Identification of the need and uses of a reference standard

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General Chapter of the European Pharmacopoeia
5.12 Pharmaceutical Reference Standards

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- ESTABLISHMENT
- USE
- PRESENTATION

of pharmaceutical reference standards in general & European Pharmacopoeia reference standards in particular.
Classification of reference standards

Type

- Chemical Reference Substance (CRS)
- NEW: Herbal Reference Standards (HRS)
- Biological Reference Preparations

Establishment

- **Primary standards**
  (without comparison to an existing standard)
- **Secondary standards**
  (by comparison with a primary standard)

Use

- **Qualitative** (Identification, system suitability)
- **Quantitative** (Assay, external standard)
A European Pharmacopoeia reference standard is an integral and essential part of the monograph and as such is an official standard that is alone authoritative in case of doubt or dispute.

i.e. a « legally binding » standard
European Pharmacopoeia Reference Standards

Chemical reference substance (CRS)

A chemical compound or mixture of compounds which has been established for use as a standard in an identity test, a purity test and/or an assay as prescribed in a monograph.

The standard is valid only for the specific test(s) for which it has been established.
A chemical compound which has been established as a standard for **qualitative use** in an identity test.

The standard is valid only for the specific test(s) for which it has been established.
EXAMPLE: CRS FOR IDENTIFICATION

IDENTIFICATION
A. Infrared absorption spectrophotometry (2.2.24).
   *Comparison: tiotropium bromide monohydrate CRS.*
B. It gives reaction (a) of bromides (2.3.1).
Impurity CRS / CRS for peak identification & system suitability

A chemical compound or mixture of compounds which has been established as a standard for qualitative or quantitative use in a purity test.

The standard is valid only for the specific test(s) for which it has been established.
In general an impurity is to be identified, i.e. located in the chromatogram or electropherogram:
- when it has an individual limit and/or
- when a correction factor is to be applied
**EXAMPLE: Impurity CRS qualitative use - CRS for peak ID & SST / 1**

**Related substances.** Liquid chromatography (2.2.29).

*Test solution (a).* Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 ml with the mobile phase.

*Test solution (b).* Dilute 10.0 ml of test solution (a) to 100.0 ml with the mobile phase.

*Reference solution (a).* Dissolve 50.0 mg of *benazepril hydrochloride CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase. Dilute 10.0 ml of this solution to 100.0 ml with the mobile phase.

*Reference solution (b).* Dissolve the contents of a vial of *benazepril for system suitability CRS* (containing impurities B, C, D, E, F and G) in 1.0 ml of test solution (a).

*Reference solution (c).* Dilute 1.0 ml of reference solution (a) to 50.0 ml with the mobile phase.

**Column:**
- *size:* \( l = 0.30 \) m, \( \Omega = 3.9 \) mm;
- *stationary phase:* end-capped octadecylsilyl silica gel for chromatography \( R \) (10 \( \mu m \))\(^{(1)}\).

**Mobile phase:** add 0.2 ml of *glacial acetic acid R* to 1000 ml of a mixture of 360 volumes of water \( R \) and 640 volumes of *methanol R2*; add 0.81 g of *tetrabutylammonium bromide R* and stir to dissolve.

*Flow rate:* 1.0 ml/min.

*Detection:* spectrophotometer at 240 nm.

*Injection:* 25 \( \mu l \) of test solution (a) and reference solutions (b) and (c).

*Run time:* 3 times the retention time of benazepril.
**EXAMPLE: Impurity CRS qualitative use**

**CRS for peak ID & SS / 2**

*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 peaks due to benazepril and impurity B and minimum 1.5 between the peaks due to impurities E and F.

*Limits:*

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 0.5; impurity F = 0.7;
- *impurity B*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.5 per cent);
- *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.3 per cent);
- *impurities D, E, F, G*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent);
EXAMPLE: Impurity CRS qualitative and quantitative use

**Enantiomeric purity.** Liquid chromatography (2.2.29).

Buffer solution pH 6.0. Dissolve 3.58 g of disodium hydrogen phosphate R and 9.66 g of potassium dihydrogen phosphate R in water R and dilute to 1000.0 ml with the same solvent.

