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

Ph. Eur. reference standards Establishment

2019 Training Session
“The European Pharmacopoeia”
Dr Jochen Pauwels
EDQM Laboratory Department

10 – 11 September 2019, Iselin, New Jersey, USA
OUTLINE

- Terms and definitions
- Establishment of reference standards: general principles
- Qualitative reference standards
- Quantitative reference standards

PH.EUR. REFERENCE STANDARDS

Terms and definitions
TERMS AND DEFINITIONS

5.12. REFERENCE STANDARDS
This chapter is published for information.

- Terminology
- Use of Ph.Eur. Reference Standards
- Establishment of Reference Standards
- Manufacturing, Labelling, Storage and Distribution of Ph.Eur Reference Standards
- Re-Test Programme of Ph.Eur. Standards

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TERMS AND DEFINITIONS

ISO GUIDE 30 / Ph.Eur. 5.12.

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

* quantitative or qualitative
**TERMS AND DEFINITIONS**

ISO GUIDE 30 / Ph.Eur. 5.12.

**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.

**TERMS AND DEFINITIONS**

ISO GUIDE 30 / Ph.Eur. 5.12.

**Primary measurement standard**
A standard designated or widely acknowledged as having the highest metrological qualities and whose property value is accepted without reference to other standards of the same property or quantity, within a specific context.

**Secondary measurement standard**
Standard whose property value is assigned by comparison with a primary standard of the same property or quantity.
TERMS AND DEFINITIONS

Ph.Eur. 5.12.

Reference Standard (RS)

**General term** covering reference substances, preparations and spectra.

European Pharmacopoeia reference standard (Ph.Eur. RS)

A reference standard **established** under the aegis of and **adopted** by the European Pharmacopoeia Commission.

European Pharmacopoeia chemical reference substance (CRS)

Substance or mixture of substances intended for **use as stated in** a monograph or general chapter of the **European Pharmacopoeia**.

CRSs are in general **primary standards**, except for those (notably antibiotics) that are calibrated in International Units. The latter are secondary standards traceable to the international standard.

*Note: HRS and BRP are other types of RS.*
TERMS AND DEFINITIONS

EUROPEAN PHARMACOPOEIA
COMPENDIAL STANDARD = MONOGRAPH + REFERENCE STANDARD

TERMS AND DEFINITIONS

REFERENCE STANDARDS
LEGAL ASPECTS

Ph.Eur. General Notices

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

These reference standards are available from EDQM.
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).

These compendial materials should be used for the purpose described in the appropriate monograph unless otherwise authorised by the National Competent Authority.

* Eudralex Volume 4, EU guidelines for good manufacturing practice for medicinal products for human and veterinary use
5.12. REFERENCE STANDARDS

Terminology

- Use of Ph.Eur. Reference Standards
- Establishment of Reference Standards
- Manufacturing, Labelling, Storage and Distribution of Ph.Eur Reference Standards
- Re-Test Programme of Ph.Eur. Standards

EU guideline for GMP* Part 1 – 6.20

Reference standards should be established as suitable for their intended use. Their qualification and certification as such should be clearly stated and documented.

* Eudralex Volume 4, EU guidelines for good manufacturing practice for medicinal products for human and veterinary use
ESTABLISHMENT: GENERALS

Use

- BATCH TESTING
  - e.g. Identification, Assay, Impurities
- EVALUATION OF A MEASUREMENT SYSTEM
  - e.g. System suitability test
- VERIFICATION OF A MEASUREMENT SYSTEM
  - e.g. TGA, KF, LOD equipment
- ESTABLISHMENT OF A SECONDARY STANDARD
  - e.g. Working standards

ESTABLISHMENT: GENERALS

Need for a new or a replacement batch of a reference standard

- Procurement
- Pre-establishment / feasibility
- Sorption/desorption profile (if needed)
- Manufacture

- Establishment / content assignment
  - Monitoring
  - Approval / Adoption

- Release for distribution
Establishment of qualitative RS

- Single substance RS subject of a Ph. Eur. monograph
  - Key quality attribute = identity.
  - Verification of:  
    * identity (full structural elucidation: NMR, QTOF-MS)
    * compliance with relevant requirements of monograph
    * intended use
  - Overall, characterisation is less elaborated than for RS used quantitatively.
ESTABLISHMENT OF QUALITATIVE RS

- Single substance RS not subject of a Ph. Eur. monograph (e.g. impurity)
  - Key quality attribute = **identity**.
  - Verification of:
    * identity (full structural elucidation: NMR, QTOF-MS)
    * intended use
  - Overall, characterisation is less elaborated than for RS used quantitatively.

