New Frontiers in the Quality of Medicines

Workshop
Reference Standards: How to characterise them, key elements and qualification

Moderators:
Dr John Miller
Dr Adrian F. Bristow

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Strasbourg, France
Reference Standards: how to characterise them, key elements & qualification

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European Directorate for the Quality of Medicines & Healthcare (EDQM)
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REFERENCE STANDARDS

- Define the need for a reference standard
- For what purpose they are required
- Primary or secondary
- Active pharmaceutical substance and/or pharmaceutical product
REFERENCE STANDARDS

• IDENTIFICATION
  – Infrared spectrophotometry
  – Nuclear magnetic resonance spectrometry
  – Chromatography
• SYSTEM SUITABILITY
  – Chromatography
• IDENTIFICATION OF IMPURITIES
  – Chromatography
• ESTIMATION OF IMPURITIES
  – Chromatography
  – Spectrophotometry
• ASSAY OF CONTENT
  – Chromatography
  – Spectrophotometry

• Biological Reference Preparations vs Chemical Reference Standards
• Impurity Reference Standards
• Herbal Reference Standards
• Reference Standards for Raw Materials (API) & Formulations
Primary Reference Standard

“A standard shown to have suitable properties for the intended use, the demonstration of suitability being made without comparison to an existing standard.”

Secondary Reference Standard

“A standard established by comparison with a primary standard.”

- it is used, usually, in routine quality control of production to avoid the use of the primary reference standard which may be limited in quantity or availability,
- an official primary standard is used, whenever possible, for establishment of secondary standards.
European Pharmacopoeia Reference Standard

CRS with an assigned content/potency for use in the assay of a substance for pharmaceutical use may be suitable for determining the content of that substance in a pharmaceutical preparation.
Provided that ….

- The chromatographic assay method described in the active substance monograph is employed;
- The user verifies the applicability of the method to the particular pharmaceutical preparation;
- Any pre-treatment of the sample is validated for the particular pharmaceutical preparation;
- The use is approved by the competent authority.
Reference Standards

- Reference standards 5.12 European Pharmacopoeia 5th Ed. (2007), Council of Europe, Strasbourg;
- “General Guidelines for the Establishment, Maintenance & Distribution of Chemical Reference Substances”, 41st WHO Expert Committee on Specifications for Pharmaceutical Preparations (2006);
New Frontiers in the Quality of Medicines
EDQM, June 2007

Reference standards: how to characterise them, key elements and quantification

Standards for biologically defined products

Adrian Bristow
National Institute for Biological Standards and Control
United Kingdom
Member Ph.Eur. Group 6

1 Properties and applications of an EP Biological Reference Preparation
2 Calibration/value assignment
3 Scientific issues
Properties and applications of an EP Biological Reference Preparation

Calibration/value assignment

Scientific issues

The Ph. Eur. CRS for Erythropoietin

UNITAGE
Each vial contains 32 500 UNITS of erythropoietin, recombinant

VIAL CONTENTS
Each vial contains the residue, after freeze-drying, of 1ml of a solution which contained:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>rEPO</td>
<td>approx. 250μg</td>
</tr>
<tr>
<td>Trehalose</td>
<td>60 mg</td>
</tr>
<tr>
<td>Arginine</td>
<td>9 mg</td>
</tr>
<tr>
<td>Tween-20</td>
<td>0.3 mg</td>
</tr>
<tr>
<td>NaCl</td>
<td>13.5 mg</td>
</tr>
<tr>
<td>Na₂HPO₄·1H₂O</td>
<td>10.6 mg</td>
</tr>
</tbody>
</table>
The Ph. Eur. BRP for Erythropoietin

Supported analytical technology

The European Pharmacopoeia monograph for Erythropoietin

Specifies tests establishing:
- Identity
- Potency
- Purity
- Safety

Identification A
Gives the appropriate response when examined using the conditions described under assay

Assay 80-125% of the stated potency in IU

Either:
- In vivo ex-hypoxic polycythaemic mouse bioassay
- In vivo normocythaemic mouse bioassay

Principle: EPO stimulates dose-dependent increase in reticulocyte count in normal mice
Identification B
Capillary Zone electrophoresis.
Distribution of peaks is qualitatively and quantitatively similar to the peaks in the reference electropherogram, which must be obtained using the Ph. Eur CRS

Identification A
Gives the appropriate response when examined using the conditions described under assay
Identification B
Capillary Zone electrophoresis.
Distribution of peaks is qualitatively and quantitatively similar to the peaks in the reference electropherogram, which must be obtained using the Ph. Eur CRS
Identification C:
SDS PAGE/western blotting
Test and reference solutions correspond