Test solution. Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (a). Dissolve 5.0 mg of benzapril impurity A CRS in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the mobile phase.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 10.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the test solution.

**Column:**
- size: i = 0.10 m, O = 4.0 mm;
- stationary phase: spherical silica gel AGP for chiral chromatography R (5 μm);
- temperature: 30 °C.

Mobile phase: methanol R2, buffer solution pH 6.0 (20:80 V/V).
Flow rate: 0.9 ml/min.
Detection: spectrophotometer at 210 nm.
Injection: 50 μl of the test solution and reference solutions (b) and (c).
Run time: 3.5 times the retention time of benzapril.
Relative retention with reference to benzapril (retention time = about 6 min): impurity A = about 1.9.

**System suitability: reference solution (c):**
- peak-to-valley ratio: minimum 2.5, where \( H_P \) = height above the baseline of the peak due to impurity A and \( H_V \) = height above the baseline of the lowest point of the curve separating this peak from the peak due to benzapril.

**Limit:**
- impurity A: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 per cent).
A chemical compound or mixture of compounds which has been established as a standard for **quantitative use** in an assay.

The standard is valid only for the specific test(s) for which it has been established.
EXAMPLE: ASSAY CRS

**Benazepril Hydrochloride**

Benazeprili hydrochloridum

C<sub>24</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>5</sub>  
M<sub>r</sub> 461.0

DEFINITION

[(3S,3'-(1S)-[(Ethoxycarbonyl)-3-phenylpropyl]amino]-2-oxo-2,4,5-tetrahydro-1H-1-benazeprin-9]-lactonic 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<sub>24</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>5</sub> from the declared content of benazepril hydrochloride CRS.

**Assigned Content (as is):**

(100 – loss on drying) x chromatographic purity (%) / 100 = 99.5% of C<sub>24</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>5</sub>
Establishment of CRS
CRS Establishment Process

1. Need for a new CRS or for a replacement batch
2. Procurement of the proposed candidate
3. Candidate examined by the EDQM Laboratory
4. Filling / Production
5. [ Collaborative study for assay CRS ]
6. Approval by the Group of Experts
7. Adoption by the Ph. Eur. Commission
Step 3: Lab examination of the candidate CRS

The extent of analytical testing depends on the intended use of the CRS.

- **Identification** => confirmation of identity / structure compliance with the monograph

- **Peak ID, system suitability** => confirmation of identity & fitness for purpose.

- **External standard** => confirmation of the identity / structure & purity

- **Assay**: assignment based on interlaboratory study
CRS used in the test for related substances

**Qualitative use**
- System suitability
- Peak identification

**Quantitative use**
- Limit test (e.g. TLC)
- Quantitative test (e.g. LC / GC)
Establishment of Impurity CRS: qualitative use

Individual impurity: the preferred option.

... in case of availability problems, the following alternative materials may be employed:

- Mixtures of impurities
- Batches containing one or more impurities
- Spiked samples
Impurity CRS: Quantitative use

- Individual impurities: value assigned when necessary (purity below 95%)
- Batch containing the impurity: value assigned in all cases
CRS Establishment Process

- Need for a new CRS or for a replacement batch
- Procurement of the proposed candidate
- Candidate examined by the EDQM Laboratory
  If required feasibility of production is verified
- Filling / Production
- Collaborative study for assay CRS
- Approved by the Group of Experts
- Adopted by the Ph. Eur. Commission
Assay CRS

Assay methods:
- LC
- GC
- UV spectrophotometry
- Microbiological assay
Content assignment (method-specific) based on an interlaboratory study involving usually five laboratories i.e.

• the EDQM Laboratory ;  
• members of the OMCL(*) network and/or  
• Experts of the Ph. Eur.. 