ESTABLISHMENT OF QUALITATIVE RS

- Mixture RS
  - Key quality attributes: identity of impurities, homogeneity, fitness for purpose
  - **Identity of impurity peaks**
    Spiking with authentic impurity samples
  - **Homogeneity**
    In particular for compounded mixtures (evaporation, lyophilisation)
ESTABLISHMENT OF QUALITATIVE RS

- **Mixture RS**

  - **Fitness for purpose**
    - Using method of intended use
    - Amount of each impurity (detectable and/or suitable for system suitability)
    - System suitability assessment, if applicable
    - Chromatogram for the RS leaflet

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**Example fitness for purpose:**  Risperidone for system suitability CRS

Monograph 01/2011:1559 corrected 7.4 for risperidone: peak-to-valley ratio impurity D ≥ 1.5
Establishment of quantitative RS

A candidate RS is characterised for:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity</td>
<td>Structural elucidation (NMR, qTOF-MS)</td>
</tr>
<tr>
<td>Identity of counter-ion</td>
<td>Various methods; specific or screening</td>
</tr>
<tr>
<td>Related substances</td>
<td>Method of intended use (LC/GC)</td>
</tr>
<tr>
<td>Volatile impurities</td>
<td>Loss on drying, thermogravimetry or water (+ residual solvents)</td>
</tr>
<tr>
<td>Inorganic impurities</td>
<td>Sulfated ash (if amount allows) or screening</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>Method of relevant parameter</td>
</tr>
</tbody>
</table>

**Content** by mass balance or quantitative NMR, **assigned only if below 95.0 %**.

Confirmation of assigned content by orthogonal methods e.g. elemental analysis.
Example orthogonal techniques: Phenobarbital impurity A CRS 1

Analytical results:
- Identity: confirmed
- Loss on drying: 0.1 %
- LC-purity: 99.7 %
- Content by quantitative NMR (expressed ‘as is’, as free base): 79 %
- Elemental analysis: does not match the theoretical composition
- Identification of nitrate as the counter ion (not on CoA)
- Quantification of nitrate by ion-exchange chromatography: 20.6 %

→ Good match with quantitative NMR and elemental analysis

ESTABLISHMENT OF QUANTITATIVE RS

• RS used as external standard in related substances test (impurities)

Stoichiometric conversion factor

- Applied for new batches of impurity RS to be used as external standards, if the RS is supplied in a different salt form than the substance to be examined.
- (If required) provided in the leaflet accompanying the RS, together with instructions for its use.
- Given separately from the assigned content, if any.
- Can vary from batch to batch of the RS.

Note: a stoichiometric conversion factor can also be provided if the substance to be examined is a hydrate (even if the salt form is the same).
Example stoichiometric conversion factor: Rivastigmine impurity D CRS 2

- Rivastigmine impurity D CRS is used as external standard in the Ph.Eur. monographs for rivastigmine and rivastigmine hydrogen tartrate.
- Rivastigmine impurity D CRS 2 is supplied as hydrogen tartrate salt.
- The hydrogen tartrate salt of impurity D has a molecular mass of 400.4.
- Impurity D as a free base has a molecular mass of 250.3.
- The calculated stoichiometric conversion factor for use of rivastigmine impurity D CRS 2 in the Ph.Eur. monograph for rivastigmine is: 400.4 / 250.3 = 1.3 (rounded to one decimal).
- For use in the Ph.Eur. monograph for rivastigmine hydrogen tartrate no stoichiometric conversion factor is needed.

ESTABLISHMENT OF QUANTITATIVE RS

Example stoichiometric conversion factor: Rivastigmine impurity D CRS 2

<table>
<thead>
<tr>
<th>INFORMATION LEAFLET Ph. Eur. Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivastigmine impurity D CRS batch 2</td>
</tr>
</tbody>
</table>

**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): 2629, 2630.
- **2.2 Analytical information related to intended use, when applicable**

For the calculation of the amount of impurity D in monograph 2629 for rivastigmine, multiply the peak area of impurity D obtained with reference solution (a) by a stoichiometric conversion factor of Mr A / Mr B = 1.6.

For the calculation of the amount of impurity D in monograph 2630 for rivastigmine hydrogen tartrate, no stoichiometric correction is required.