Identification D:
Peptide map
Profiles obtained with test and reference solutions correspond

Identification E:
N-terminal sequence analysis:
Reference material independent
Tests

Dimers and aggregates:
Refers to CRS (system suitability/validation)

SEC of EPO CRS

Tests:

Protein
Sialic acid
Endotoxins

Reference material independent
In a monograph for a biotechnology-derived biological, such as EPO:

The significant tests of identity, potency and even purity are mostly reference material-dependent

1 Properties and applications of an EP Biological Reference Preparation
2 Calibration/value assignment
3 Scientific issues
RM value assignment - 3 cases:
1. Peptides/proteins value-assigned and dosed in SI
2. Proteins value assigned in SI with a defined IU/mg specific activity
3. Proteins/glycoproteins value assigned and dosed in IU
Value assignment of Leuprorelin CRS batch 2

Method:
- gravimetry
- determination of moisture content
- determination of acetic acid
- HPLC purity

Test | Mean | RSD
--- | --- | ---
Water | 3.07% | 14.6%
Acetic Acid | 6.28% | 4.22%
Purity (HPLC) | 98.77% | 0.10%
Content (bulk) | 5.67 mg/vial | 0.82%
Peptide content | (mg substance – (water + acetic acid)) x 0.9877 – 5.07 mg/vial

Note:
- Assumptions: only peptide, water, acetic acid and measured impurities are present.
- Leuprorelin content is obtained indirectly by subtraction, not by direct measurement.
- Each CRS is a primary standard, with no traceability to previous (or later) CRS.
- Assignment is in SI but formal traceability (i.e., uncertainty statement) is not considered.
RM value assignment - 3 cases:

1. Peptides/proteins value-assigned and dosed in SI
2. Proteins value assigned in SI with a defined IU/mg specific activity
3. Proteins/glycoproteins value assigned and dosed in IU

Insulin, somatropin (GH), oxytocin, calcitonin are considered to have intrinsic, non-variable specific activity, ie determine the mg content and you have, by definition, determined the IU.

Establishment of the 2nd Ph. Eur. CRS for Somatropin (rec growth hormone)

Methods:
- 1st WHO IS is primary standard calibrated in SI (mg) by amino-acid analysis defined in terms of total protein.
- Subsequent WHO IS's are calibrated against this standard by HPLC.
- Ph Eur CRS are secondary standard, calibrated by HPLC.
Calibration by SE-HPLC (i.e., monomer content) of 2nd P. Eur. CRS for Somatropin.

1.70 mg protein/vial

Notes:
- Here, the EP standard is a secondary standard.
- Calibration is traceable to a direct (AAA) determination of somatropin, not an indirect subtractive method.
- No assumptions about content are made.
- The WHO standard defines total somatropin proteins.
- Value assignment of the Ph. Eur. CRS defines somatropin content for the method used only.
- Formal uncertainty is again not considered.
- Specific activity is not re-defined.

Calibration by SE-HPLC (i.e., monomer content) of 2nd P. Eur. CRS for Somatropin.

1.70 mg protein/vial
RM value assignment - 3 cases:
1 Peptides/proteins value-assigned and dosed in SI
2 Proteins value assigned in SI with a defined IU/mg specific activity
3 Proteins/glycoproteins value assigned and dosed in IU

Establishment of the 2nd Ph. Eur. BRP for Erythropoietin
Value assignment methodology: In vivo bioassay
Calibration of Ph. Eur. BRP batch 2 by in vivo bioassay against the WHO IS

Table 1 — Results in vivo assays (IU/vial)

<table>
<thead>
<tr>
<th>Batch</th>
<th>Assay 1</th>
<th>Assay 2</th>
<th>Assay 3</th>
<th>Assay 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRP 1</td>
<td>Combined</td>
<td>32396 (96-104%)</td>
<td>32994 (96-104%)</td>
<td></td>
</tr>
<tr>
<td>BRP 2</td>
<td>32396 (96-104%)</td>
<td>32994 (96-104%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Assigned value: 32500 IU/vial
Notes:

- The Ph. Eur. BRP is a secondary standard calibrated in terms of the primary, WHO IS

- The process is an arbitrary value assignment rather than a formal metrological calibration

- It is costly, and vulnerable

- Individual assays are imprecise

- Experience tells us that the EP model for BRP’s (ie replace every 4-5 years) is not optimal

1 Properties and applications of an EP Biological Reference Preparation

2 Calibration/value assignment

3 Scientific issues
1 The assumption we saw with peptide RM's is that if you weigh it, and measure everything you know isn't peptide, what's left is the answer. How far is this valid. Is it for instance valid for biosynthetic proteins?

