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

Ph. Eur. Reference Standards: establishment and use

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Introduction

Outline:

→Terms and definitions

→Establishment and use of CRS

→Reference Standards for general chapters

→Secondary standards

Terms and definitions

Terms and definitions

07/2018:51200
corrected 11.3

5.12. REFERENCE STANDARDS

This chapter is published for information.

Terms and definitions

Reference Material

Certified Reference Material (CRM)

Primary measurement standard

Secondary measurement standard

European Pharmacopoeia reference standard (Ph.Eur. RS)

European Pharmacopoeia chemical reference substance (CRS)

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

Reference Material

Certified Reference Material (CRM)

Primary measurement standard

Secondary measurement standard

European Pharmacopoeia reference standard (Ph.Eur. RS)

European Pharmacopoeia chemical reference substance (CRS)

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

Reference Material

Certified Reference Material (CRM)

Primary measurement standard

Secondary measurement standard

European Pharmacopoeia reference standard (Ph.Eur. RS)

European Pharmacopoeia chemical reference substance (CRS)

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.

Terms and definitions

Reference Material

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European Pharmacopoeia reference standard (Ph.Eur. RS)

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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.

Standard whose property value is assigned **by comparison** with a primary standard **of the same property or quantity**.

Terms and definitions

Reference Material

Certified Reference Material (CRM)

Primary measurement standard

Secondary measurement standard

European Pharmacopoeia reference standard (Ph.Eur. RS)

European Pharmacopoeia chemical reference substance (CRS)

A reference standard **established** under the aegis of and **adopted** by the European Pharmacopoeia Commission. (substances, preparations, spectra)

Terms and definitions

Reference Material

Certified Reference Material (CRM)

Primary measurement standard

Secondary measurement standard

European Pharmacopoeia reference standard (Ph.Eur. RS)

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**.

Note: HRS and BRP are other types of RS.

Terms and definitions

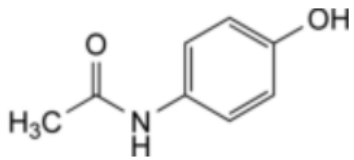
Ph. Eur. General Notices

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

These reference standards are available from EDQM.

Establishment and use of CRS

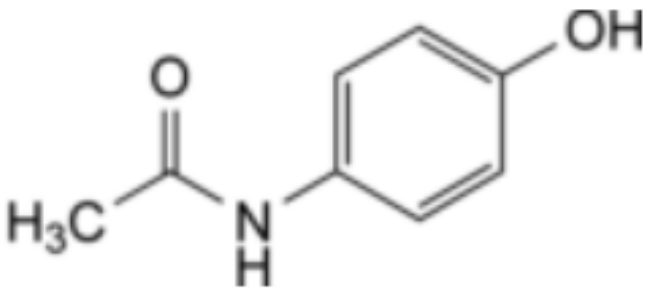
Establishment and use of CRS

	PARACETAMOL Paracetamolum 	
	RS for identification	Impurity RS for qualitative use Mixture RS
	Assay RS	Impurity RS as external standard