Note: Molecular masses used for the calculation of the stoichiometric conversion factor in this leaflet:
- Mr A: Rivastigmine impurity D as hydrogen tartrate salt: C₁₄H₂₂ZnN₂O₂ × C₄H₅O₅ = 400.4 g/mol
- Mr B: Rivastigmine impurity D as free base: C₁₄H₁₉ZnN₂O₂ = 250.3 g/mol.
**ESTABLISHMENT OF QUANTITATIVE RS**

- **RS used for assay**

A candidate RS is characterised for:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identity</td>
<td>Structural elucidation (NMR, qTOF-MS)</td>
</tr>
<tr>
<td>Compliance with monograph</td>
<td>As in monograph, relevant requirements only</td>
</tr>
<tr>
<td>Volatile impurities</td>
<td>Residual solvents (GC)</td>
</tr>
<tr>
<td>Inorganic impurities</td>
<td>Sulfated ash</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>Usually loss on drying or water (and/or residual solvents)</td>
</tr>
</tbody>
</table>

If required, **inter-laboratory study** for parameters significantly contributing to assigned content: related substances (LC/GC), water / loss on drying, residual solvents.

**Content is assigned** by mass balance.

Confirmation of assigned content by orthogonal methods e.g. quantitative NMR, elemental analysis.

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**Example inter-laboratory study: Raltegravir potassium CRS 1**

04/2018:2887

**RALTEGRAVIR POTASSIUM**

Raltegravirum kalicum

\[C_{23}H_{25}FKN_2O_5\]  [871038-72-1]  \[M, 482.5\]

**DEFINITION**

Potassium 4-[(4-fluorophenyl)ethyl][carbamoyl]-1-methyl-2-[(5-methyl-1,3,4-oxadiazol-2-yl)formamido]propan-2-yl]-6-oxo-1,6-dihydropyrimidin-5-oate.

Content: 98.0 per cent to 102.0 per cent (anhydrous substance).

**ASSAY**

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

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

Calculate the percentage content of \(C_{23}H_{25}FKN_2O_5\), taking into account the assigned content of *raltegravir potassium CRS*. 

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ESTABLISHMENT OF QUANTITATIVE RS

Example inter-laboratory study: Raltegravir potassium CRS 1

Characterisation EDQM Lab

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>RSD</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Almost white powder</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>Mass spectrometry (in-house method) 2.2.43.</td>
<td>m/z found in accordance with sum formula</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>Nuclear magnetic resonance spectrometry (in-house method) 2.2.33.</td>
<td>NMR spectra in accordance with structure</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>Identification reactions of ions and functional groups 2.3.1.</td>
<td>Positive reaction b) of potassium</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>Infrared absorption spectrophotometry 2.2.24.</td>
<td>KBr disc and ATR spectra recorded</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>Related substances by liquid chromatography 2.2.29. / 2.2.46.</td>
<td>See inter-laboratory study</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Semi-micro determination of water 2.5.12.</td>
<td>See inter-laboratory study</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Micro determination of water 2.5.32.</td>
<td>0.16 % sd: 0.02</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Residual solvents by headspace gas chromatography 2.2.28. / 2.4.24.</td>
<td>Acetonitrile and ethanol: see inter-laboratory study Sum of other residual solvents: below 0.10 % (Traces of toluene detected)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Differential scanning calorimetry (in-house method) 2.2.34.</td>
<td>Melting point above 205 °C → molar purity could not be determined</td>
<td>n/a</td>
<td>1</td>
</tr>
<tr>
<td>Quantitative nuclear magnetic resonance spectrometry (in-house method) 2.2.33.</td>
<td>About 99.4 %</td>
<td>n/a</td>
<td>3</td>
</tr>
<tr>
<td>Elemental analysis (contracted out to Solvias AG Switzerland)</td>
<td>C: 49.8 % (theory 49.8 %) H: 4.2 % (theory 4.2 %) N: 17.4 % (theory 17.4 %)</td>
<td>n/a</td>
<td>3</td>
</tr>
</tbody>
</table>

