European Pharmacopoeia Reference Standards

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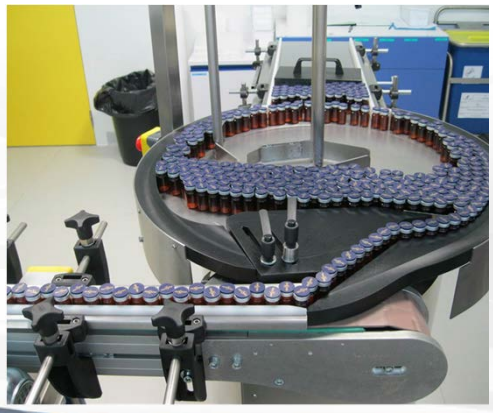

TOPICS

- Ph.Eur. Reference Standards - References and Definitions
- Establishment of quantitative standards
- Establishment of qualitative standards
- Labelling and use of Ph.Eur. Reference Standards
- Secondary Standards

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TERMS AND DEFINITIONS

ISO GUIDE 30

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

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

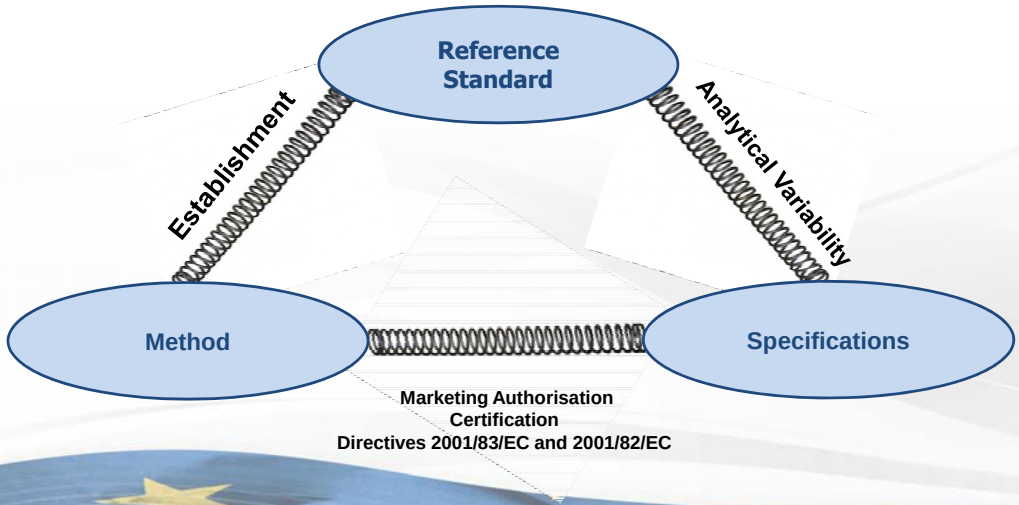
What is a Ph.Eur. Reference Standard?

- Reference standard" (RS) is a **general term** covering reference substances, preparations and spectra.
- **European Pharmacopoeia reference standard**
  A reference standard established under the aegis of and adopted by the European Pharmacopoeia Commission.
- **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.

Ph.Eur. Chapter 5.12.

EUROPEAN PHARMACOPOEIA

COMPENDIAL STANDARD = MONOGRAPH + REFERENCE STANDARD



TERMS AND DEFINITIONS

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.

ISO Guide 30 (2015) / Ph. Eur. Chapter 5.12.

Secondary measurement standard

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

ISO GUIDE 30 (2015) / Ph. Eur. Chapter 5.12.

Ph.Eur. Chapter 5.12. – Reference Standards (07/2018)

- **Terminology**
- **Use of Ph.Eur. Reference Standards**
- **Establishment of Reference Standards**
  - Primary Standards
  - Ph.Eur CRS
  - Ph.Eur HRS
  - Ph.Eur. BRP and Chemical RS for Biologicals
- **Manufacturing, Labelling, Storage and Distribution of Ph.Eur Reference Standards**
- **Re-Test Programme of Ph.Eur. Standards**

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.