RS for identification

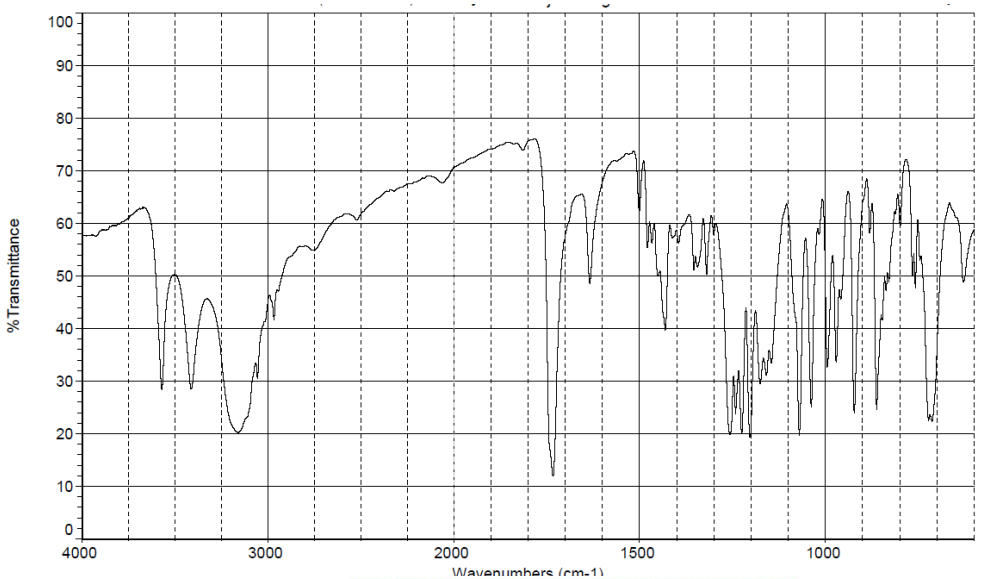
PARACETAMOL

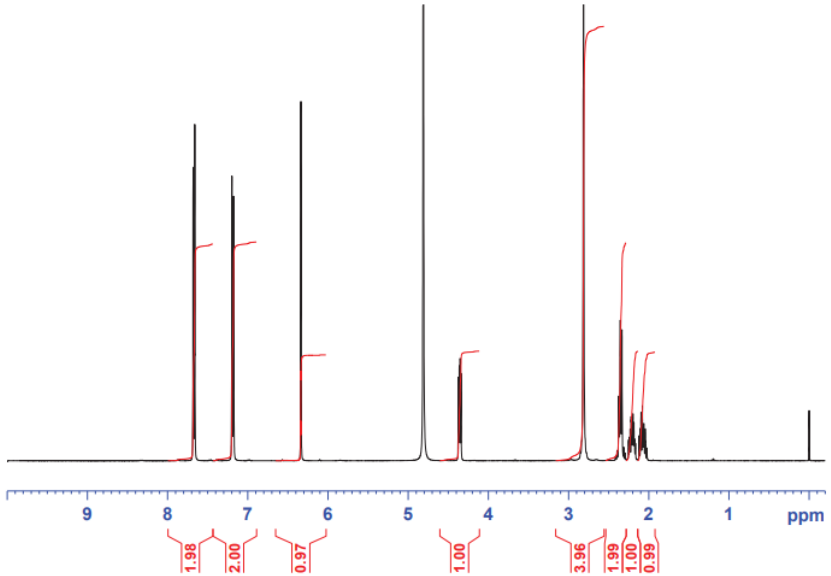
Paracetamolum

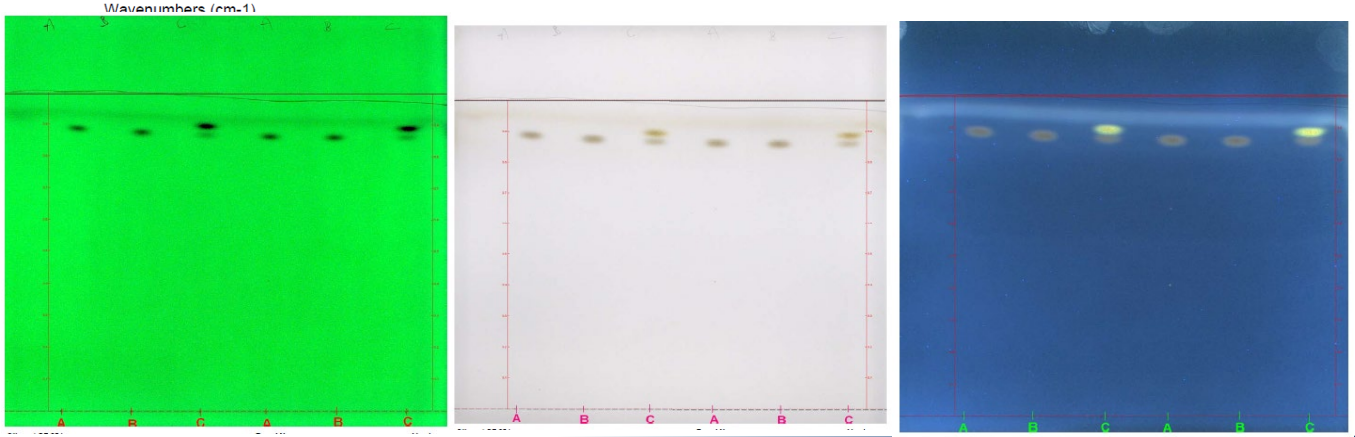


RS for identification

Identification of substances subject of a Ph. Eur. monograph







RS for identification

Establishment

→Key quality attribute= identity

→Identity: full structural elucidation (NMR, MS), whenever possible

→Compliance with relevant requirements of the monograph

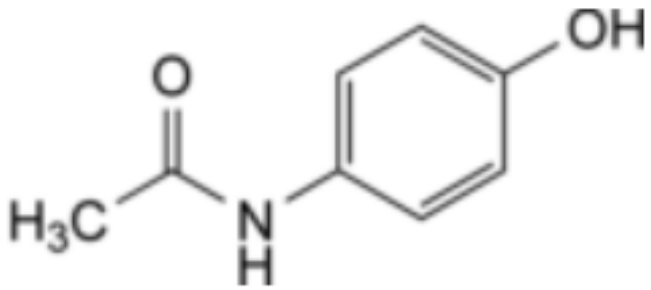
→Intended use

→Characterisation focused on the substance rather than impurities

Assay RS

PARACETAMOL

Paracetamolum



Assay RS

→ Quantitative benchmarks in assay procedures such as LC, GC, microbiology

→ Substance compliant with relevant requirements of corresponding Ph.Eur. monograph

→ Exceptional cases: other salt form, other hydrate, lyophilised RS

→ Content is assigned based on mass balance approach (pharmacopoeial + complementary tests)

→ Uncertainty of the assigned value is estimated and shall be negligible compared to content limits in the monograph

Assay RS

Establishment

→Key quality attributes: Identity and content (qualitative and quantitative)

→Characterisation focused on substance and its impurities

→Identity

→Compliance with relevant requirements of the monograph

→Volatile impurities (LOD, residual solvents (HS-GC) and water)

→Inorganic impurities (sulfated ash for screening, further testing may be required)

Assay RS

Establishment (continued)

→Homogeneity (LOD or water, residual solvents in specific cases)

→Confirmation of assigned content/ purity by orthogonal methods (qNMR, elemental analysis, titration, …), whenever possible

→Inter-laboratory study for parameters with significant contribution to assigned content

Example: Pemetrexed disodium heptahydrate CRS 3

PEMETREXED DISODIUM HEPTAHYDRATE

Pemetrexedum dinatricum heptahydricum

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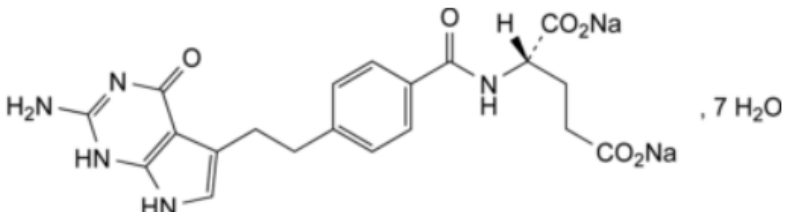

ASSAY

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or store them at 2-8 °C for not more than 24 h.*

Acetate buffer. Mix 1.7 mL of glacial acetic acid R and 900 mL of water for chromatography R, adjust to pH 5.3 with a 760 g/L solution of sodium hydroxide R in water for chromatography R and dilute to 1000 mL with water for chromatography R.

Test solution. Dissolve 30.0 mg of the substance to be examined in water for chromatography R and dilute to 200.0 mL with the same solvent.

Reference solution. Dissolve 30.0 mg of pemetrexed disodium heptahydrate CRS in water for chromatography R and dilute to 200.0 mL with the same solvent.

Column:

- *size*: *l* = 0.15 m, Ø = 4.6 mm;
- *stationary phase*: base-deactivated octylsilyl silica gel for chromatography R (3.5 µm);
- *temperature*: 30 °C.

Mobile phase: acetonitrile R, acetate buffer (11:89 *V/V*).

Flow rate: 2.0 mL/min.

Detection: spectrophotometer at 285 nm.

Injection: 20 µL.

Run time: twice the retention time of pemetrexed (retention time = about 3 min).

Calculate the percentage content of $C_{20}H_{19}N_5Na_2O_6$ taking into account the assigned content of pemetrexed disodium heptahydrate CRS.

Example: Pemetrexed disodium heptahydrate CRS 3

Characterisation EDQM Lab

Test	Result	%RSD	n
Appearance	White powder	n/a	1
Infrared absorption spectrophotometry 2.2.24.	Concordant with CRS 2	n/a	1
Mass spectrometry (in-house method) 2.2.43.	m/z found in accordance with sum formula	n/a	1
Identification reactions of ions and functional groups 2.3.1.	Positive identification reaction a) for Na	n/a	1
Nuclear magnetic resonance – other (in-house method) 2.2.33.	NMR spectra of CRS 2 and proposed CRS 3 are concordant	n/a	1
Enantiomeric purity, Liquid chromatography 2.2.29. / 2.2.46.	Baseline separation between impurity E and pemetrexed	n/a	1
	Symmetry factor: 1.1	n/a	1
	Impurity E: 0.08%	n/a	2
Related substances by liquid chromatography 2.2.29. / 2.2.46.	Peak to valley ratio imp. B / imp. C: 7.8	n/a	1
	No impurity above reporting threshold	n/a	6
	Reporting threshold: 0.03%	-	-

Test	Result	%RSD	n
Semi-micro determination of water 2.5.12.	See collaborative study	-	-
Residual solvents by headspace gas chromatography (in-house method) 2.2.28. / 2.4.24.	<0.10%	n/a	2
Assay by liquid chromatography 2.2.29. / 2.2.46.	78.7% (as is)	0.41%	3
Quantitative nuclear magnetic resonance spectrometry (in-house method) 2.2.33.	78.4% $C_{20}H_{19}N_5Na_2O_6$	0.37%	3
	Internal standard: dimethylmalonic acid	-	-

Elemental analysis (contracted out to SGS France)	Atom	Theoretical value[1]	Experimental value	-	-
	C	40.0 %	40.2 %	-	3
	H	5.6 %	5.5 %	-	3
	N	11.7 %	11.6 %	-	3
	O	35.1 %	34.6 %	-	3

[1] Theoretical values corrected for water content.