2 With peptide RM's, how do we handle a situation where the "new primary standard" approach produces apparent discontinuity

3 Does the Pharmaceutical industry have a scientific justification for not dealing with uncertainties when value assigning reference materials?

ISO 17511 defines a primary reference measurement procedure as
...having the highest metrological qualities, whose operation can be completely described and understood, for which a Complete uncertainty statement can be written down in Terms of SI units, and where results are therefore accepted Without reference to a measurement standard of the quantity Being examined

4 How do we handle value assignment using alternative methods?

EPO as an example of the problems encountered switching from in vivo to in vitro assay methods

With peptide RM's, how do we handle a situation where the "new primary standard" approach produces apparent discontinuity

**Current**

```
<table>
<thead>
<tr>
<th>Current</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SI</td>
<td>CRS 1</td>
</tr>
<tr>
<td></td>
<td>CRS 2</td>
</tr>
</tbody>
</table>
```

When you check CRS 1 against CRS 2 And they are not equivalent, what happens?

**"Gold standard" approach**

```
<table>
<thead>
<tr>
<th>Primary standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary standard</td>
</tr>
</tbody>
</table>
```

```
<table>
<thead>
<tr>
<th>&quot;Gold standard&quot; approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI</td>
</tr>
<tr>
<td>Pharmacopeial gold standard, held and not distributed</td>
</tr>
<tr>
<td>CRS 1</td>
</tr>
<tr>
<td>CRS 2</td>
</tr>
<tr>
<td>CRS 3,...</td>
</tr>
</tbody>
</table>
```
1. The assumption we saw with peptide RM's is that if you weigh it, and measure everything you know isn't peptide, what's left is the answer. How far is this valid. Is it for instance valid for biosynthetic proteins?

2. With peptide RM's, how do we handle a situation where the "new primary standard" approach produces apparent discontinuity.

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4. How do we handle value assignment using alternative methods?

EPO as an example of the problems encountered switching from in vivo to in vitro assay methods
The two don’t correlate

The problem:

International standard for Erythropoietin, IU/vial

Regional (eg pharmacopoeial) Standards for EPO

Product A Working standard

Product B Working standard

In vivo bioactivity (IU/mg)

In vitro bioactivity (IU/mg)

?  r = -0.802  p < 0.02

Challenge: to transfer the in vivo unitage from the International standard to the in vitro unitage of the two products, knowing that:

1. The ratio of in vivo : in vitro activities will not be the same, and
2. The two in vitro assays may have different properties

Product A U/dose

Product B U/dose

In vitro bioassay
Applying an in vitro unitage to a sub-standard must be manufacturer–specific.

For the pharmacopoeial standards, an in vitro unitage must dictate manufacturer-specific monographs.

The alternative would be something like:

"the activity of erythropoietin is determined by measuring the proliferation of cells in vitro. It is determined against a standard of the substance to be examined, whose unitage has been assigned using the in vivo assay against the BRP for EPO (which is itself assigned by in vivo assay)."

---

Thanks to:

Groupe d'experts/Group of Experts No 6
Substance Erythropoietin

Biological Unitation

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Secretary: Laure Toconet

EDQM:

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Guy Rautmann
REFERENCE SUBSTANCES OF THE EUROPEAN PHARMACOPOEIA
ESTABLISHMENT AND USE

Ulrich Rose
EDQM

Content of the presentation

• Definitions and guidelines
• Testing
• Examples
• Assignment and use
• Monitoring
• Conclusion
Classification

- Chemical reference substances - Biological reference preparations
- Primary standards - secondary standards
- Classification according to intented purpose:
  - Identification
  - Test for related substances
  - Assay

Definitions and Guidelines

- WHO Guidelines 1975, 1982, 1999:
  « A designated primary chemical reference substance is widely acknowledged as having appropriate qualities within a specified context, and whose value is accepted without reliance on comparison to another chemical substance »
  « A secondary chemical reference substance is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance. This definition may apply to some substances termed working standards »
Definitions and Guidelines (2)

- ISO Guidelines 30, 31 and 34, 35:

RM (Guide 35): 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.

Primary standard (Guide 30): Standard that is designated or widely acknowledged as having the highest metrological qualities and whose value is accepted without reference to other standards of the same quantity, within a specified context.