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – quality, safety and efficacy

Brussels, 28 March 2014

EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4
EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

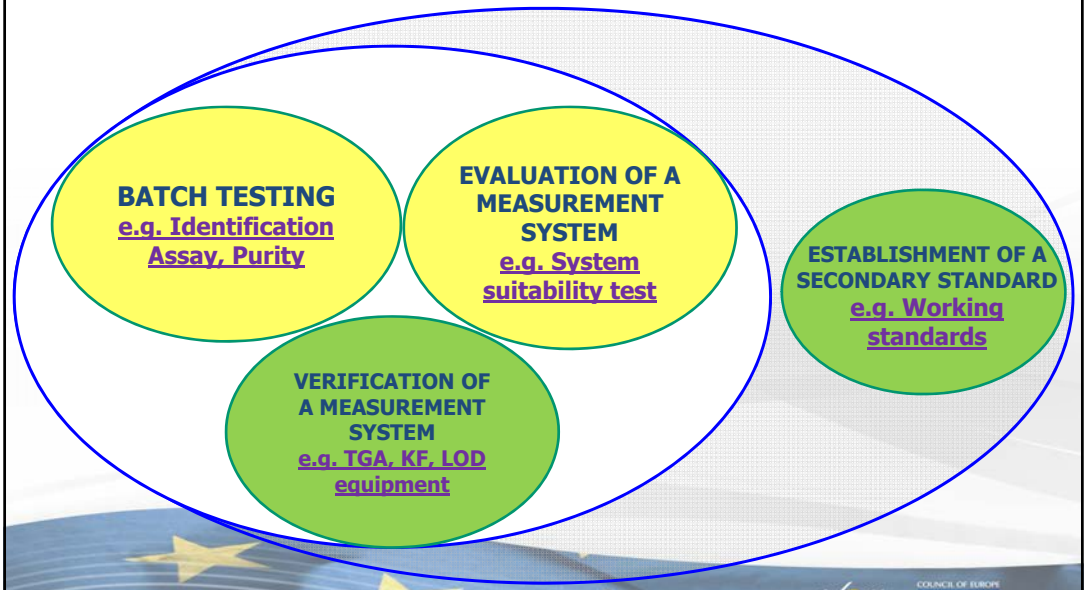
Part 1
Chapter 6: Quality Control

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.

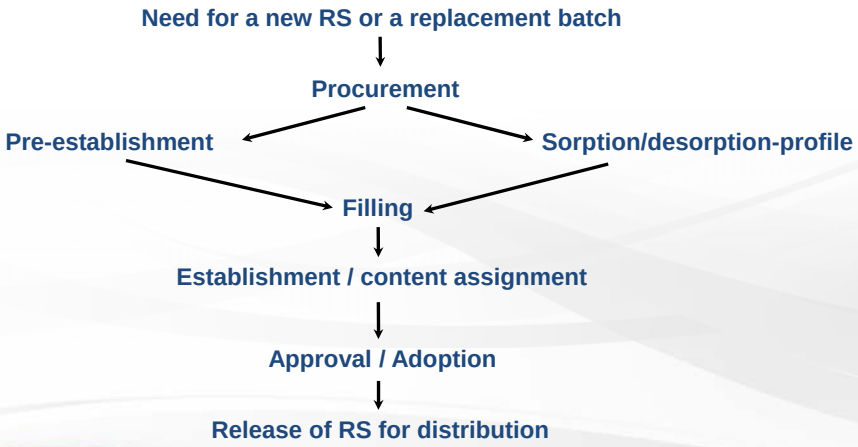
Whenever compendial reference standards from an official source exist, these should preferably be used as primary reference standards unless fully justified (the use of secondary standards is permitted once their traceability to primary standards has been demonstrated and is documented).

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

Use of Ph.Eur. Reference Standard



Establishment of quantitative RS



REFERENCE STANDARDS USED AS EXTERNAL STANDARDS IN THE ASSAY

Establishment / Content assignment

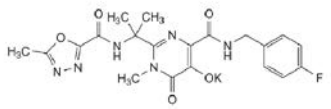
- Structure elucidation
- Compliance with the relevant requirements of the monograph
- Verification of batch homogeneity
- Inter-laboratory study to assign a content (if required)
  - water determination / loss on drying
  - related substances (LC, GC, CE)
  - other minor components e.g. inorganic impurities, residual solvents etc.
- Content assigned by “mass balance”
- Assigned value checked by orthogonal techniques (e.g. qNMR where applicable).

Example: Raltegravir Potassium CRS 1

04/2018:2887

RALTEGRAVIR POTASSIUM

Raltegravirum kalicum



$C_{20}H_{20}FKN_6O_5$ [871038-72-1] M_r 482.5

DEFINITION

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

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 $C_{20}H_{20}FKN_6O_5$ taking into account the assigned content of *raltegravir potassium CRS*.