LC suitability

<table>
<thead>
<tr>
<th>System suitability</th>
<th>Lab 1</th>
<th>Lab 2</th>
<th>Lab 3</th>
<th>Lab 4</th>
<th>Lab 5</th>
<th>Acceptance criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution imp. E / raltegovir [ref. sol. (c), n = 1]</td>
<td>3.1</td>
<td>3.6</td>
<td>3.9</td>
<td>3.9</td>
<td>3.2</td>
<td>≥ 1.5</td>
</tr>
<tr>
<td>Symmetry factor raltegovir [ref. sol. (b), n = 1]</td>
<td>1.3</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.2</td>
<td>0.8 to 1.5</td>
</tr>
<tr>
<td>Signal-to-noise ratio raltegovir [ref. sol. (a), n = 1]</td>
<td>45</td>
<td>151</td>
<td>38</td>
<td>68</td>
<td>136</td>
<td>≥ 35</td>
</tr>
<tr>
<td>RSD peak area raltegovir [ref. sol. (b), n = 3]</td>
<td>1.9 %</td>
<td>0.7 %</td>
<td>3.4 %</td>
<td>3.4 %</td>
<td>1.5 %</td>
<td>≤ 5.0 %</td>
</tr>
<tr>
<td>All system suitability requirements fulfilled?</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td></td>
</tr>
</tbody>
</table>

ESTABLISHMENT OF QUANTITATIVE RS

Example inter-laboratory study: Raltegravir potassium CRS 1

LC suitability

<table>
<thead>
<tr>
<th>System suitability</th>
<th>Lab 1</th>
<th>Lab 2</th>
<th>Lab 3</th>
<th>Lab 4</th>
<th>Lab 5</th>
<th>Acceptance criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution imp. E / raltegovir [ref. sol. (c), n = 1]</td>
<td>3.1</td>
<td>3.6</td>
<td>3.9</td>
<td>3.9</td>
<td>3.2</td>
<td>≥ 1.5</td>
</tr>
<tr>
<td>Symmetry factor raltegovir [ref. sol. (b), n = 1]</td>
<td>1.3</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.2</td>
<td>0.8 to 1.5</td>
</tr>
<tr>
<td>Signal-to-noise ratio raltegovir [ref. sol. (a), n = 1]</td>
<td>45</td>
<td>151</td>
<td>38</td>
<td>68</td>
<td>136</td>
<td>≥ 35</td>
</tr>
<tr>
<td>RSD peak area raltegovir [ref. sol. (b), n = 3]</td>
<td>1.9 %</td>
<td>0.7 %</td>
<td>3.4 %</td>
<td>3.4 %</td>
<td>1.5 %</td>
<td>≤ 5.0 %</td>
</tr>
<tr>
<td>All system suitability requirements fulfilled?</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td></td>
</tr>
</tbody>
</table>
ESTABLISHMENT OF QUANTITATIVE RS

Example inter-laboratory study: Raltegravir potassium CRS 1

LC results

<table>
<thead>
<tr>
<th>Impurity</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>Imp. C</td>
<td>0.159 % (RR 0.77)</td>
<td>0.143 % (RR 0.76)</td>
<td>0.143 % (RR 0.76)</td>
<td>0.184 % (RR 0.75)</td>
<td>0.144 % (RR 0.77)</td>
<td></td>
</tr>
<tr>
<td>Imp. E</td>
<td>0.046 % (RR 0.95)</td>
<td>0.042 % (RR 0.95)</td>
<td>0.044 % (RR 0.95)</td>
<td>0.048 % (RR 0.95)</td>
<td>0.043 % (RR 0.95)</td>
<td></td>
</tr>
<tr>
<td>Imp. F</td>
<td>0.040 % (RR 1.18)</td>
<td>0.036 % (RR 1.18)</td>
<td>0.039 % (RR 1.19)</td>
<td>&lt; rep. threshold</td>
<td>0.038 % (RR 1.17)</td>
<td></td>
</tr>
<tr>
<td>Imp. G</td>
<td>0.059 % (RR 1.12)</td>
<td>0.055 % (RR 1.12)</td>
<td>0.053 % (RR 1.12)</td>
<td>&lt; rep. threshold</td>
<td>0.054 % (RR 1.12)</td>
<td></td>
</tr>
<tr>
<td>Unspec. imp. 1</td>
<td>&lt; rep. threshold</td>
<td>&lt; rep. threshold</td>
<td>&lt; rep. threshold</td>
<td>&lt; rep. threshold</td>
<td>0.096 % (RR 1.86)</td>
<td></td>
</tr>
<tr>
<td>Sum of impurities</td>
<td>0.303 % n = 2</td>
<td>0.276 % n = 2</td>
<td>0.279 % n = 2</td>
<td>0.232 % n = 2</td>
<td>0.375 % n = 2</td>
<td>0.29 % n = 5 sd: 0.05</td>
</tr>
</tbody>
</table>

