European Pharmacopoeia Reference Standards
A Lodi, Head of the Laboratory Department, EDQM, Council of Europe

Content

Ph. Eur. Reference Standards

- General notices, terms and definitions
- Key attributes
- Establishment
- Distribution and storage

Secondary Standards
Ph. Eur. General Notices

Certain monographs require the use of reference standards. The European Pharmacopoeia Commission establishes the official reference standards, which are alone authoritative in case of arbitration.

These reference standards are available from the European Directorate for the Quality of Medicines & HealthCare (EDQM).

LIMITS

Ph. Eur. General Notices

The limits prescribed in a monograph are based on data obtained in normal analytical practice; they take account of normal analytical errors, of acceptable variations in manufacture and compounding and of deterioration to an extent considered acceptable.

No further tolerances are to be applied to the limits prescribed to determine whether the article being examined complies with the requirement of the monograph.

Chapter for information

Content:

- Terminology
- Use of Reference Standards
- Establishment of Reference Standards
- Processing, Labelling, Storage and Distribution
- Re-Test Programme
The term “Reference standard” is used as a general term covering reference substances, preparations and spectra.

“Reference standards” are used to achieve adequate quality control of substances for pharmaceutical use and pharmaceutical preparations.

**Ph. Eur. Chapter 5.12. 4/2015**

**Ph.Eur. RS:** reference standard established under the aegis of and adopted by the European Pharmacopoeia Commission.

**Ph. Eur. chemical reference substance (CRS) & biological reference preparation (BRP):** substance or mixture of substances intended for use as stated in a monograph or general chapter of the European Pharmacopoeia.

**Ph. Eur. herbal reference substance (HRS):** herbal drug preparation or herbal drug intended for use as stated in a monograph or general chapter of the European Pharmacopoeia.
TERMS AND DEFINITIONS


Reference Material
Material, sufficiently homogeneous and stable with respect to one or more specified properties\(^1\), which has been established to be fit for its intended use\(^2\) in a measurement process.

\(^1\) Properties can be quantitative or qualitative

\(^2\) Uses may include calibration/assessment of a measurement system/procedure, assigning values to other materials and quality control


Certified Reference Material (CRM)
Reference material characterized 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.
TYPES OF PH. EUR. REFERENCE STANDARDS

- Identification: 45%
- Assay: 17%
- Impurities (quantitative): 11%
- Impurities (qualitative): 11%
- Mixtures for SST/peak ID.: 16%

CRS LIFECYCLE

- Ph. Eur. need
- Procurement
- Processing
- Packaging
- QC
- SDS
- Adoption
- Characterization
- Establishment
- Information leaflet
- Release
- Distribution
- Validity statement
- USERS
- Help Desk
- Monitoring
- Replacement
- Batch needed
EXAMPLE: RS FOR IDENTIFICATION

TIOTROPIUM BROMIDE MONOHYDRATE

Tiotropii bromidum monohydricum

C₃H₁₂BrNO₅S·H₂O

**DEFINITION**

C₃H₂BR₃NO₅S·7(5-hydroxy-2,4-dinitrophen-2-yacetate(ox)(9H-dimethyl)xan-5- azoniatriacyclo

**IDENTIFICATION**

A. Infrared absorption spectrophotometry (2.2.24).

**Comparison:** tiotropium bromide monohydrate CRS.

B. It gives reaction (a) of bromides (2.3.J).

EXAMPLE: RS FOR PEAK ID / SST

Relative retention with reference to benazepril (retention time = about 6 min): impurity E = about 0.3; impurity F = about 0.4; impurity C = about 0.5; impurity B = about 1.8; impurity D = about 2.0; impurity G = about 2.5.

**Identification of impurities:** use the chromatogram supplied with benazepril for system suitability CRS and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, D, E, F and G.

**System suitability:** reference solution (b)

- **resolution:** minimum 2.5 between the minimum 1.5 between the peaks due to:

**Limits:**

- **impurity D:** not more than 2.5 times the obtained with reference solution (c) if
- **impurity E:** not more than 1.5 times the obtained with reference solution (c) if
- **impurities D, E, F, G:** for each impurity the chromatogram obtained with refer
EXAMPLE HRS
(quantitative use)

LC assay Valerian dry extract HRS with assigned content for valerenic acid:

ASSAY CRS

BENAZEPRI, HYDROCHLORIDE

Benazepril hydrochloridum

C_H10N3Cl

DEFINITION

Benzepril (E3177) is a dipeptidyl-peptidase-4 inhibitor. It is the hydrochloride of benazepril acid.

ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

Injection: test solution (b) and reference solution (a).

Calculate the percentage content of C_H13N3O4 from the declared content of benazepril hydrochloride CRS.
Ph. Eur. assay reference standards – why no uncertainty?

ISO GUIDE 34 : 2009 – 5.17
ISO GUIDE 31 : 2015 – 5.3.2

In some cases that are covered by specific legislation (e.g. most pharmacopoeia assay standards) the uncertainties of the assigned values are not stated since they are considered to be negligible in relation to the defined limits of the method specific assays for which they are used.
Monitoring (retest-programme)

No expiry date is given: see batch validity statement

- After establishment and adoption there is a standardized testing procedure in order to assure the « fitness for use » of the reference standards.
- Depending on the use and the known or predicted stability, substances are retested every 12, 24, 36 or 60 months
- Items of retesting: All properties which might be subject to change in the life cycle of a CRS, e.g.:
  - Water content
  - Purity by LC, GC or TLC
  - Possibly IR, UV

SECONDARY STANDARDS
Secondary Standards - Requirements

Ph.Eur. 5.12 paragraph 4-5. (for information)

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 is not so great 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.

➔ It is the responsibility of the user to justify/document the suitability of secondary standards.

EU GMP
Annex VI - 6.20

Whenever compendial reference standards from an official source exist, these should preferably be used as primary reference standards unless fully justified

the use of secondary standards is permitted once their traceability to primary standards has been demonstrated and is documented.
TRACEABILITY

Metrological traceability

property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty

International vocabulary of metrology – Basic and general concepts and associated terms (VIM) 3rd edition

Commercial “Secondary Standards”

Example: Paracetamol Ph.Eur. CRS (no assigned content value)

Used in monograph 0049 – Paracetamol for:

➢ Identification by IR

Assay determination in the monograph: Titration
Secondary Standards

Ph. Eur. CRS
- official, legally binding standards, an essential part of Ph. Eur. monographs;
- established and guaranteed for their intended use(s);
- EDQM provides RS information (leaflet) and assistance (Helpdesk);
- Ph. Eur. policy on reference standard is reflected in general chapter 5.12.

Secondary standards
- metrological traceable to primary standards for the relevant property,
- their suitability for use has to be justified, documented and maintained.

take home messages
Thank you for your attention!