

General European OMCL Network (GEON) QUALITY MANAGEMENT DOCUMENT

PA/PH/OMCL (11) 204 R9

Handling and Use of Non-Compensial Reference Standards in the OMCL Network

Full document title and reference	Handling and Use of Non-Compensial Reference Standards in the OMCL Network <i>PA/PH/OMCL (11) 204 R9</i>
Document type	Guideline
Legislative basis	Council Directive 2001/83/EC and 2001/82/EC, as amended
Date of first adoption	4 April 2012
Date of original entry into force	May 2012
Date of entry into force of revised document	July 2020
Previous titles/other references / last valid version	Last adopted version: <i>PA/PH/OMCL (11) 204 6R</i>
Custodian Organisation	The present document was elaborated by the OMCL Network / EDQM of the Council of Europe
Concerned Network	GEON

N.B. This OMCL Quality Management System document is applicable to members of the European OMCL Network only. Other laboratories might use the document on a voluntary basis. However, please note that the EDQM cannot treat any questions related to the application of the documents submitted by laboratories other than the OMCLs of the Network.

Note: Mandatory requirements in this annex are defined using the terms “shall” or “must”. The use of “should” indicates a recommendation. For these parts of the text other appropriately justified approaches are acceptable. The term “can” indicates a possibility or an example with non-binding character.

1. Introduction

The Standard ISO/IEC 17025:2017 describes the requirements for the management of the reference standards (RS) in chapter 6.4 “Equipment” and 6.5 “Metrological traceability”. According to the chapter, 6.4.1 reference standards are defined as equipment.

“The laboratory shall establish a calibration program, which shall be reviewed and adjusted as necessary in order to maintain confidence in the status of calibration.” (6.4.7)

“The laboratory shall have a procedure for handling, transport, storage, use and plan maintenance of equipment in order to ensure proper functioning and to prevent contamination or deterioration”(6.4.3)

Therefore, the relevant clauses have to be fulfilled.

The aim of this document is to provide guidance to the OMCL Network on the analytical and/or documental work to be carried out to verify the suitability of non-compendial reference standards such as:

- 1) standards obtained from marketing authorisation holders (MAH);
- 2) standards obtained by purchasing from commercial sources.

It is the responsibility of the OMCL to verify the available data i.e. the certificate of analysis accompanying the reference standard and, where insufficient information is provided, to confirm the suitability of the reference standard by undertaking, where possible, appropriate analytical work, the extent of which depends on the intended use and is based on scientific judgement. For references (reference materials or quality control materials) used to ensure the validity of results in accordance with Standard ISO/IEC 17025:2017 chapter 7.7, their suitability must be ensured.

It is outside the scope of this document to provide guidance on the establishment, manufacturing, labelling, storage, distribution and retesting of European Pharmacopoeia (Ph. Eur.) reference standards, which is covered in Ph. Eur. Chapter 5.12. ‘Reference Standards’.

2. Terminology

Refer to Ph. Eur. Chapter 5.12. ‘Reference Standards’. The term “non-compendial reference standard” means that the reference standard is not sourced from a Pharmacopoeia organisation (EP, USP, BP, WHO or JP). It encompasses primary and secondary reference standards, the latest intended as standard traceable to a primary standard.

3. Suitability of a reference standard in an OMCL

In order to fulfil the ISO/IEC 17025:2017 requirements it is recommended that, alongside this Guideline, the OMCL shall have a procedure in place to ensure that the reference standard conform with the ISO/IEC 17025:2017 and the laboratory requirements before being used.

The suitability of a reference standard shall be demonstrated by verification of the accompanying documentation and/or appropriate physico-chemical or biological critical quality

attributes for the intended purpose/s (e.g. identity by IR spectrum or by comparing immuno-diffusion gels, or alternatively by HPLC/DAD i.e. comparison of spectra/chromatograms). Examples are provided in Table 1.

In principle, use of reference standards for a scope outside the intended use should be avoided. In such cases, e.g. when a reference standard is used outside the scope of its intended use (e.g. assay of the active ingredient in a finished product when only identification is mentioned in the certificate of analysis) or in a method/technique different from the ones given by MAH or monographs, the laboratory shall *demonstrate the suitability for the new intended use. This can be done by carrying out supplementary tests to verify the suitability of the reference standard for the new use (especially if a assigned content is given by another technique), but it can also be done by scientific justification/rationale.*

3.1 Biological reference standards

This section applies to biological reference standards used for routine testing (e.g. OCABR). The principles are not applicable to biological reference standards used in *ad hoc* analytical supporting activities (e.g. CAP).

Biological reference material may include biological standards for potency determination or biological controls used to confirm the validity of assays. A switch from one lot to another may lead to a shift in the results obtained; thus an experimental check and comparison of results obtained with the old and new reference, i.e. a bridging study, is required. In any bridging study, influences from other factors not related to the reference i.e. assay reagents or materials (sometimes also supplied by manufacturers) should be taken into consideration. Qualification of these materials should also be carried out to determine if there is an impact on the values obtained. Changes of reference standards – as well as materials, reagents or controls of biological origin – should therefore be anticipated in order to facilitate continuity of results.

