European Pharmacopoeia Reference Standards

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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.

EUROPEAN PHARMACOPOEIA
LINK BETWEEN TEXTS AND REFERENCE STANDARDS

Ph.Eur. Chapter 5.12.

Chapter for information

Content:

- Terminology
- Use of Reference Standards
- Establishment of Reference Standards
- Processing, Labelling, Storage and Distribution
- Re-Test Programme

PH. EUR. REFERENCE STANDARDS

Ph. Eur. Chapter 5.12. 4/2015

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. REFERENCE STANDARDS

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

ISO GUIDE 30:2015 - Ph. Eur. Chapter 5.12. 4/2015

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

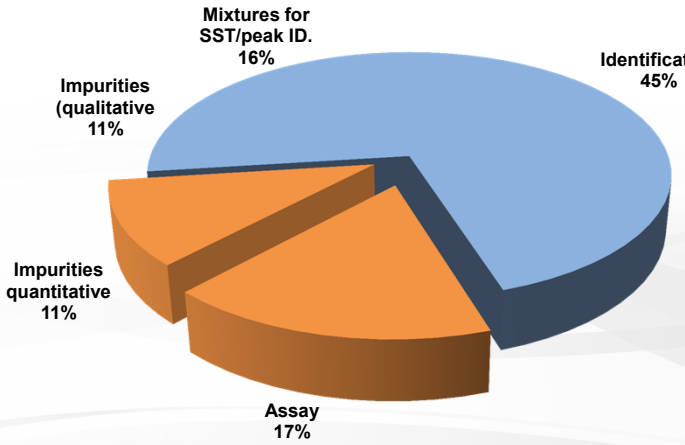
[2] Uses may include calibration/assessment of a measurement system/procedure , assigning values to other materials and quality control

ISO GUIDE 30:2015 - Ph. Eur. Chapter 5.12. 4/2015

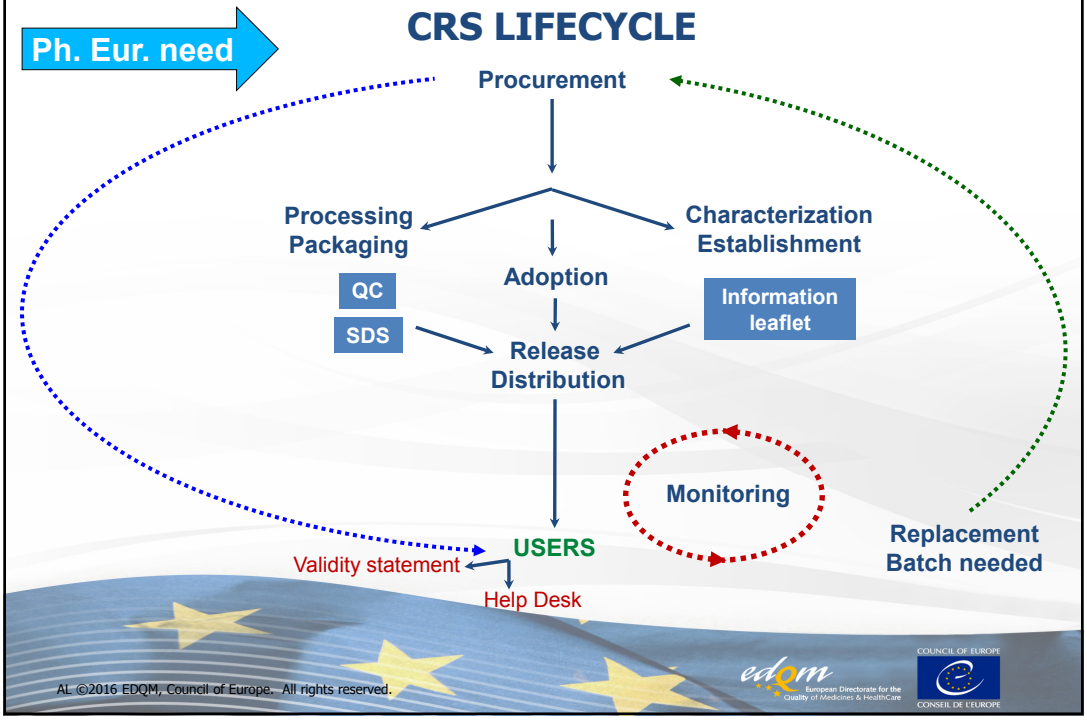
Certified Reference Material (CRM)