5 Relative retention.

ESTABLISHMENT OF QUANTITATIVE RS

Example inter-laboratory study: Raltegravir potassium CRS 1

Content assignment

(100 % - water % - residual solvents %) x [(100 % - sum of impurities by LC %) / 100 %] = 99.1 % of C_{20}H_{20}FKN_{6}O_{5}

The estimated uncertainty is 0.10 %, i.e. negligible in relation to the content limits given in the monograph.
Uncertainty estimation

Example inter-laboratory study: Raltegravir potassium CRS 1

\[ u_{IS} = \sqrt{\frac{\sigma_{LC}^2 + \sigma_{w}^2 + \sigma_{s}^2}{n}} \]

\[ U_{exp.} = \sqrt{u_{IS}^2 + u_{hom}^2 \times k} \]

- **\( u_{IS} \)** = standard uncertainty of inter-laboratory study
- **\( \sigma_{LC} \)** = standard deviation total impurities by LC
- **\( \sigma_{w} \)** = standard deviation water
- **\( \sigma_{s} \)** = standard deviation residual solvents
- **\( n \)** = number of participants
- **\( U_{exp.} \)** = expanded uncertainty
- **\( u_{IS} \)** = standard uncertainty of inter-laboratory study
- **\( u_{hom} \)** = standard uncertainty of homogeneity
- **\( k \)** = coverage factor (normally 2)

Note: The stability component of the uncertainty is not included as considered negligible based on existing data.

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**Example inter-laboratory study: Raltegravir potassium CRS 1**

**Leaflet**

**INFORMATION LEAFLET Ph. Eur. Reference Standard**

**Raltegravir potassium CRS batch 1**

1. **Identification**
   - Catalogue code: Y001943
   - Unit Quantity: ca 100 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): 2887, 2938, 2939.
   - **2.2 Analytical information related to intended use, when applicable**
     The "as is" content is: 99.1% of C20H20FKN6O5

No uncertainty
ESTABLISHMENT OF QUANTITATIVE RS

• RS used as external standard in assay – assigned value

  ➢ RS = material filled as such in a suitable container

    Content (m/m), assigned on an ‘as is’ basis.

    TO BE WEIGHED – NO NEED TO DRY

  ➢ RS = freeze-dried material

    Amount per vial, e.g. 2.05 mg/vial.

    TO BE RECONSTITUTED, NOT WEIGHED

Ph.Eur. 5.12.

A European Pharmacopoeia reference standard with an assigned content / potency for use in the assay of a substance for pharmaceutical use (...) may be suitable to determine the content/potency of that substance in a pharmaceutical preparation provided all of the following conditions are fulfilled:

  – the chromatographic assay method described in the active substance monograph is employed;
  – the applicability of the method to the particular pharmaceutical preparation (absence of interference) is verified by the user;
  – any pre-treatment of the sample (e.g. extraction, filtration) is validated for the particular pharmaceutical preparation.
Example risks off-label use: Artemisinin RS (not Ph.Eur.)

**LC-UV assay method:** RP C18 column – Isocratic elution

**Detection wavelength:** 210 nm

**Limits:** 97.0 % to 102.0 %

**Content** of the reference standard for LC-UV assay:

- mass balance: 99.9 % (contains 0.1 % impurity A)
- by quantitative NMR: 99.9 %

Can the standard be used in a direct UV assay method at 210 nm?

---

**EXAMPLE RISKS OFF-LABEL USE: ARTEMISININ RS (NOT PH.EUR.)**

**Difference in response at 210 nm**

Impurity A needs a correction factor of 0.027 corresponding to a response factor of 37!

Impurity A is *separated* in the LC-UV assay → no impact.

However, impurity A is *not separated* in the direct UV assay → the presence of 0.1 % of impurity A results in a UV signal at 210 nm which is equivalent to 3.7 % of artemisinin.

**Conclusion:**

The standard with an assigned content of 99.9 % is not suitable for use in a direct UV assay method.
Any value assigned to a reference standard is valid for the intended use.

If a reference standard (be it qualitative or quantitative) is to be used for any purpose other than that for which it has been established, its suitability for the new use has to be fully demonstrated by the user.

ACKNOWLEDGEMENT

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Thank you for your attention

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