The manufacturer is normally invited to participate in the study.

(*) Official Medicines Control Laboratory
Establishment of assay CRS: internal preliminary work

- Verification of the structure of the candidate CRS
- Verification of compliance with the monograph requirements
- Additional tests, such as residual solvents, DSC purity, non-aqueous titration, content by NMR.
Establishment of assay CRS: interlaboratory study

1. Protocol prepared / tested by the EDQM Laboratory
2. Protocol and samples sent to participants
3. Participants obtain and send results
4. Results evaluated by the EDQM Lab.
5. Report with proposed assigned value
6. Approval from the group of experts
7. Adoption by the Commission
Example protocol: CRS for LC-assay

Collaborative study:

**Determination of water** (by KF / coulometry) or **Loss on drying**

**Quantitative determination of the impurities** by LC

**Residual solvents** by head-space GC
Example:
Collaborative trial Benazepril HCl / 1

LC acceptance criteria

<table>
<thead>
<tr>
<th></th>
<th>VALUE</th>
<th>ACCEPTANCE CRITERION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution</td>
<td></td>
<td>Resolution :</td>
</tr>
<tr>
<td>Reference solution (b)</td>
<td>RS benazepril / imp. B :</td>
<td>Minimum 2.5 between the peaks due to benazepril and impurity B.</td>
</tr>
<tr>
<td></td>
<td>RS imp. E / imp. F :</td>
<td>Minimum 1.5 between the peaks due to impurity E and impurity F.</td>
</tr>
<tr>
<td>Symmetry factor</td>
<td>Symmetry factor benazepril:</td>
<td>Symmetry factor of benazepril:</td>
</tr>
<tr>
<td>Reference solution (a)</td>
<td></td>
<td>0.8 – 1.5</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>S/N benazepril:</td>
<td>S/N benazepril : minimum 40</td>
</tr>
<tr>
<td>Reference solution (a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeatability of injection</td>
<td>RSD :</td>
<td>RSD (n = 3) : ≤ 5%</td>
</tr>
</tbody>
</table>

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_{8}H_{12}ClN_{2}O_{2} from the declared content of benazepril hydrochloride CRS.
Example: Collaborative trial Benazepril HCl / 2

<table>
<thead>
<tr>
<th>Test</th>
<th>Lab 1</th>
<th>Lab 2</th>
<th>Lab 3</th>
<th>Lab 4</th>
<th>Lab 5</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss on drying</td>
<td>0.18%</td>
<td>0.21%</td>
<td>0.24%</td>
<td>0.14%</td>
<td>0.18%</td>
<td>0.19%</td>
</tr>
<tr>
<td>(2.2.32, 105°C in vacuum for 3h)</td>
<td>n = 3</td>
<td>n = 3</td>
<td>n = 3</td>
<td>n = 3</td>
<td>n = 3</td>
<td>n = 5</td>
</tr>
<tr>
<td>SD</td>
<td>0.01</td>
<td>0.06</td>
<td>0.02</td>
<td>0.02</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Impurity B</td>
<td>0.066%</td>
<td>0.07%</td>
<td>0.06%</td>
<td>0.06%</td>
<td>0.06%</td>
<td></td>
</tr>
<tr>
<td>Impurity C</td>
<td>0.008%</td>
<td></td>
<td>0.06%</td>
<td>0.06%</td>
<td>0.06%</td>
<td></td>
</tr>
<tr>
<td>Impurity D</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Impurity E</td>
<td>0.047%</td>
<td>0.05%</td>
<td>0.05%</td>
<td>0.04%</td>
<td>0.04%</td>
<td></td>
</tr>
<tr>
<td>Impurity F</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Impurity G</td>
<td>0.108%</td>
<td>0.11%</td>
<td>0.10%</td>
<td>0.10%</td>
<td>0.11%</td>
<td></td>
</tr>
<tr>
<td>unspec. imp. 1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.02%</td>
<td>0.04%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(rel. ret. 0.69)</td>
<td>(rel. ret. 0.80)</td>
<td></td>
</tr>
<tr>
<td>unspec. imp. 1</td>
<td>0.045%</td>
<td>0.05%</td>
<td>0.05%</td>
<td>0.04%</td>
<td>0.04%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(rel. ret. 0.71)</td>
<td>(rel. ret. 0.80)</td>
<td>(rel. ret. 0.77)</td>
<td>(rel. ret. 0.78)</td>
<td>(rel. ret. 0.80)</td>
<td></td>
</tr>
<tr>
<td>Sum of impurities</td>
<td>0.27%</td>
<td>0.28%</td>
<td>0.26%</td>
<td>0.27%</td>
<td>0.25%</td>
<td>0.27%</td>
</tr>
<tr>
<td></td>
<td>n = 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