Example: Pemetrexed disodium heptahydrate CRS 3

Results of inter-laboratory study

	Lab 1	Lab 2	Lab 3	Lab 4	Lab 5	Result
Result	21.29 % n = 3 sd: 0.02 rsd: 0.1 %	21.93 % n = 3 sd: 0.16 rsd: 0.7 %	21.03 % n = 3 sd: 0.19 rsd: 0.9 %	21.49 % n = 3 sd: 0.09 rsd: 0.4 %	21.55 % n = 3 sd: 0.00 rsd: 0.0 %	21.46 % n = 5 sd: 0.33
Acceptance criterion fulfilled? **(rsd ≤ 1.5 %)**	Yes	Yes	Yes	Yes	Yes	-

Example: Pemetrexed disodium heptahydrate CRS 3

Content assignment

[100% (m/m) - water% (m/m) by semi-micro determination of water – inorganic impurities% (m/m) - residual solvents% (m/m)] x [100% - sum of impurities by relative%] / 100%

=

78.5 % of $C_{20}H_{19}N_5Na_2O_6$

RS for control of related substances (qualitative)

RS for control of related substances (qualitative)

Qualitative RS for impurity control

→Chromatographic separation techniques (LC, GC, TLC)

→Batch testing: identification of signals (specified impurities or CF)

→System suitability testing

→Similarities in establishment

RS for control of related substances (qualitative)

RS strategy

→ Single substance <-> mixtures

RS for control of related substances (qualitative)

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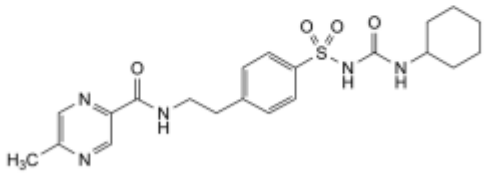
GLIPIZIDE

Glipizidum



$C_{21}H_{27}N_5O_4S$ [29094-61-9] M_r 445.5

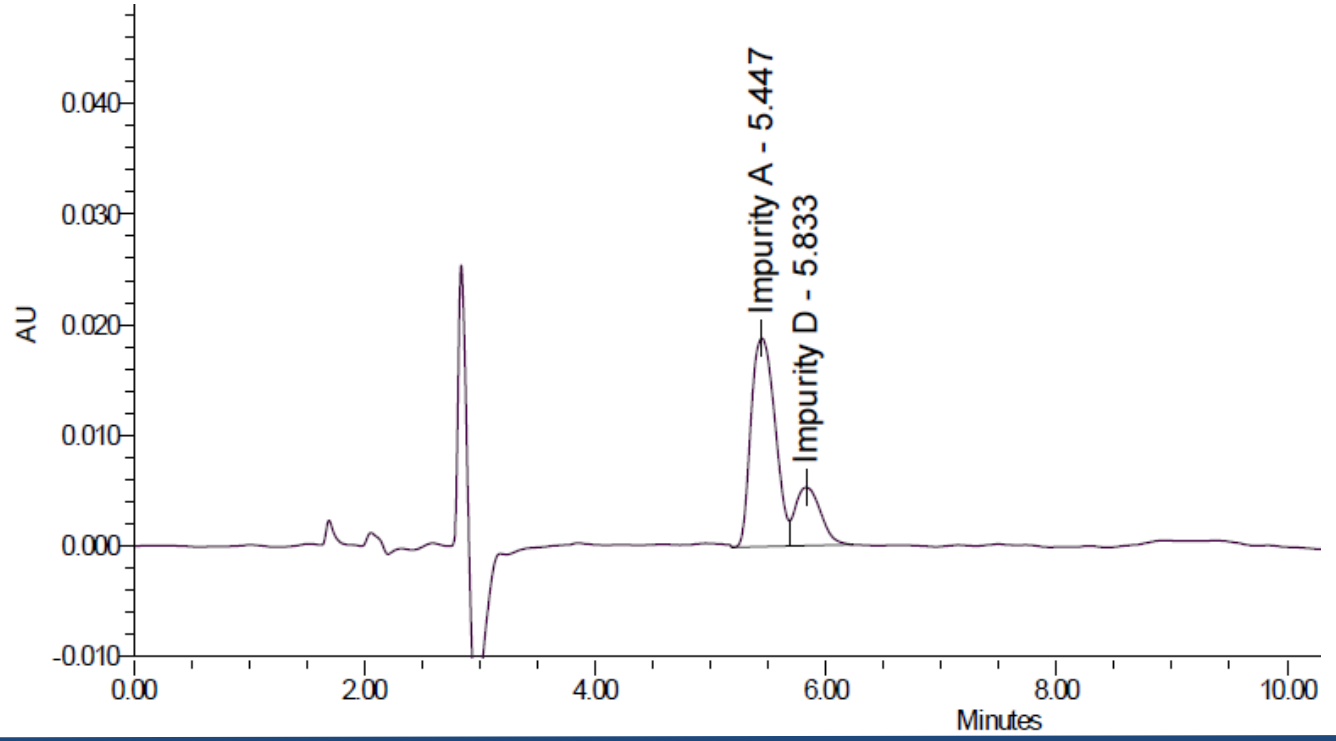
Related substances. Liquid chromatography (*2.2.29*).

Reference solution (b). Dissolve 6.0 mg of *glipizide impurity A CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (d). Dissolve 2 mg of *glipizide impurity D CRS* in the solvent mixture and dilute to 250 mL with the solvent mixture. Dilute 1 mL of the solution to 20 mL with reference solution (b).

System suitability: reference solution (d):

– *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity A.



RS for control of related substances (qualitative)

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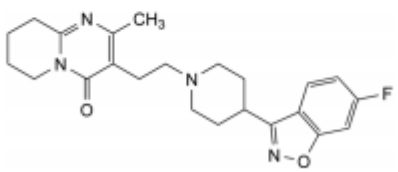
RISPERIDONE

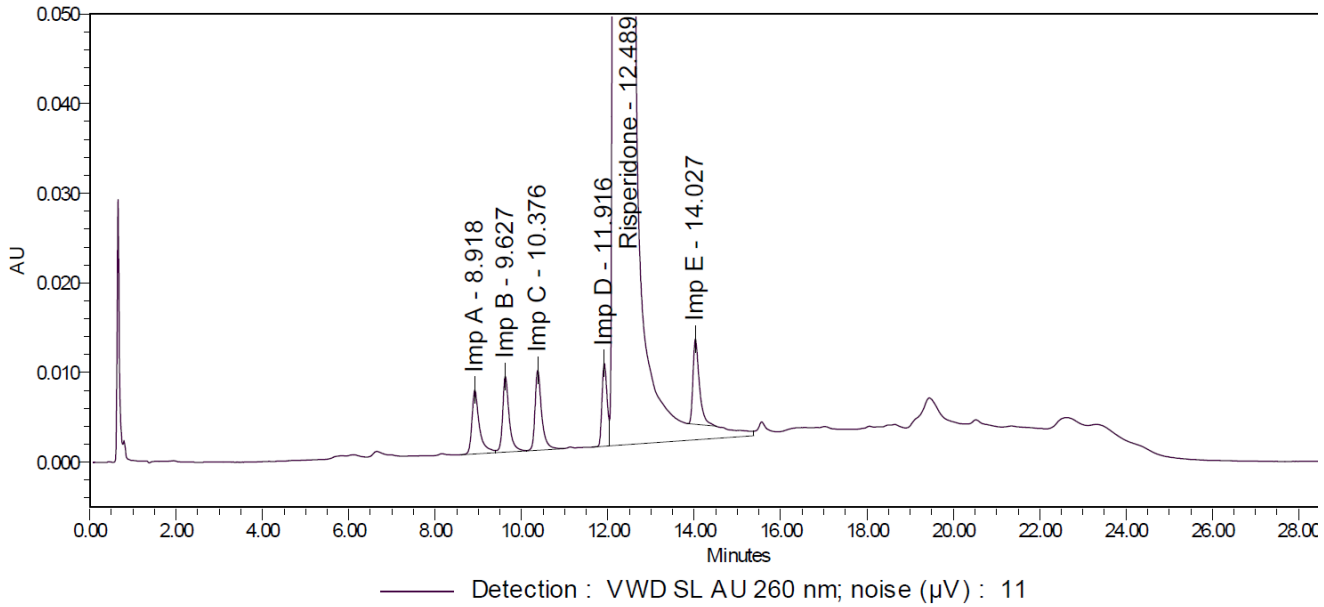
Risperidonum



$C_{23}H_{27}FN_4O_2$ [106266-06-2] M_r 410.5

Related substances. Liquid chromatography (*2.2.29*).
Test solution. Dissolve 0.100 g of the substance to be examined in *methanol R* and dilute to 10.0 mL with the same solvent.
Reference solution (a). Dissolve 10 mg of *risperidone for system suitability CRS* (containing impurities A, B, C, D and E) in 1.0 mL of *methanol R*.