Biological standards are often used to ensure traceability to the first clinical lot. They may be product specific and therefore supplied by the manufacturer. The laboratory should define an appropriate bridging strategy to ensure continuity of results between lots. This can be crucial to avoid repeated invalid results, the occurrence of OOS or delays in testing. In the case of successive bridging of a reference standard, this strategy may include the use of corrective factors for the value assigned to the reference standards in order to align test results over time. There should be a degree of certainty that any shift in results obtained is indeed due to the change of reference lot before considering use of a correction factor.

For the bridging of controls used to confirm the validity of each assay, if the data obtained (e.g. mean, coefficient of variation) with the new control are within the same range as the previous one, limits of acceptability could be kept, although it may be desirable to refine control limits once a sufficient number of data points is available for the new control material. If not, a new control chart should be set up and new limits defined. It may be possible to apply manufacturer's control limits in the OMCL control charts e.g. if the same method is used and there is no indication of systematic differences at the OMCL.

It is strongly recommended to communicate in an appropriate and timely manner with the manufacturer to avoid shortage of reagents and materials and facilitate smooth performance of bridging studies.

Table 1 Summary of the analytical and/or documental work that can be carried out to verify suitability of a reference standard (non-exhaustive list)

Intended use	Example of methods/tests in which the standard is used	Examples of tests to perform ¹
Qualitative: identification ² of active ingredient, preservatives, excipients, peak identification/system suitability mixtures	IR, Raman, TLC, LC, MS, LC/DAD, LC/MS, SDS-PAGE, GC/MS, NMR	<ol style="list-style-type: none"> 1. Plausibility check by scrutinising the documentation accompanying the RS i.e. Certificate of analysis. 2. IR or Raman: comparison with spectrum in literature³ or a spectrum obtained from a primary standard or a standard traceable to a primary standard. 3. 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. 4. LC MS/MS (high resolution). 5. Gel Electrophoresis: comparison of gels obtained with old and new RS. 6. Immuno-diffusion: comparison of old and new RS on the same gel or between gels. 7. NMR
Quantitative: assay/purity of active ingredient or finished product, antimicrobial preservatives	LC, GC, UV, CE, NMR	<ol style="list-style-type: none"> 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.
Quantitative (Biologicals supplied by the MAH): reference material, controls	ELISA, HPLC-PAD, HPLC, GC, ICP-OES, UV, in vivo potency assays, nephelometry	<ol style="list-style-type: none"> 1. Plausibility check by scrutinising the documentation accompanying the RS i.e. Certificate of analysis, establishment data supplied by the MAH. 2. Reference material for routine use (e.g. OCABR): OMCL to generate data and calculate bridging factors where applicable. 3. Controls supplied by manufacturer: manufacturer limits may be used or, for biological reference materials for routine use, a new control chart can be set up if there are significant differences.

¹ it is the responsibility of the OMCL to decide when suitability tests should be performed i.e. before use or during analysis of test samples.

² whenever possible or necessary, orthogonal techniques (e.g. TOF-MS, NMR, elemental analysis, etc.) could provide further confirmation of the identity.

³ i.e. published literature of traceable sources or databases.

⁴ traceability of SI units as defined in ISO/IEC 17025:2017 clause 6.5.2

4. Storage of standards

The laboratory shall have a procedure for handling, transport and storage of RS. The conditions should follow recommendations provided by manufacturer or provider supplier or, in the absence of such recommendations, the laboratory should apply a scientific judgment based on experience or scientific data provided by reliable sources.

If expiry/retesting dates are not provided, it is the responsibility of the OMCL to define such a date in accordance with the data/information available (e.g. stability) and scientific judgement.

In certain cases, in order to avoid contamination or deterioration, the standard (e.g. due to moisture intake of hygroscopic substances after repeated use/opening), may be divided into several vials. This operation should be carried out under appropriate environmental conditions to preserve the quality and stability of the sample (e.g. for a frozen standard, the impact of thawing/refreezing steps).

The containers must be clearly identified. Records including relevant data such as identification, location, calibration dates or validity, any other applicable requirement as for clause 6.4.13. shall be retained.

In order to facilitate the handling of non-compensial reference substances, in particular for those intended for multiple uses within the assigned shelf life, a list of the reference standards stored in the laboratory may be established. In addition, access to the standards may be controlled.

5. Monitoring or Retesting of standards

A procedure for retesting of non-compensial reference standards shall be in place in order to guarantee the continued "fitness for purpose" (ISO/IEC 17025:2017 clause 6.4.7), whenever the laboratory decides to retest the reference standard after expiring. Intermediate checks may be performed to maintain confidence of the standard (ISO/IEC 17025:2017 clause 6.4.10). For this purpose, the laboratory may decide to test only the critical quality attributes. However, the extent of testing depends on the intended use of the reference standard and it is based on the scientific judgement. Alternatively, the laboratory may request to the provider an extended shelf life.

If retesting intervals are defined, these can be based on the known or predicted stability, the physico-chemical/biological characteristics and the intended use of the standard. Appropriate documentation to prove suitability of use after retesting shall be retained and include relevant date and period of validity.