Definitions and Guidelines (3)

- ISO GUIDE 35

Pharmacopoeial standards and substances are established and distributed by pharmacopoeial authorities following the general principles of this Guide. Specific guidance for the production of these kinds of RMs exists. It should be noted, however, that a different approach is used by the pharmacopoeial authorities to give the user the information provided by certificates of analysis and expiration dates. Also, the uncertainty of their assigned values is not stated since it is not permitted in the prescribed use of these RMs in the relevant compendia.
Definitions and Guidelines (4)

- General Chapter 5.12.
  Reference Standards (Ph. Eur. 5.6)

"European Pharmacopoeia Chemical Reference Substance (CRS)"

A substance or mixture of substances intended for use as stated in a monograph or general chapter of the European Pharmacopoeia. European Pharmacopoeia CRS are primary standards, except for those (notably antibiotics) that are calibrated in International Units. The latter are secondary standards traceable to the international standard.

Definitions and Guidelines (5)

Batch validity statement
Extent of analytical testing

- CRS used for identification or in the test for related substances:
  EDQM- laboratory

- CRS used in the assay:
  Collaborative trial normally including five laboratories: group of experts, OMCL’s, manufacturer, EDQM laboratory

Requirements

- Except in rare cases the CRS must comply with the requirements of the monograph
- No special purity required
- Impurities as CRS: normally purity > 90.0 %, if employed in a quantitative test, content > 95.0 %, otherwise a content is assigned
CRS for identification tests

- Type of test:
  IR (substance or reference spectrum), TLC, melting point, LC, GC, electrophoresis, SEC, NMR, UV

Examination:
The EDQM laboratory carries out all tests of the monograph. The substance is identified by IR, NMR and MS as well as by comparison to literature.

CRS in the test for related substances

- Qualitative use
  - System suitability test
  - Peak identification

- Quantitative use
  - Limit test
  - Quantitative test
CRS in the test for related substances

- An impurity must be identified, i.e. localized in a chromatographic system:
  - when the impurity is specified and/or
  - when the impurity has an individual limit and/or
  - when a correction factor must be applied

CRS in the test for related substances (2)

- Structurally related substances in the “system suitability test”
- By-products from synthesis or degradation products
- Optical isomers
- Mixtures and spiked samples
CRS in the test for related substances (3)

- Characterization:
  - Structure elucidation by IR, NMR and MS
  - Resolution test as described in the monograph
  - Purity test by LC, GC, TLC, DSC
  - Water determination by Karl Fischer or coulometry, LOD, semi-micro LOD or TGA
  - If required: representative chromatogram, supplied together with the CRS when mentioned in the monograph

CRS in the test for related substances: Examples
System suitability or peak identification mixtures

- Monograph Ketorolac trometamol
  - Specified impurities A, B, C, D (each 0.1 %)
  - Resolution: minimum 1.5 between impurity B and ketorolac
  - Correction factors: impurity A 0.67, impurity B 0.52, impurity C 2.2
CRS in the test for related substances: Examples
System suitability or peak identification mixtures

- Monograph Risperidone
  - Specified impurities A, B, C, D, E (each 0.2 %)
  - System suitability: Hp/Hv minimum 1.5 for separation between impurity D and risperidone
CRS in the test for related substances: Examples
System suitability or peak identification mixtures

CRS in the assay (assay standards)

- Assay methods in which a CRS with declared content is used:
  - UV spectrophotometry
  - HPLC
  - GC
  - Microbiological assay
  - Bio- or immunoassay
Procedure for the establishment of assay standards (1)

- Verification of the structure of the candidate CRS by IR-spectrophotometry, NMR and mass spectrometry
- Verification of compliance with the monograph requirements
- Additional tests, such as residual solvents, DSC, sulphated ash, non aqueous titration (inorganics?)

Procedure for the establishment of assay standards (2)

- Collaborative trial (usually 5 participants)
- Method-specific approach
- Project leader (EDQM laboratory) defines protocol and organises the study
- Report prepared by the project leader
- Presentation to group of experts concerned
- Adoption by the Commission
Assay standards

- Example HPLC assay

The protocol for the collaborative trial requires the following determinations:

- Loss on drying or semi-micro determination of water (or coulometry)
- Quantitative determination of the impurities by HPLC
- Residual solvents by head-space GC
- In addition absolute methods such as:
  - Non aqueous titration, DSC

Assay standards

- Example HPLC assay

System suitability requirements and acceptance criteria in the protocol:

- Maximum rsd or sd for water determination or LOD
- Resolution test in HPLC
- Symmetry factor between 0.8 and 1.5
- Repeatability requirement for the area of the principal peak of the reference solution (5 %)
Assay standards
Assignment of content