System suitability: reference solution (a):
- the chromatogram obtained is similar to the chromatogram supplied with *risperidone for system suitability CRS*;
- *peak-to-valley ratio*: minimum 1.5, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to risperidone.



RS for control of related substances (qualitative)

RS strategy

→ Single substance <-> mixtures

→ Alternative to RS: commercial reagent or in situ degradation

→ If impurities are specified→ batches containing the impurities normally available

→A chromatogram is supplied in the RS leaflet if referred to in the monograph

RS for control of related substances (qualitative)

Establishment: single substance RS not subject of a Ph. Eur. monograph (e.g. impurity)

→Key quality attribute: identity (qualitative)

→Full structural elucidation, when possible

→Intended use

→Characterisation is less elaborated than for RS used quantitatively

RS for control of related substances (qualitative)

Establishment: mixture RS

→Key quality attributes: identity of impurities, content, fitness for purpose

→Identity of impurity peaks

→Spiking with authentic samples

→Homogeneity

→Intended use

RS for control of related substances (quantitative)

RS for control of related substances (quantitative)

Use

→ Mostly in chromatographic methods

→ External standard for impurities with a response very different from that of substance subject of the monograph

→Otherwise, correction factor is given (if response factor is outside 0.8–1.2)

RS for control of related substances (quantitative)

→Content of RS is critical: ≥ 95.0 % or not?

→Single substance RS

→Materials obtained via processes that do not guarantee the required degree of purity and homogeneity

→Salt form has impact on use

- →easier to handle, less hygroscopic, volatile, procurement issues…
- →solubility?
- →need for stoichiometric conversion factor?

RS for control of related substances (quantitative)

→Stoichiometric conversion factor:

→Specification limit for impurity in same salt form

→Need to identify presence and identity of counter-ion

→Different from the monograph form

→Exception: if impurity cannot form the salt

RS for control of related substances (quantitative)

Establishment

→Key quality attributes: identity and content

→Identity: Full structural elucidation, if possible

→Identity of counter-ion: specific or screening

→Related substances: method of intended use (LC/GC)

→Volatile impurities: Loss on drying, thermogravimetry or water (+ residual solvents)

RS for control of related substances (quantitative)

Establishment

→Inorganic impurities: Sulfated ash (if amount allows), total ash or screening

→qNMR

→Homogeneity

→Content assignment (when <95.0%): mass balance or qNMR

→Orthogonal methods

RS for control of related substances (quantitative)

Example: Phenobarbital impurity A CRS 1

→Analytical results

→Identity: confirmed

→Loss on drying: 0.1 %

→LC-purity: 99.7 %

} Mass balance: 99.6 %

No need for assigned content

→Content by qNMR (expressed 'as is', as free base): 79 %

→Elemental analysis: does not match the theoretical composition

Investigation

→Identification of ions (2.3.1)

→Chloride: negative

→Sulfate: negative

→Nitrate: positive (not on COA)

→Quantification of nitrate by ion-exchange chromatography: 20.6 %

Reference Standards for general chapters

Reference standards for general tests

Ph. Eur. 2.4.24. Identification and control of residual solvents

2.4.24. IDENTIFICATION AND CONTROL OF RESIDUAL SOLVENTS

The test procedures described in this general method may be used:

i. for the identification of the majority of Class 1 and Class 2 residual solvents in an active substance, excipient or medicinal product when the residual solvents are unknown;

ii. as a limit test for Class 1 and Class 2 solvents when present in an active substance, excipient or medicinal product;

iii. for the quantification of Class 2 solvents when the limits are greater than 1000 ppm (0.1 per cent) or for the quantification of Class 3 solvents when required.

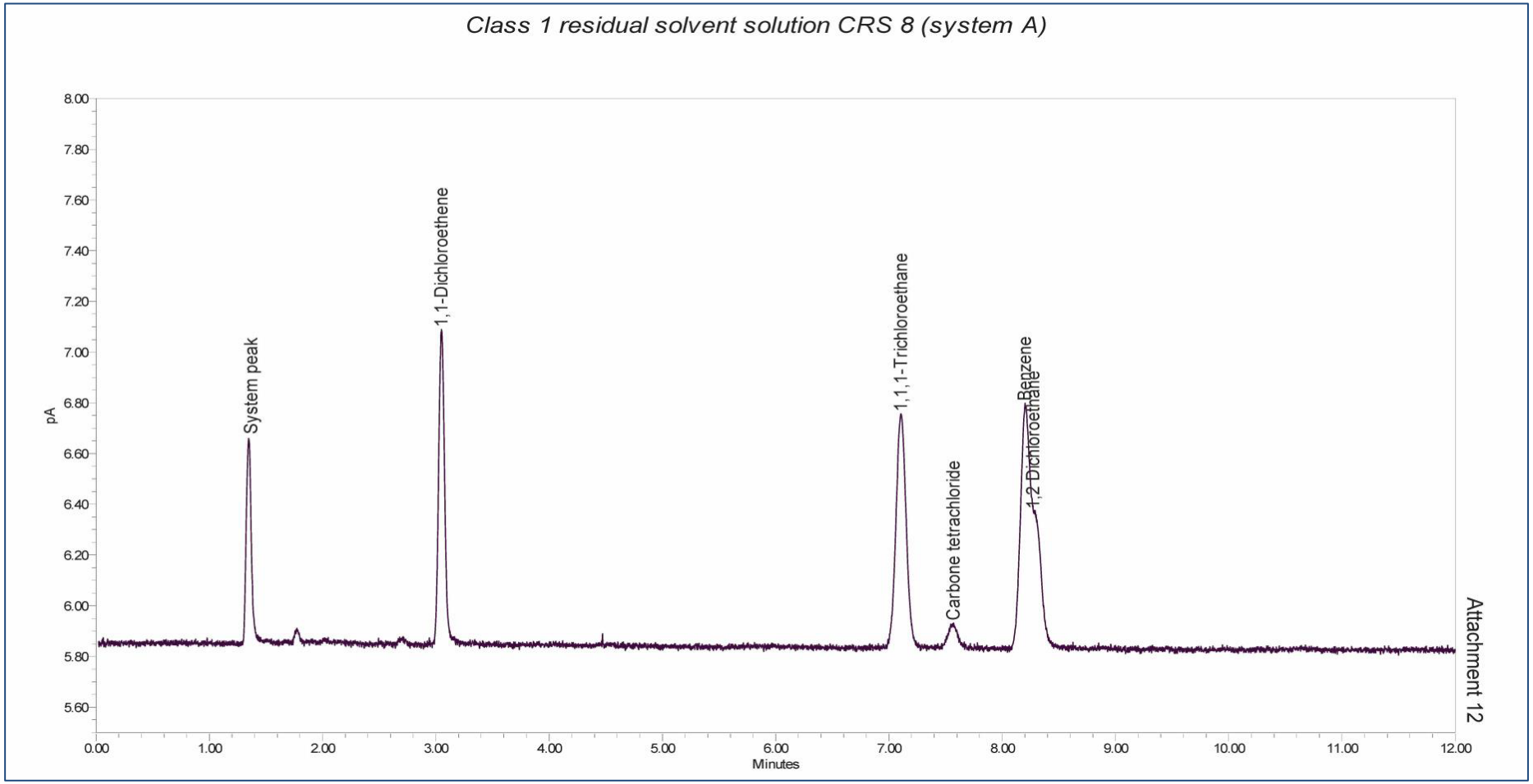
Solvent solution (a). To 1.0 mL of *Class 1 residual solvent solution CRS*, add 9 mL of *dimethyl sulfoxide R* and dilute to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 100 mL with *water R*. Dilute 1.0 mL of this solution to 10.0 mL with *water R*.

