found it valid;

9.14.6. For all non-compendia reference standards, re-testing is performed in order to guarantee their continued "fitness for use"; retesting procedure can include the test mentioned in the annex V(Summary of analytical and documental work that can be carried out to verify suitability of a reference standard (non-exhaustive list.);

9.14.7. Re-test the standard when it happen that it is beyond its shelf-life and in any situation where the purity of non-compendial standard is doubtful.

9.14.8. Choose one standard per major equipment and prepare its control chart;

9.14.9. Retest once per month the selected standard for trend analysis;

9.14.10. When the trend analysis predict a significant change in the properties of the standard, its use is suspended;

9.14.11. One Quality Control Product is selected and used to collect trending chart, per each major equipment;

10. APPENDICE

10.1. Appendix I: Register For Control of reference substance and reference materials, (QCL/REG/006)

SN	Ref. No of the substance or material	precise description of the substance or material	the source	the date of receipt	the batch designation or other identification code given by manufacturer	intended use of the substance	location of storage in the laboratory, and any special storage conditions	Further Information	Expiry date or retest date;	batch validity statement, if applicable.	CoA

10.2. Appendix II: Format of List of Reference Substances and Reference Materials (QCL/FMT/002)

RWANDA FDA

Format for list of reference substance and reference material

Quality Control Laboratory-QCL/FMT/002

A. List of reference substance					
SN	**Name of the article and Its description(lot no, amount, eur.crs or…)**	**Prefix letter**	**Number of the article's batch**	**Code**	**Comment**
1	**Abacavir sulfate, lot RO28LO, 200mg**	RSA_1-	01	RSA_1-01	Eur. CRS.
2	Abacavir sulfate, LOT 1.0, 20 mg	RSA_1-	02	RSA_1-02	USP CRS
3	**Acetazolamide, LOT 1.1, 100mg**	RSA_2-	01	RSA_2-01	Eur. CRS.
4	**Aciclovir, lot 3.0, 75mg**	RSA_3-	01	RSA_3-01	Eur. CRS.
B. List of reference Impurities					
SN	**Name of the article and Its description(lot no, amount, eur.crs or…)**	**Prefix letter**	**Number of the article's batch**	**Code**	**Comment**
1	Name 1 (whose initial is A)	RIA_1-	01	RIA_1-01	
2	Name 1(whose initial is A also)	RIA_1-	02	RIA1-02	
3	Name2(whose initial is A also)	RIA_2-	01	RIA2-01	
4	Name3(whose initial is A also)	RIA_3-	01	RIA3-01	
5	Name 4(whose initial is B)	RIB_1-	01	RIB_1-01	
c. Reference materials (RM)					
SN	**Name of the article and its description(lot no, amount, eur.crs or…)**	**Prefix letter**	**Number of the article's batch**	**Code**	**Comment**

10.3. Appendix III: Temperature monitoring form

RWANDA FDA Rwanda Food and Drugs Authority	**Division:** **QUALITY CONTROL LABORATORIES** **Title: Temperature monitoring form**	Doc. No: QCL/FOM/017 Revision No: 0 Revision date: 01 June 2021 Effective Date:14 June 2021

Month/year:	Name of Laboratory:				Equipment:				Acceptable temperature range:			
Date:	In Build Thermometer (^{0}C)				Independent thermometer (^{0}C)				Remark		Initial and Signature	
	Morning		Afternoon		Morning		Afternoon		Morning	Afternoon	morning	Afternoon
	Time	T^OC	Time	T^OC	Time	T^OC	Time	T^OC				
1												
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10.4. Appendix IV: Reference substances and materials log(QCL/FMT/003)

Date	Name of standard	RS Code	Issued to:	Amount taken, mg	Time of return	REMARK(firstly open or finished or …)	SIGNATURE
Ex:14.12.2020	Ex.:Paracetamol RS	RSP_1-10	Name of analyst	15mg	10:00am	finished	-------

10.5. **Appendix V: Summary of the analytical and/or documental work that can be carried out to verify suitability of a reference standard.**

Intended use	**Example of methods in which the standard is used**	**Example of test to perform**
Qualitative: identification of active ingredient, identification/system suitability mixtures	IR, TLC, LC, MS, LC/DADGC/MS	1.Plausibility check by scrutinising the documentation accompanying the RS i.e. Certificate of analysis. 2. IR: comparison with spectrum in literature 3 LC/DAD: a spectrum obtained from a primary standard or a standard traceable to a primary standard. 4. LC/DAD: comparison of the spectrum and/or retention time of the peak with the one generated using primary standard or

		a standard traceable to a primary standard.
Quantitative: assay/purity of active ingredient or finished product	LC, GC, UV	1. Plausibility check by verification of the documentation accompanying the RS i.e. Certificate of analysis. If content, shelf life and traceability to International System (SI) units4 are proven, no additional tests are required. 2. LC/DAD: comparison of the content with a primary standard or a standard traceable to primary standard. 3. For screening tests a Certificate of analysis including the declared content and the shelf-life is sufficient.

10.6. Appendix VI: Document Revision History

Date of revision	Revision number	Author(s)	Changes made and/or reasons for revisio
24 August 2020	0	TUYISHIME Felix	First Issue
01 June 2021	1	TUYISHIME Felix	Clause 10.5 added Section 7: rephrased Clause 9.1 and 9.2 were rephrased

11. **Reference**

11.1. ISO/IEC 17025:2017 Clause 6.4.1," Laboratory shall have access to equipment (including, but not limited to, measuring instruments, software, measurement standards and reference materials."

11.2. WHO Good Practices For Pharmaceutical Quality Control Laboratories

11.3. Guideline for Handling And Use Of Reference Standards In The OMCL Network-PA/PH/OMCL (11) 204 3R;