THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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What GMP inspectors expect on Reference Standards

EDQM Training Webinars 2024

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European regulatory requirements - reference standards

EU GMP Part II / ICH Q7

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – quality, safety and efficacy

EudraLex

The Rules Governing Medicinal Products in the European Union
Volume 4

Good Manufacturing Practice

Medicinal Products for Human and Veterinary Use

Part II: Basic Requirements for Active Substances used as Starting Materials

Part 1
Chapter 6: Quality Control

ICH HARMONISED TRIPARTITE GUIDELINE

GOOD MANUFACTURING PRACTICE GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS
Q7

Ph. Eur.

EUROPEAN PHARMACOPOEIA 11.3

07/2018:51200
corrected 11.3

5.12. REFERENCE STANDARDS

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EU GMP Part II / ICH Q7 section 11

11.17

→ Primary reference standards should be obtained as appropriate for the manufacture of APIs.

→ The source of each primary reference standard should be documented.

→ Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations.

→ Primary reference standards obtained from an officially recognised source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

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How to comply?

1. Obtain the correct standards

→ EDQM catalogue https://crs.edqm.eu/

Cat. No.	Name	Batch No.
B1220000	Ibuprofen impurity B CRS	11
I0020000	Ibuprofen CRS	6
Y0000140	Ibuprofen impurity F CRS	3
Y0000881	Ibuprofen for peak identification CRS	11

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20 mg of the substance to be examined in 2 mL of *acetonitrile R* and dilute to 10.0 mL with mobile phase A.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with mobile phase A. Dilute 1.0 mL of this solution to 10.0 mL with mobile phase A.

Reference solution (b). Dilute 1.0 mL of *ibuprofen impurity B CRS* to 10.0 mL with *acetonitrile R* (solution A). Dissolve 20 mg of *ibuprofen CRS* in 2 mL of *acetonitrile R*, add 1.0 mL of solution A and dilute to 10.0 mL with mobile phase A.

Reference solution (c). Dissolve the contents of a vial of *ibuprofen for peak identification CRS* (mixture of impurities A, J and N) in 1 mL of *acetonitrile R* and dilute to 5 mL with mobile phase A.

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How to comply?

2. Store & use in accordance with instructions on information leaflet

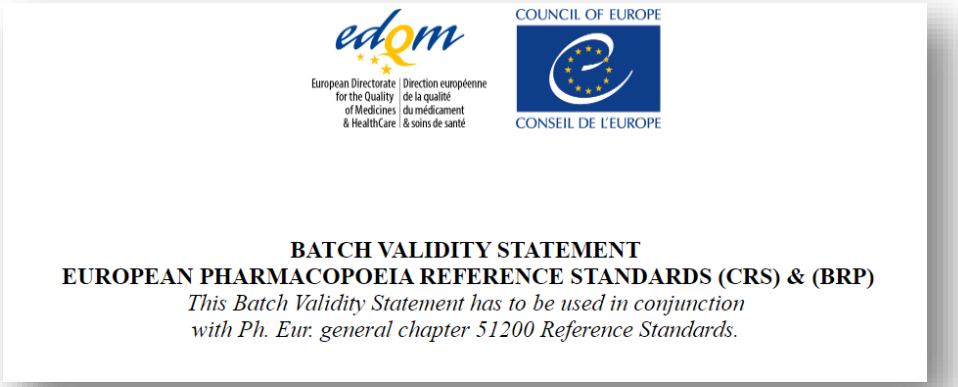
2.5 Instructions for use

The container should not be opened until required for use. Allow the closed container to equilibrate at ambient temperature before opening to avoid uptake of moisture. Use "as is". Do not dry/desiccate before use. Ph. Eur. RS are for immediate use. Once the container has been opened, its entire content must be used immediately. Any further storage and re-use are not warranted.

Storage conditions

In the original container at +5°C ± 3°C, protected from light. Re-instate promptly upon receipt.

3. Ensure the standard batch is valid at the time of use



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BATCH VALIDITY STATEMENT
EUROPEAN PHARMACOPOEIA REFERENCE STANDARDS (CRS) & (BRP)
This Batch Validity Statement has to be used in conjunction with Ph. Eur. general chapter 51200 Reference Standards.

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EU GMP Part II / ICH Q7 section 11

11.18

→ Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established.

→ Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard.

→ Appropriate documentation of this testing should be maintained.

5.12. REFERENCE STANDARDS

4. ESTABLISHMENT OF REFERENCE STANDARDS

4-1. *PRIMARY STANDARDS*

A substance or preparation to be established as a primary standard is characterised by a variety of analytical techniques chosen to demonstrate its suitability for use.