The reference solutions correspond to the following limits:

- benzene: 2 ppm;
- carbon tetrachloride: 4 ppm;
- 1,2-dichloroethane: 5 ppm;
- 1,1-dichloroethene: 8 ppm;
- 1,1,1-trichloroethane: 10 ppm.

Reference standards for general tests

Class 1 residual solvent solution CRS



Reference standards for general tests

Ph.Eur. Chapter 2.5.42. N-Nitrosamines in Active Substances

Analytical procedures for the detection of various *N*-nitrosamines in particular active substances.
Procedures A and B have been validated as limit tests (30 ppb) and procedure C has been validated as a quantitative test. With these three procedures, it is possible to analyse NDMA, NDEA, NDBA, NMBA, NDiPA, NEiPA and NDPA.

Last update : 01/09/2023

Cat. No.	Name	Batch No.	Unit Quantity
Y0002258	N-Nitroso-diethylamine CRS	1	1 mL
Y0002259	N-nitroso-dimethylamine CRS	1	1 mL
Y0002260	N-nitroso-N-methyl-4-aminobutyric acid CRS	1	1 mL
Y0002261	N-Nitroso-dibutylamine CRS	1	1 mL
Y0002262	N-nitroso-ethyl-isopropylamine CRS	1	1 mL
Y0002263	N-nitroso-diisopropylamine CRS	1	1 mL
Y0002264	N-Nitroso-dipropylamine CRS	1	1 mL

Reference standards for general tests

2.4.20. DETERMINATION OF ELEMENTAL IMPURITIES

VALIDATION REQUIREMENTS:

ACCURACY

Verify the accuracy using a certified reference material or by performing a test for recovery. *Elemental impurity solutions CRS* may be used.

The recovery may be determined on a sample of the substance to be examined, spiked with a known quantity of a reference standard of the element of interest (3 concentration levels in the range of 50-150 per cent of the intended specification limit, even if the original concentration of the reference standard is at the specified value), in triplicate.

Reference standards for general tests

Elemental impurity chemical reference substances (CRS) :

→Class 1

→Lead solution CRS (0.9996 mg/g)

→Cadmium solution CRS (1.0012 mg/g)

→Mercury solution CRS (0.999 mg/g)

→Arsenic solution CRS (1.001 mg/g)

→Class 2

→Nickel solution CRS (1.001 mg/g)

→Palladium solution CRS (0.996 mg/g)

→Platinum solution CRS (0.999 mg/g)

CRS for quantitative use

INFORMATION LEAFLET Ph. Eur. Reference Standard

Arsenic solution CRS batch 1

1. Identification

Catalogue code: Y0002004 Unit Quantity: ca 10 mL

2. Scientific Information

2.1 Intended use

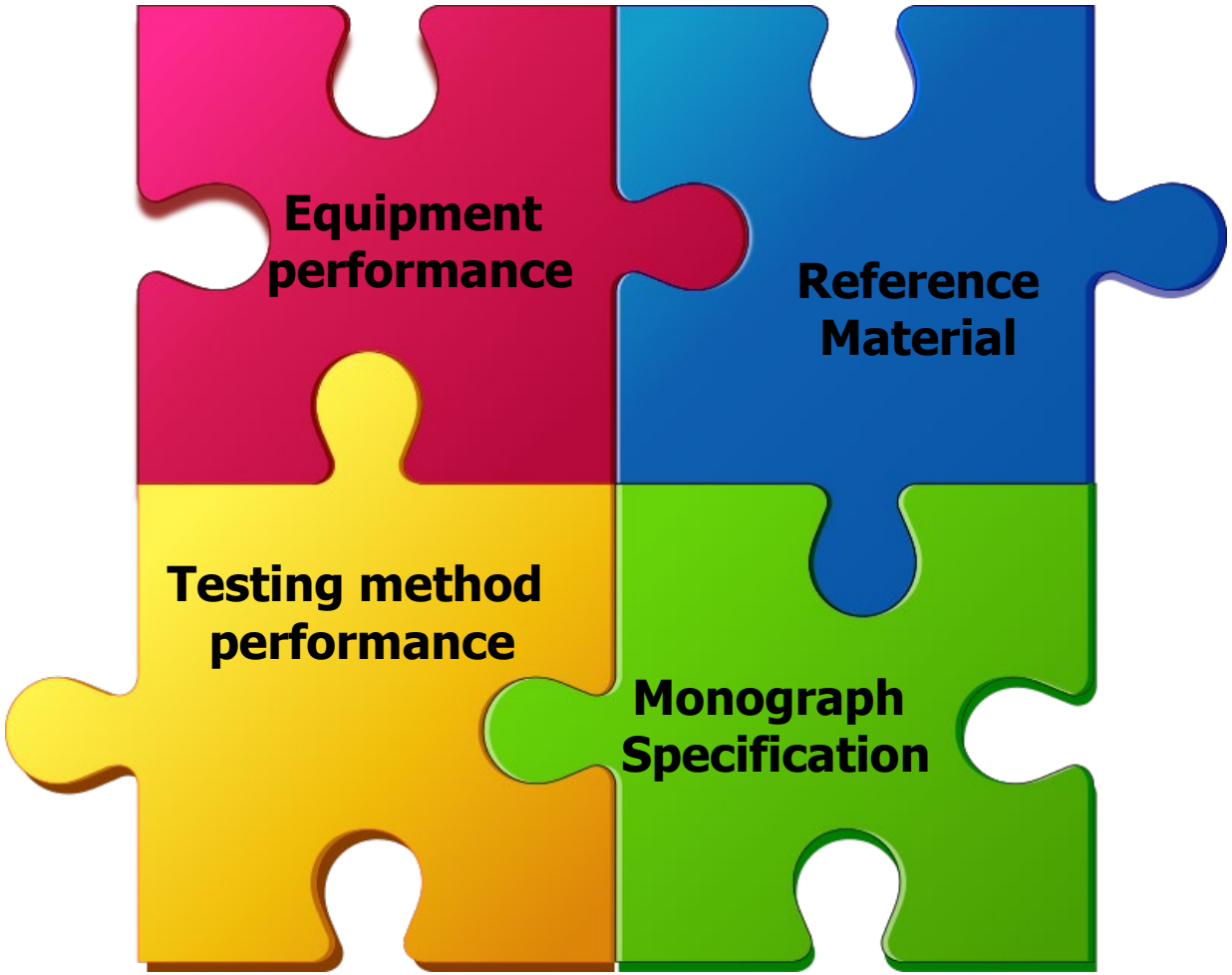
Reference Standard for laboratory tests as prescribed in the European Pharmacopoeia.
Established for use with chapter: 20420.