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



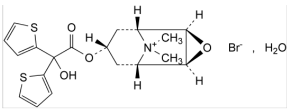
CRS LIFECYCLE



EXAMPLE: RS FOR IDENTIFICATION

TIOTROPIUM BROMIDE MONOHYDRATE

Tiotropii bromidum monohydricum



$C_{19}H_{22}BrNO_4S_2,H_2O$

DEFINITION

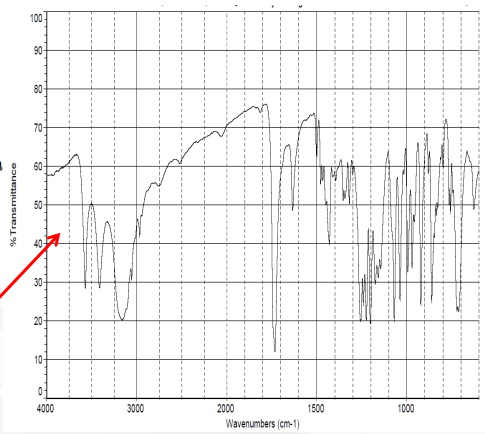
(1*R*,2*R*,4*S*,5*S*,7*s*)-7-[(2-Hydroxy-2,2-dithiophen-2-ylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo
[3.3.1.$0^{2,4}$]nonane bromide monohydrate.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *tiotropium bromide monohydrate CRS.*

B. It gives reaction (a) of bromides (*2.3.1*).



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

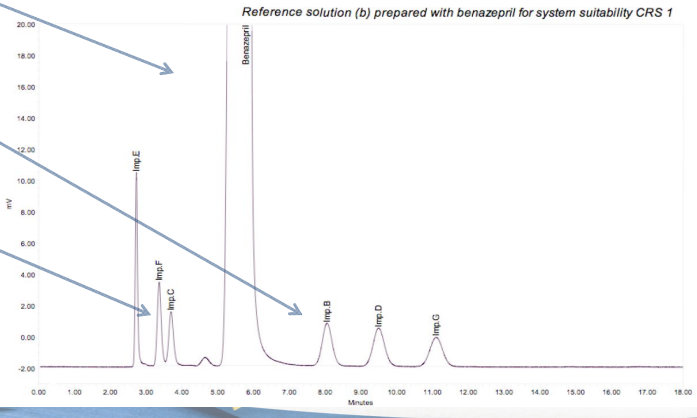
System suitability: reference solution (b)

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

Limits:

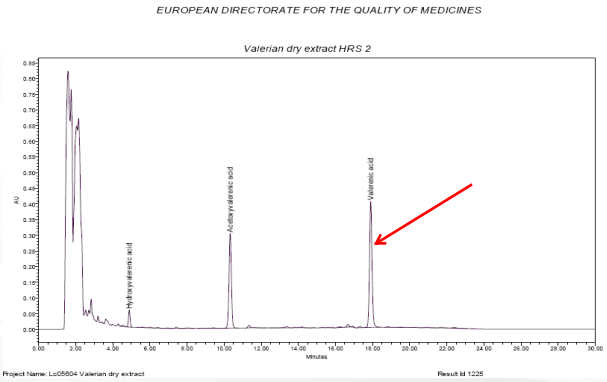
- *correction factors*: for the calculation
  following impurities by the correspon
  impurity F = 0.7;
- *impurity B*: not more than 2.5 times tl
  obtained with reference solution (c) (C
- *impurity C*: not more than 1.5 times tl
  obtained with reference solution (c) (C
- *impurities D, E, F, G*: for each impurit
  the chromatogram obtained with refe

Reference solution (b) prepared with benazepril for system suitability CRS 1



EXAMPLE HRS (quantitative use)

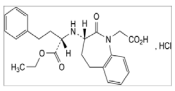
LC assay Valerian dry extract HRS with assigned content for valerenic acid:



ASSAY CRS

BENAZEPRIL HYDROCHLORIDE

Benazeprili hydrochloridum



$C_{24}H_{28}ClN_2O_5$ [86541-74-4] M_r 461.0

DEFINITION

[(3*S*)-3-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid hydrochloride.

Content: 97.5 per cent to 102.0 per cent (dried substance).

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 $C_{24}H_{29}ClN_2O_5$ 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.

European Directorate for the Quality of Medicines & HealthCare
European Pharmacopoeia (Ph. Eur.)
7, Allée Kastner CS 30026, F-67081 Strasbourg (France)
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For any questions: www.edqm.eu (HelpDesk)

CRS INFORMATION LEAFLET
Ph. Eur. Reference Standard

Tribenoside CRS batch 3

1. **Identification**
Catalogue code: Y0000165 Unit Quantity: ca 150 mg

2. **Scientific Information**
2.1 Intended use
Reference Standard for laboratory tests as prescribed in the European Pharmacopoeia only.
Established for use with the monograph(s): 1740.

2.2 Analytical information related to intended use
The "as is" content is : 99.3 % C29H3406

2.3 Uncertainty of the assigned value, when applicable
According to ISO Guide 34 and ISO Guide 35, for this Pharmacopoeial standard the uncertainty of the assigned value is not stated since it is considered to be negligible in relation to the defined limits of the method-specific assays for which the reference standard is used. Please also refer to Ph. Eur. chapter 5.12.

