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

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1. Introduction

The ISO Standard ISO/IEC 17025 describes the requirements for the establishment, use and handling of reference standards (RS) and reference materials (RM) in chapter 5.6.3 "Reference standards and reference materials" which states:

"The laboratory shall have a program and a procedure for the calibration of its reference standards." (5.6.3.1)

"Checks needed to maintain confidence in the calibration status of reference, primary, transfer or working standards and reference materials shall be carried out according to defined procedures and schedules." (5.6.3.3)

"*The laboratory shall have procedures for safe handling, transport, storage and use of reference standards and reference materials in order to prevent contamination and deterioration and in order to protect their integrity."(5.6.3.4)*

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.

Commercial sources should be registered as approved suppliers in the Quality Management system.

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) and it encompasses primary and secondary reference standards.

3. Suitability of a reference standard in an OMCL

In order to fulfil the ISO 17025 requirements it is recommended that, alongside this Guideline, the OMCL has a procedure in place which addresses the analytical and/or documental work needed to verify the suitability of the reference standard.

The suitability of a reference standard can be demonstrated by verification of the 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. However, if this is not possible, it is strongly recommended to carry out supplementary tests 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.

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 each assay. 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. It is recommended to 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	1. Plausibility check by scrutinising the documentation accompanying the RS i.e. Certificate of analysis. 2. IR (KBr disc/ATR) or Raman: comparison with spectrum in literature[3] or previous reference standard. 3. LC/DAD: overlay of spectrum and comparison of retention times. 4. LC MS/MS (high resolution). 5. 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.
Quantitative: assay/purity of active ingredient or finished product, antimicrobial preservatives	LC, GC, UV, CE, NMR	1. Plausibility check by scrutinising the documentation accompanying the RS: Certificate of analysis. If content, shelf life and traceability to International System (SI) units [4] are proven, no additional tests are required. 2. IR (KBr disc/ATR) or Raman: comparison with spectrum in literature[3] or previous reference standard. 3. Raman. 4. LC/DAD: spectrum overlay and comparison of retention time of the licensed product under test and secondary standard. 5. 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	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 17025:2005 clause 5.6.

4. Storage of standards

Reference standards should be handled and stored according to the recommendations given by the manufacturer/supplier or, in the absence of such recommendations, this should be done in accordance with the 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 order to avoid contamination or deterioration of the standard after repeated use/opening (e.g. moisture sensitive, hygroscopic substances), it can 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 identifiable and records including relevant data such as standard name, batch number/vial number, date of opening, expiry date or retest period and storage conditions, should be available.

In order to guarantee controlled handling of non-compendial reference substances intended for multiple uses within the assigned shelf life, a list of the reference standards stored in the laboratory should be available. In addition, access to the standards should be controlled. Responsible persons for purchase, registration and approval for use of standards should be appointed.

5. Monitoring or Retesting of standards

A procedure and programme for retesting of non-compendial reference standards should be in place (ISO/IEC 17025 clause 5.6.3.3, Intermediate checks) in order to guarantee the continued "fitness for purpose". Once a reference standard has expired, it must be retested before use (ISO/IEC 17025 clause 5.6.3.1 reference standards) or the scope of the standard has to be changed (for example a standard for assay may, under certain conditions, be used for identity only). For this purpose only the critical quality attributes should be tested. However, the extent of testing depends on the intended use of the reference standard and it is based on the scientific judgement of the analyst. Alternatively, an extended shelf life can be certified by the supplier.

If retesting intervals are defined, these should 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 should be produced and labelling/records updated.