- Characterisation of the substance (structural elucidation) by appropriate chemical attributes such as structural formula, empirical formula, molecular mass or composition. A number of techniques may be used including:
  - nuclear magnetic resonance spectrometry;
  - mass spectrometry;
  - infrared spectrophotometry;
  - elemental analysis.
- Determination of purity:
  - determination of the content of related substances by an appropriate separation technique and/or spectrometric method, where applicable;
  - quantitative determination of water;
  - determination of the content of residual solvents;
  - determination of loss on drying, which may in certain circumstances replace the determinations of water and residual solvents;
  - determination of inorganic impurities (e.g. sulfated ash, atomic absorption spectrometry, inductively coupled plasma spectrometry, X-ray fluorescence spectrometry); the results are usually not used to determine an assigned content, except where they would have an appreciable impact upon it;
  - determination of purity by an independent method (e.g. quantitative nuclear magnetic resonance spectrometry, differential scanning calorimetry or titration where appropriate; the results of these determinations are usually used to support and confirm the results obtained from separation techniques; they are not used in the calculation of the assigned content).

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EU GMP Part II / ICH Q7 section 11

11.19

→ Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored.

→ The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard.

→ Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

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How to comply?

→ Document & justify approach
- Written protocol with acceptance criteria

→ Primary standard traceability & correct usage
- Batch validity
- Storage conditions
- First time opening vial?

→ Secondary standard
- Use for same purpose as primary standard
- Consider & justify (data) for:
  - shelf life / re-test → period requalification
  - storage conditions
  - single use / multi use?

5.12. REFERENCE STANDARDS

Secondary standard. A standard whose property value is assigned by comparison with a primary standard of the same property or quantity.

4-5. *SECONDARY STANDARDS*
A secondary standard should exhibit the same property or properties as the primary standard, relevant for the test(s) for which it is established. The extent of testing may not be as comprehensive as is required for the establishment of a primary standard. The secondary standard is established by comparison with the primary standard to which it is traceable. An official primary standard is used wherever possible for establishment of secondary standards.

Secondary standards. A secondary standard is usually established to reduce the use of the primary standard and may be used for routine quality control purposes. A secondary standard shall exhibit the same property or properties as the primary standard to which it is traceable. It shall therefore be used for the same purpose as the primary standard.

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Summary - what inspectors check (amongst other things…)

→ Availability of current Ph. Eur. reference standards

→ Correct usage in accordance with Ph. Eur. method (or other registered method)

→ Storage conditions, labelling and compliance with Ph. Eur. instructions for use

→ Approach to secondary standards

- Qualification against primary standard
- Shelf life/ periodic re-qualification
- Storage conditions & labelling
- Data to support approach

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EDQM inspections – reference standard deficiencies

- Review of 198 EDQM inspection reports (2011-2024 Q3):

→ 50 deficiencies concerning reference standards identified
  - 5 major
  - 45 other

→ Incidence of reference standard deficiencies decreasing
  - 2011-2015: ~44% of inspections
  - 2016-2024: ~14% of inspections

→ Problems addressed in re-inspections
  - Effective CAPAs - few or no deficiencies observed during re-inspections

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Example deficiencies

Ph. Eur. Reference Standards

→ Ph. Eur. reference standards were not available for the active substance/impurities, as required by the specific monograph.

→ The company assumed that the content of the Ph. Eur. reference standard vial was exactly 100 mg which was not correct. As a result, the results for released API batches were not fully accurate.

→ Instead of using Ph. Eur. related substance reference standards as required by the test method, the company diluted the sample solution 1000-fold.

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Example deficiencies

In-house primary reference standards

→ Appropriate testing was not performed to fully establish the identity and purity of the primary reference standards in the absence of an officially recognized source.

→ Only the first batch of internally manufactured reference standard was established as an "in-house primary reference standard" with a full physicochemical characterization, and used to qualify a batch of working standard. After that, the suitability of the subsequent batches of working standards was only verified against the previous working standard batch and not established against a fully characterised primary reference standard.

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Example deficiencies

Secondary reference standards

→ Only internally manufactured secondary reference standards were used however they were not qualified against Ph. Eur. reference standards.

→ The suitability of secondary standards was not adequately determined by comparison against the CRS. Only an identification test by IR was performed.

→ There was no evidence that secondary reference standards were appropriately re-qualified. The SOP outlined an expiry period of 1 year however no stability data or other documentation for such an expiry date could be presented.

→ There was a lack of traceability in relation to qualification of secondary standards; the secondary standard CoA did not include reference to the batch number of the official Ph. Eur. standard against which it had been qualified.

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Example deficiencies

Storage of reference standards

→ The Ph. Eur. reference standard was stored at room temperature, which was outside of the recommended storage temperature range of 2 – 8°C.

→ There was no temperature monitoring for the fridge used to store reference standards.

Validity of CRS

→ Batch Validity Statements for Ph. Eur. reference standards were not periodically checked on the EDQM website.

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