2.2 Analytical information

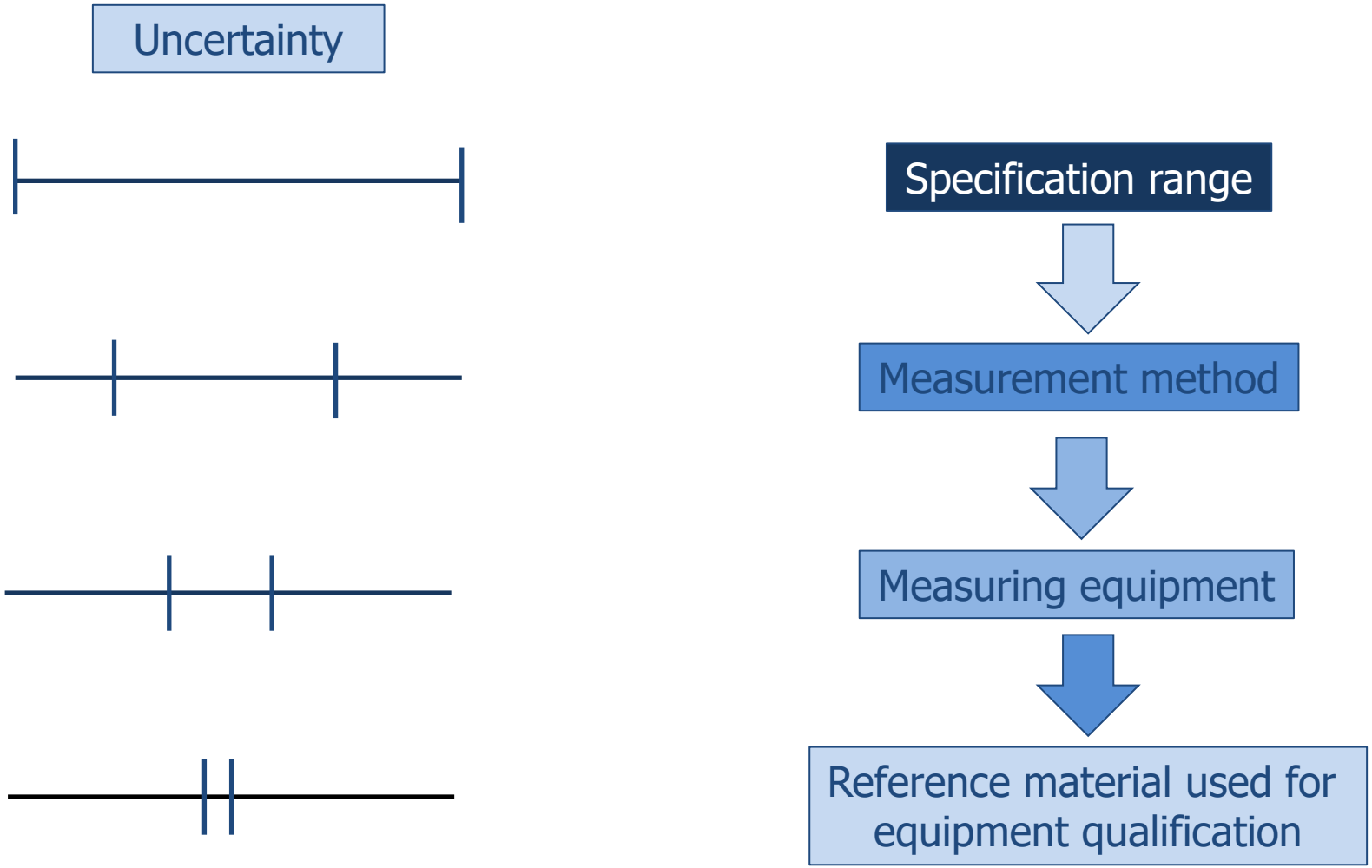
Mass fraction of arsenic in the solution:	1.001 mg/g
Associated expanded uncertainty:	U = 0.015 mg/g, k = 2
Density of the solution:	1.015 g/mL at 20.0 °C
Solvent composition:	about 2.5 % m/m nitric acid

Traceability to the SI base units kilogram and mole is achieved through an uninterrupted chain of calibration measurements that link arsenic solution CRS 1 to a primary material characterised by a National Metrology Institute at the highest metrological level (High purity copper BAM-Y001).
The IUPAC standard atomic weight for arsenic shall be applied.
Dilutions of arsenic solution CRS 1 should be made with 2.5 % nitric acid.

CRS for equipment qualification



CRS for equipment qualification



CRS for equipment qualification

PARACETAMOL FOR EQUIPMENT QUALIFICATION CRS

Ph.Eur. Chapter 2.2.48. Raman Spectroscopy

	Wavenumber[A] [cm^{-1}]	Tolerances	
		Benchtop [cm^{-1}]	Handheld [cm^{-1}]
Paracetamol[C]	797.2	± 1.5	± 2.5
	857.9	± 1.5	± 2.0
	1168.5	± 1.5	± 2.0
	1236.8	± 1.5	± 2.0
	1323.9	± 1.5	± 2.5
	1648.4	± 1.5	± 3.0
	2931.1	± 2.0	NA[E]

CRS for equipment qualification

NICOTINIC ACID FOR EQUIPMENT QUALIFICATION CRS

Ph. Eur. Chapter 2.2.25. Absorption Spectrophotometry UV/Vis

Control of absorbance accuracy. Control the absorbance accuracy at an appropriate number of wavelengths in the intended spectral range using suitable solid or liquid filters to check that the absorbance measured at the test wavelength matches the certified absorbance of the filter or the absorbance value that is calculated from a certified specific absorbance. *Nicotinic acid for equipment qualification CRS* may be used.

Acceptance criteria

The difference between the measured absorbance and the absorbance of the certified material is ± 0.010 or ± 1 per cent, whichever is greater, for each combination of wavelength and absorbance assessed (applies to absorbance values not greater than 2). Tolerances for higher absorbance values should be defined on the basis of a risk assessment.

CRS for equipment qualification

Extract of the leaflet accompanying the CRS:

2.2 Analytical information related to the intended use

Specific absorbance:

213 nm: $A_{1cm}^{1\ per\ cent}$ **= 430.7**

261 nm: $A_{1cm}^{1\ per\ cent}$ **= 422.5**

2.3 Uncertainty of the assigned property values

Uncertainty of the assigned specific absorbance values, expressed as expanded uncertainty (95% confidence interval, coverage factor of k=2): U_{213nm}: ±3.5, U_{261m} ±2.8

CRS for equipment qualification

CALCIUM OXALATE MONOHYDRATE CRS

Ph. Eur. Chapter 2.2.34. Thermal Analysis - Thermogravimetry

Calibration of the electrobalance. Place an appropriate quantity of a suitable certified reference material (**c*alcium oxalate monohydrate CRS may be used*)** in the sample holder and record the mass.