Based on these results it can be envisaged to assign a content of

\[
(100 - \text{loss on drying}) \times \text{chromatographic purity (\%)} / 100 = 99.5\% \text{ of C}_{24}\text{H}_{30}\text{ClN}_{2}\text{O}_{5}
\]

The estimated uncertainty of this value is 0.05\%, i.e., it is negligible in relation to the content limits given in the monograph (97.5 to 102.0\%).

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Estimation of the uncertainty of the assigned content

Ph. Eur. Commission policy:
the uncertainty of the value assigned as a result of an interlaboratory study should be within a predetermined limit which is calculated in relation with the intended use.
Dealing with uncertainty

Maximum accepted uncertainty % vs. Assay upper limit %

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CRS Establishment Process

- Need for a new CRS or for a replacement batch
- Procurement of the proposed candidate
- Candidate examined by the EDQM Laboratory
  If required feasibility of production is verified
- Filling / Production / Labelling
- Collaborative study for assay CRS - report
- Approved by the Group of Experts
- Adopted by the Ph. Eur. Commission
Production techniques

Include:

• Powder filling
• Liquid Filling
• Freeze drying / evaporation
• Spray drying
Production conditions

**Highly toxic/highly potent substances:**
glove box under negative pressure for containment and protection of the operators, final external decontamination

**Hygroscopic substances:**
controlled humidity

**Substances sensitive to oxidation:**
under inert gas
Single use container to minimise the risk of decomposition, contamination, or water uptake

Amount per unit

Calculated based on amount indicated in the monograph

In case of assay CRS produced by powder-filling, the fill weight is twice the amount indicated in the monograph i.e. sufficient for two weighings
LABELLING
CRS for qualitative use

IBUPROFEN CRS
IBUPROFÈNE SCR
ca 160 mg

Batch/lot no 4.0
ASSIGNED CONTENT

Powder-filled CRS

Content (m/m) assigned on an « as is » basis: for example

\[ X(\%) = [100.0 - (\text{water}+\text{solvents})] \times \frac{\% \text{chromatographic purity}}{100} \]

TO BE WEIGHED - NO NEED TO DRY

Freeze-dried CRS

The value assigned corresponds to the amount per vial, for example 2.05 mg/vial

TO BE RECONSTITUTED, NOT WEIGHED
CRS with assigned content
% m/m

MISOPROSTOL CRS
MISOPROSTOL SCR
99.2% of C_{22}H_{38}O_{5}

ca 30 mg

Batch/lot n° 2.0
CRS with assigned content

“per vial”

4.93 mg C\textsubscript{59}H\textsubscript{84}N\textsubscript{18}O\textsubscript{14} per vial
PEEL-OFF SECONDARY LABEL

Order code
Batch number
approx. Amount per vial
Unique identifier per label
Sentences for customs
CRS name
2D barcode

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✓ Need of a new Ref Std or need of a replacement
✓ Procurement of the proposed candidate
✓ Candidate examined at the EDQM Lab.
✓ Production
✓ Inter-laboratory study for assay CRS
✓ Approved by the Group of Experts
✓ Adopted by the Ph. Eur. Commission
✓ Labelling
✓ Release
✓ Monitoring
Monitoring programme CRS

Once established, adopted and released, the CRS undergoes **periodic testing** in order to ensure its continuous fitness for use.