2.4 Validity
A statement on the validity of the batch (Batch Validity Statement) can be printed directly from the EDQM website (Reference Standards Database).

2.5 Instructions for use
Use "as is". Do not dry before use.
Allow the closed container to equilibrate at ambient temperature before opening to avoid uptake of moisture.

Once opened, the vial/ampoule is for immediate use and the stability of the contents of opened vials or ampoules cannot be guaranteed.

3. **Storage conditions**
Store the original container at -20°C ± 5°C, protected from light. The container should not be opened until required for use.

4. **Safety**
CLP Hazard Classification

Cat. Code: Y0000165 Date of issue: 24/04/2014 Rev.2 1/2

Reference Standard Leaflet

For laboratory use only. Handle in accordance with good occupational hygiene, safety and laboratory practices and take precautions to avoid exposure.

For substances subject to GHS classification, the corresponding safety data sheet can be accessed via the EDQM website (Reference Standards Database) or is available upon request from the EDQM (Helpdesk-FAQ section).

5. **Shipping conditions**
Please check shipping conditions on the EDQM website (Reference Standards Database).

6. **Warranties, Liability and disputes**
a) Warranties
The Council of Europe does not offer any warranty concerning the quality or safety of any item supplied, the absence of any defects, or its fitness for any particular purpose except that of use as a Ph. Eur. CRS, BRP or RS for use as reference standards in tests and assays carried out in accordance with the official methods of the European Pharmacopoeia (Ph. Eur.) by professionals with the necessary technical skills. In particular, the Council of Europe (EDQM) does not guarantee that the items will meet the customer's specific expectations. The Council of Europe also does not guarantee that the purchase or use of the items will not infringe any intellectual property rights, in particular patents.

The Council of Europe (EDQM) only guarantees that the items meet the above conditions in the moment they are handed over to the carrier being responsible for the delivery of the item to the purchaser and that the carrier and the purchaser have received clear and accurate instructions for the item's delivery and reception.

No other warranty, either express or implied, is given by the Council of Europe (EDQM).

b) Liability
The Council of Europe (EDQM) shall not be liable for the failure to meet the requirements of the legislation of the country where the items are delivered. It is the purchaser's responsibility to check with the local, regional or national authorities and to make sure that the goods or services that they intend to order may be imported or used in that country. The purchaser is solely responsible for the choice of items, their storage from the time of delivery and their use.

In no event shall the Council of Europe (EDQM) be liable for any damages due to the use of items, including, but not limited to, lost profits, loss of use, costs of procurement of substitute goods, services or systems, or for any indirect, special, incidental, punitive, or consequential damages, however caused and, whether in contract, tort or under any other theory of liability, whether or not the Purchaser has been advised of the possibility of such damage.

c) Disputes
In accordance with the provisions of article 21 of the General Agreement on the Privileges and Immunities of the Council of Europe, all disputes between the Council of Europe (EDQM) and the customer as regards the application of this contract shall be submitted, if a mutual agreement cannot be reached between the parties, to arbitration as laid down in Order No. 481 of the Secretary General, approved by the Committee of Ministers.

7. **Citation**
Users shall ensure that any reference made to an EDQM Reference Standard in any publication, presentation or public document (ex. scientific articles, data sheets for kits) bears the exact name, and catalogue code of the Reference Standard and the exact name and address of EDQM as given on the first page of this information leaflet.

8. **Adoption**
The present reference standard has been officially adopted by the European Pharmacopoeia Commission.

9. **Signature**
This document is electronically signed by:

Dr Pierre Leveau
Head of the Quality, Safety and Environment Division

Cat. Code: Y0000165 Date of issue: 24/04/2014 Rev. 2 2/2

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

Certificate of Analysis

ISO GUIDE 34 ACLASS Cert# AR-1470

ISO/IEC 17025 ACLASS Cert# AT-1467

ACETAMINOPHEN
(Paracetamol)
CERTIFIED REFERENCE MATERIAL

CERTIFIED PURITY: 99.96%, U_{rel} = ±0.3% k = 2
(Mass Balance/as is basis)

NOMINAL PACKAGE SIZE: 1g

CATALOG #: PHR1005 LOT #: LRAA7900

CERTIFICATE VERSION: LRAA7900.1 ISSUE DATE: 31 July 2015

Note: Certificates may be updated due to Pharmacopeial Lot changes or the availability of new data. Check our website at: www.sigma-aldrich.com for the most current version.

CRM EXPIRATION: 31 December 2019 (Proper Storage and Handling Required).

RECEIPT DATE: _____
Note: this space is provided for convenience only and its use is not required.

ASSAY vs. EP CRS (as is basis)

ASSAY VALUE	vs. EP BATCH
99.6%	**4.1**
	Labeled Content = None
	Assigned Content = 100.9%*

*The assigned content of the EP CRS was determined by assay against the USP Reference Standard and BP CRS

Traceability ???

take home messages

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.

Thank you for your attention!