… Measure the difference on the graph between the initial and final mass-temperature or mass-time plateaux, which corresponds to the loss of mass. **The declared loss of mass for the certified reference material is stated on the label.**

CRS for equipment qualification

CALCIUM OXALATE MONOHYDRATE CRS

Extract of the leaflet accompanying the CRS:

2.2 Analytical information related to intended use, when applicable

Loss of mass by thermogravimetry (Ph. Eur. 2.2.34.)(1): 12.1%
Associated expanded uncertainty(2): U = 0.1%, k = 2
Test procedure: Determined on a nominal mass of 10 mg of Calcium oxalate monohydrate CRS 2 applying the following temperature program: Heat to 250 °C at a rate of 10 °C/min; then hold at 250 °C for 40 min.

(1) Unweighted mean value of means of accepted sets of results, each set having being obtained in a different laboratory with the method described above.
(2) Estimated expanded uncertainty U with a coverage factor k = 2, corresponding to a level of confidence of about 95 % as defined in the Guide to the Expression of Uncertainty in Measurement (GUM), ISO, 1995. Uncertainty contributions arising from characterisation as well as homogeneity assessments were taken into account.

CRS for equipment qualification

Sodium aminosalicylate dihydrate for equipment qualification:

Ph. Eur. 2.5.12. Water: Semi-micro determination

… Instrument qualification is carried out according to established quality system procedures, for example using a suitable certified reference material (**sodium aminosalicylate dihydrate for equipment qualification CRS** may be used).

CRS for equipment qualification

ESTABLISHMENT:

→ Test for compliance with the Ph. Eur. Monograph for sodium aminosalicylate dihydrate

→ Inter-laboratory study

→ Homogeneity assessment on a representative number of randomly sampled containers (n=39)

→ Calculation of the assigned property value as mean result of the inter-laboratory study

CRS for equipment qualification

ESTABLISHMENT:

→ Calculation of the associated expanded uncertainty

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

Where:

$U_{exp.}$ = expanded uncertainty

u_{IS} = standard uncertainty from inter-laboratory study

u_{hom} = standard uncertainty from homogeneity study

k = 2 (coverage factor at 95% confidence level)

CRS for equipment qualification

Extract of the leaflet accompanying the CRS:

2.1 Intended use
Reference Standard for laboratory tests as prescribed in the European Pharmacopoeia only.
Established for use with the monograph(s): 2.2.32., 2.5.12.,2.5.32.

2.5.12. – Semi-micro determination of water

Certified water content[1)]: 171.6 mg/g
Uncertainty[2)]: 1.0 mg/g

Test procedure: Carry out the test in triplicate using 100 mg of substance per determination.

Hydranal composite 5 was found suitable. If other solvents/titrants are used, carry the suitability test described in Ph. Eur. 2.5.12.

1) Unweighted mean value of means of accepted sets of results, each set having being obtained in a different laboratory with the method described above.
2) Estimated expanded uncertainty U with a coverage factor k = 2, corresponding to a level of confidence of about 95 % as defined in ISO/IEC Guide 98-3:2008 - Uncertainty of measurement -- Part 3: Guide to the expression of uncertainty in measurement (GUM: 1995). Uncertainty contributions arising from characterisation as well as homogeneity assessments were taken into account.

CRS for equipment qualification

Additional leaflet info:

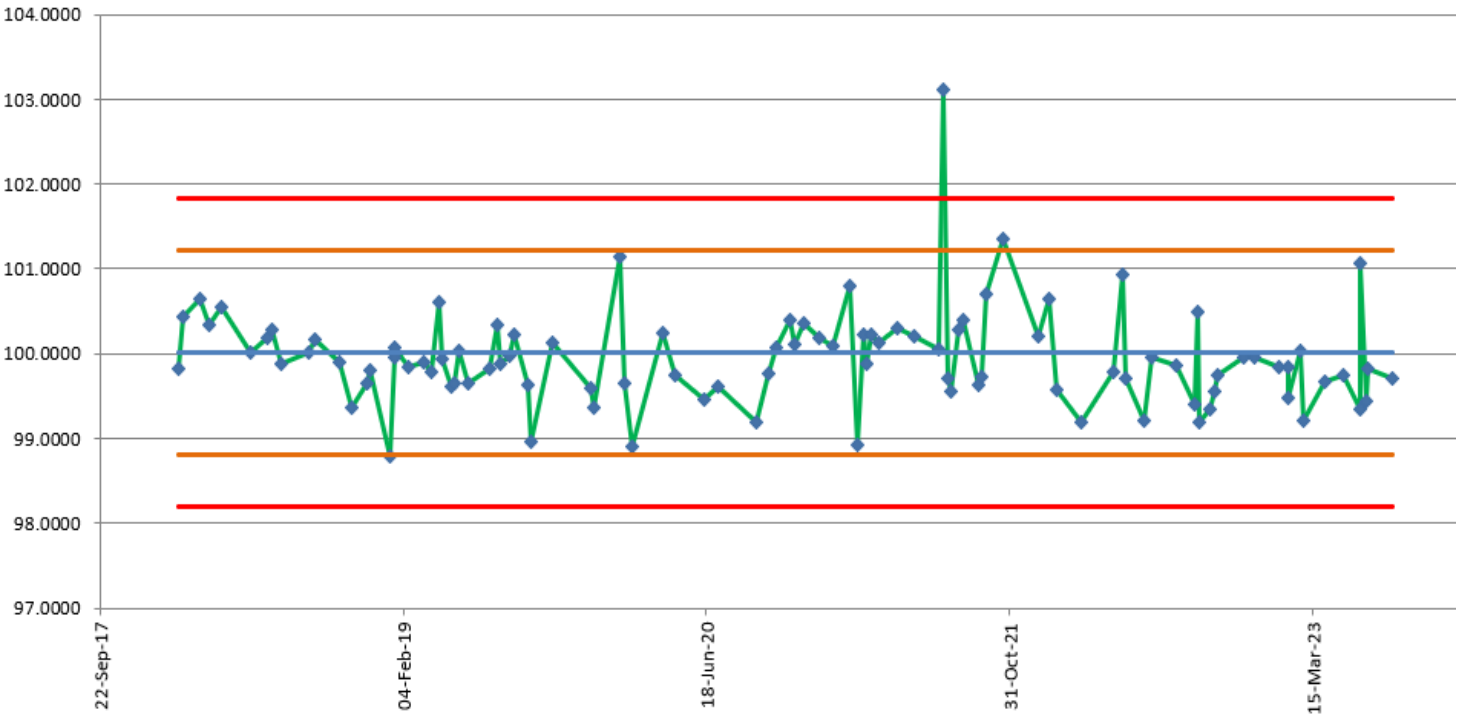
Suggested acceptance criteria:
Taking into account inter-laboratory standard deviation as well as the mean intra-laboratory standard deviation obtained the inter-laboratory study for the value assignment, the result of a measurement performed (following the above experimental conditions) is considered acceptable if the mean of 3 replicate determinations falls within the following limits:

Loss on drying (2.2.32.):	167.2 mg/g to 172.0 mg/g
Semi-micro determination of water (2.5.12.):	165.4 mg/g to 177.8 mg/g
Micro determination of water (2.5.32):	167.3 mg/g to 173.7 mg/g

It is understood that a laboratory may apply a different approach to set acceptance criteria.