- For standards used in physico-chemical assays:
  - Declaration of the content (m/m) on an « as is » basis:
    \[ X (\%) = \frac{100.0 - \text{water/solvents}}{100} \times \text{chromatographic purity} \]
  Alternatively for lyophilized substances:
  Exact quantity per vial is assigned. The amount of substance to be dispensed by freeze-drying is based on the results of the purity-, water- and solvent analyses of the bulk drug
  Example: Vindesine sulphate CRS 2 : 5.11 mg per vial

Estimation of the uncertainty of the assigned content

- The European Pharmacopoeia Commission has adopted the policy that the value assigned to a reference substance as a result of an interlaboratory trial should have an uncertainty not greater than a predetermined value.

<table>
<thead>
<tr>
<th>RANGE OF CONTENT LIMITS</th>
<th>MAXIMUM UNCERTAINTY</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.15</td>
</tr>
<tr>
<td>20</td>
<td>0.24</td>
</tr>
<tr>
<td>30</td>
<td>0.36</td>
</tr>
<tr>
<td>40</td>
<td>0.48</td>
</tr>
<tr>
<td>50</td>
<td>0.60</td>
</tr>
<tr>
<td>60</td>
<td>0.72</td>
</tr>
<tr>
<td>70</td>
<td>0.84</td>
</tr>
<tr>
<td>80</td>
<td>0.98</td>
</tr>
<tr>
<td>90</td>
<td>1.05</td>
</tr>
<tr>
<td>100</td>
<td>1.20</td>
</tr>
<tr>
<td>120</td>
<td>1.44</td>
</tr>
</tbody>
</table>
Estimation of the uncertainty of the assigned content (2)

\[
\sqrt{\frac{\sigma_i^2 + \sigma_w^2 + \sigma_s^2}{n}} \times t_{(n-1)}
\]

Where there are:
- \(\sigma_i^2\) = variance for the estimation of impurities
- \(\sigma_w^2\) = variance for the estimation of water
- \(\sigma_s^2\) = variance for the estimation of residual solvents

Estimation of the uncertainty of the assigned content (3)

Example: Ciprofloxacin HCl CRS 2

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Related Substances</th>
<th>Impurities (%)</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.08</td>
<td>5.88</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.04</td>
<td>5.94</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.07</td>
<td>6.07</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>5.77</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.04</td>
<td>6.08</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>6.07</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.03</td>
<td>5.96</td>
<td></td>
</tr>
</tbody>
</table>

Mean \(0.05\ (n=7)\) \(6.0\ (n=7)\)

SD (\(\sigma\)) \(0.018\) \(0.116\)

Variance (\(\sigma^2\)) \(0.0003\) \(0.014\)

The content of residual solvents is negligible

Approx. Uncertainty = \(\sqrt{0.0003 + 0.014} \times 2.447 = 0.11\)
Use of Ph. Eur. CRS
Assay Standards

- To be used “as is”
- To be used only with the assay method described in the monograph
- Freeze-dried substances: content must be dissolved in a given volume of solvent (do not weigh)

Use of Ph. Eur. CRS
New policy: Assay standards used for finished products (see 5.12)

- The chromatographic assay method described in the active substance monograph is employed
- The user verifies the applicability of the method to the particular pharmaceutical preparation (absence of interference)
- Any pre-treatment of the sample (e.g. extraction) is validated for the particular pharmaceutical preparation
- The use is approved by the competent authority
NEW POLICY: Reference standards for monographs on Herbal drugs and preparations (assay standards)

• « Active principle » (salicin, capsaicin, boldine, rosmarinic acid etc.)
• Inactive marker (ferulic acid, chlorogenic acid)
• Extracts with assigned content (milk thistle dry extract, agnus castus fruit dry extract, valerian dry extract)

Monitoring (retest-programme)

• After establishment and adoption there is a standardised testing procedure in order to ensure the “fitness for use” of the CRSs
• Depending on the use and the known or predicted stability substances are retested every two, three or five years
• Items of retesting: All properties which are subject to change in the life cycle of a CRS, i. e.:
  - Water content
  - Purity by HPLC, GC or TLC
  - DSC
  - Possibly IR, UV
Conclusion

- Primary standards
- Way of establishment is use-dependent
- Use for the intended purpose
- Essential requirement: suitable for the intended purpose
- Value assignment on the “as is” basis
- New Ph. Eur. policy:
  - CRS instead of reagents in herbal monographs
  - Assay standards for finished products
- Retesting instead of expiry date