The **periodicity** of testing depends on the use of the CRS and the stability information available.

The **extent** of testing also depends on the use of the CRS. In general, the focus is on the properties that may change during the life cycle of a CRS, i.e.: water content, purity by HPLC, GC or TLC, DSC.

No **expiry date is given**: see batch validity statement.
Use of Ph. Eur. CRS/BRP

• Ph. Eur. CRS/BRP are to be used in conjunction with the corresponding monograph(s).

• Ph. Eur. CRS/BRP are to be used for the purpose for which they are intended.

• Any different use is in the responsibility of the user.

• Storage of opened containers is discouraged and is in any case the responsibility of the user.
Reference Standards
INFORMATION

Non-official information intended to facilitate the use of the CRS can be found in the knowledge database and CRS database (website).

http://www.edqm.eu -> Databases
<table>
<thead>
<tr>
<th>Monograph Number</th>
<th>1649</th>
</tr>
</thead>
<tbody>
<tr>
<td>English Name</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>French Name</td>
<td>Azithromycine</td>
</tr>
<tr>
<td>Latin Name</td>
<td>Azithromycinum</td>
</tr>
<tr>
<td>State of Work</td>
<td>5</td>
</tr>
<tr>
<td>Pharmeuropa</td>
<td>17.1</td>
</tr>
<tr>
<td>Published in Supplement</td>
<td>6.0</td>
</tr>
<tr>
<td>Revision in progress</td>
<td>No</td>
</tr>
<tr>
<td>Chromatogram</td>
<td>N/A</td>
</tr>
<tr>
<td>Additional information</td>
<td>N/A</td>
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</table>

**Reference standards**

<table>
<thead>
<tr>
<th>Available since</th>
<th>Cat. No.</th>
<th>Name</th>
<th>Batch No.</th>
<th>Unit Quantity</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>26/10/2007</td>
<td>Y0000306</td>
<td>Azithromycin</td>
<td>2</td>
<td>200 mg</td>
<td>79 EUR</td>
</tr>
<tr>
<td></td>
<td>Y0000307</td>
<td>Azithromycin Impurity A</td>
<td>1</td>
<td>10 mg</td>
<td>79 EUR</td>
</tr>
<tr>
<td></td>
<td>Y0000308</td>
<td>Azithromycin Impurity B</td>
<td>3</td>
<td>0.04 mg</td>
<td>79 EUR</td>
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<tr>
<td></td>
<td>Y0000637</td>
<td>Azithromycin for peak identification</td>
<td>2</td>
<td>15 mg</td>
<td>79 EUR</td>
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<tr>
<td></td>
<td>Y0000641</td>
<td>Azithromycin for system suitability</td>
<td>1</td>
<td>0.05 mg</td>
<td>79 EUR</td>
</tr>
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</table>

**Trade Names**

<table>
<thead>
<tr>
<th>To be used in test(s)</th>
<th>Brand Name</th>
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</thead>
<tbody>
<tr>
<td>Related substances</td>
<td>XTerra MS C18</td>
</tr>
<tr>
<td>Assay</td>
<td>Asahipak ODP-50</td>
</tr>
</tbody>
</table>