CRS for equipment qualification

KF metrological equipment control chart



Check of systematic bias:

- Mean of 100 measurements: 171.5136 mg/g
- Assigned value: 171.6 mg/g; U= 1mg/g

Measurement uncertainty ($U_{exp.}$, k=2): ± 2.2 mg/g

u= √ (u² trueness + u² precision), where:

u trueness= $\sqrt{bias^2 + (\frac{sd\ bias}{\sqrt{n}})^2 + u^2\ certif}$

u precision= sd deviation of all values, i.e. sd of values from control chart

Expanded U = 2u

Secondary standards

Secondary standards

EU guideline for GMP * Part 1 – 6.20

6.20 …Whenever compendial reference standards from an officially recognised 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

Secondary standards

Establishment and use:

→Not intended use, but possible

→Under responsibility of the user

→Possible for the same property

→Necessity to ensure metrological traceability

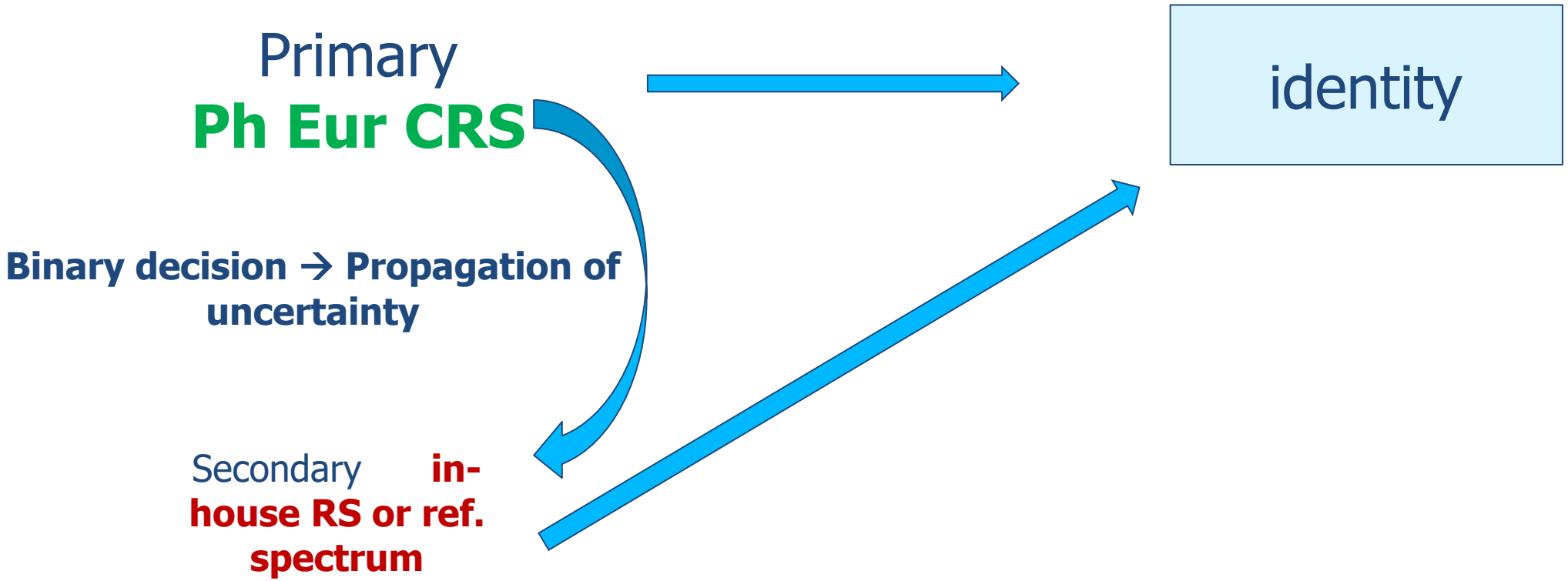
→Feasible only for qualitative properties

Secondary standards

Example: ID by IR

→Intended use of primary: identification

→Intended use of secondary: identification (assay not possible)

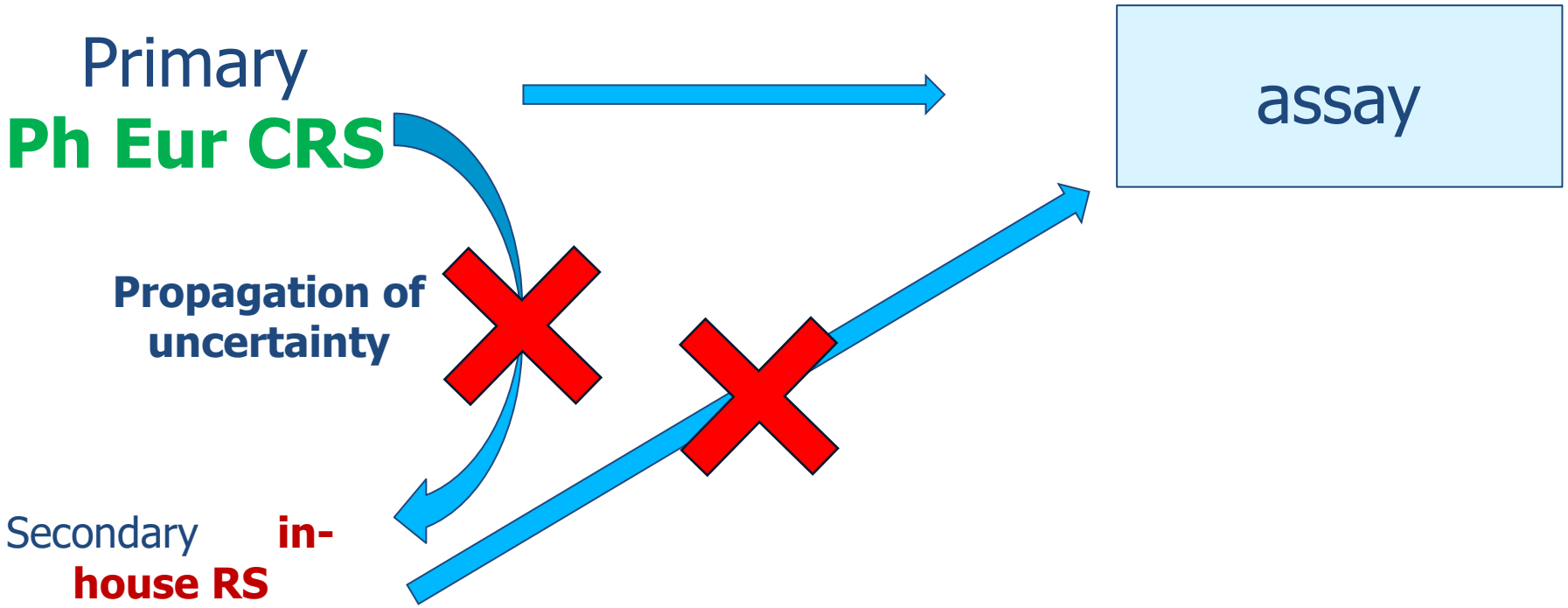


Secondary standards

Example: assay RS in LC assay

→Intended use of primary: assay

→Intended use of secondary: assay



Secondary standards

https://www.edqm.eu/en/-/joint-edqm-usp-webinar-on-secondary-standards-considerations-in-traceability-to-pharmacopeial-standards-

Conclusions

→Establishment adapted to intended use according to key quality attributes

→Suitability for off-label use to be demonstrated by user

→Reference standards described in the Ph. Eur. General methods are a highly relevant tool to ensure reliability of measurement results.

→Reference standards for equipment qualification are specifically characterised specimens that may be employed for several purposes.

→Secondary standards: possible, but…

Thank you for your attention

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