**CEP**

<table>
<thead>
<tr>
<th>Substance Number</th>
<th>Substance</th>
<th>Certificate Holder</th>
<th>Certificate Number</th>
<th>Issue Date</th>
<th>Status</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1649</td>
<td>Azithromycin monohydrate</td>
<td>Sandoz Industrial Products S.A. E 08520 Los Franqueses Del Vallès</td>
<td>R0-CEP 2002-257-Rev 02</td>
<td>05/10/2007</td>
<td>VALID</td>
<td>Chemistry</td>
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<td><strong>Catalogue Number</strong></td>
<td>Y0001025</td>
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</tr>
<tr>
<td>----------------------</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Name</strong></td>
<td>Benazepril hydrochloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current batch number</strong></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unit quantity</strong></td>
<td>160 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sale unit</strong></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Used in monograph(s)</strong></td>
<td>2388</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Assigned content</strong></td>
<td>99.5 % C$_2$H$_9$CN$_2$O$_5$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Leaflet</strong></td>
<td>no Leaflet available</td>
<td></td>
<td></td>
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<td><strong>Additional information</strong></td>
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<td><strong>Presentation</strong></td>
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<td><strong>MSDS</strong></td>
<td><a href="#">click to download Material Safety Data Sheet</a></td>
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<tr>
<td><strong>Storage conditions</strong></td>
<td>+5°C</td>
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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 01/2005:31200 Reference Standards.

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**European Directorate for the Quality of Medicines & HealthCare (EDQM) – Council of Europe**

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Phone: +33 (0)3 88 41 30 30

Fax: +33 (0)3 88 41 27 71

Internet: [http://www.edqm.eu](http://www.edqm.eu)

---

<table>
<thead>
<tr>
<th>Name</th>
<th>Benazepril hydrochloride</th>
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<tr>
<td>Catalogue code</td>
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</tr>
<tr>
<td>Batch number*</td>
<td>1</td>
</tr>
<tr>
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<td>99.5% C_{24}H_{26}ClN_{2}O_{5}</td>
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<tr>
<td>Validity</td>
<td>Batch 1 is valid at the printing date: 2009-11-7</td>
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<tr>
<td>Storage conditions</td>
<td>The standard is intended for immediate use. Recommended EDQM storage conditions for unopened containers: +5°C</td>
</tr>
<tr>
<td>Safety data</td>
<td>Safety Data Sheet is available from the detailed view or upon request.</td>
</tr>
<tr>
<td>Leaflet</td>
<td>Click on the hyperlink to download the leaflet containing the instructions for use, if available (Adobe Acrobat Reader version 5 or higher needed to open the file). No leaflet available</td>
</tr>
</tbody>
</table>

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BATCH VALIDITY STATEMENT
EUROPEAN PHARMACOPOEIA REFERENCE STANDARDS (CRS) & (BRP)

This Batch Validity Statement has to be used in conjunction

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<table>
<thead>
<tr>
<th>Name</th>
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<td>Catalogue code</td>
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<td>The standard is intended for immediate use. Recommended EDQM Storage conditions for unopened containers: +5°C</td>
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<td>Safety data</td>
<td>Safety Data Sheet is available from the detailed view or upon request. Click on the hyperlink to download the leaflet containing the instructions for use, if available (Adobe Acrobat Reader version 5 or higher, or the corresponding browser plug-in is needed to open the file) no Leaflet available</td>
</tr>
<tr>
<td>Leaflet</td>
<td>no Leaflet available</td>
</tr>
</tbody>
</table>

* Sub-batches 1.1, 1.2, 1.3, etc., are obtained from the sale batch of bulk material.
Notice: the previous classification of the sub-batches {a, b, c} will be gradually replaced with 1.1, 1.2, 1.3 etc.

This statement is valid at the date of printing: 2008-4-7

Legal notice:
The Council of Europe (EDQM) makes no representation or warranty with respect to the accuracy, completeness, or currency of the context of this statement.
The Council of Europe (EDQM) shall not be liable on account of any potential errors or omissions.
Ph. Eur. CRS take home messages

- They are official, legally binding primary standards
- They constitute an essential part of the monograph
- They are to be used only for the intended purpose
- The assay value is assigned “as is”
- Their continuous fitness for purpose is assured by a regular monitoring programme
- User interface / information => website
- The Ph. Eur. policy on reference standard is reflected in general chapter 5.12
Thank you for your attention.