Example: Raltegravir Potassium CRS 1

Test	Result	RSD	n
Appearance	Almost white powder	n/a	1
Mass spectrometry (in-house method) 2.2.43.	m/z found in accordance with sum formula (attachment 2)	n/a	1
Nuclear magnetic resonance spectrometry (in-house method) 2.2.33.	NMR spectra in accordance with structure (attachment 3)	n/a	1
Identification reactions of ions and functional groups	Positive reaction b) of potassium	n/a	1
Infrared absorption spectrophotometry 2.2.24.	KBr disc and ATR spectra recorded before and after re-crystallisation (attachments 4 to 7)	n/a	1
Related substances by liquid chromatography 2.2.29. / 2.2.46.	See inter-laboratory study (Table 3)	-	-
	Attachments 8 to 13	-	-
Semi-micro determination of water 2.5.12.	See inter-laboratory study (Table 3)	-	-
Micro determination of water[2] 2.5.32.	0.16 %	sd: 0.02	8
	Conditions: Direct introduction of about 50 mg	-	-
Residual solvents by headspace gas chromatography 2.2.28. / 2.4.24.	Acetonitrile and ethanol: see inter-laboratory study (Table 3) Sum of other residual solvents: below 0.10 % (Traces of toluene detected)	-	-

Characterisation EDQM Lab

Test	Result	RSD	n
Differential scanning calorimetry (in-house method)	Molar purity: 98.9 mol%	n/a	1
Quantitative nuclear magnetic resonance spectrometry (in-house method) 2.2.33.	99.4% Internal standard: maleic acid	0.3%	3
Elemental analysis	C: theory 49.79% found 49.8%	0.3%	3
	H: theory 4.18% found 4.2%	0.1%	3
	N: theory 17.42% Found 17.4%	0.1%	3

Example: Raltegravir Potassium CRS 1

Inter-Laboratory study (example LC - suitability):

Liquid chromatography (2.2.29.)

System suitability	Lab 1	Lab 2	Lab 3	Lab 4	Lab 5	Acceptance criterion
Resolution imp. E / raltegravir [ref. sol. (c), n = 1]	3.1	3.6	3.9	3.9	3.2	≥ 1.5
Symmetry factor raltegravir [ref. sol. (b), n = 1]	1.3	1.1	1.1	1.1	1.2	0.8 to 1.5
Signal-to-noise ratio raltegravir [ref. sol. (b), n = 1]	45	151	38	68	136	≥ 35
RSD peak area raltegravir [ref. sol. (b), n = 3]	1.9 % 1.3 %	0.7 % 3.4 %	3.4 % 2.9 %	1.5 % 0.9 %	2.9 % 1.4 %	≤ 5.0 %
All system suitability requirements fulfilled?	yes	yes	yes	yes	yes	

Example: Raltegravir Potassium CRS 1

Inter-Laboratory study (example LC - results):

Impurity	Lab 1	Lab 2	Lab 3	Lab 4	Lab 5	Mean
Imp. C (RR[$] about 0.7)	0.159 % (RR 0.77)	0.143 % (RR 0.76)	0.143 % (RR 0.76)	0.184 % (RR 0.76)	0.144 % (RR 0.77)	
Imp. E (RR about 0.95)	0.046 % (RR 0.95)	0.042 % (RR 0.95)	0.044 % (RR 0.95)	0.048 % (RR 0.95)	0.043 % (RR 0.95)	
Imp. F (RR about 1.15)	0.040 % (RR 1.18)	0.036 % (RR 1.18)	0.039 % (RR 1.19)	< rep. threshold	0.038 % (RR 1.17)	
Imp. G (RR about 1.1)	0.059 % (RR 1.12)	0.055 % (RR 1.12)	0.053 % (RR 1.12)	< rep. threshold	0.054 % (RR 1.12)	
Unspec. imp. 1 (RR about 1.9)	< rep. threshold	< rep. threshold	< rep. threshold	< rep. threshold	0.096 % (RR 1.86)	
Sum of impurities	0.303 % n = 2	0.276 % n = 2	0.279 % n = 2	0.232 % n = 2	0.375 % n = 2	**0.29 % n = 5 sd: 0.05**

[$] Relative retention.

Example: Raltegravir Potassium CRS 1

Content assignment:

(100% - water% - residual solvents%) x [(100% - sum of impurities by LC%) / 100%] =

99.1% of $C_{20}H_{20}FKN_6O_5$

The estimated uncertainty of this value is 0.10%

Example: Raltegravir Potassium CRS 1

Estimated uncertainty:

$$u_{IS} = \sqrt{\frac{\sigma_w^2 + \sigma_{LC}^2}{n}}$$

u_{IS} = standard uncertainty of inter-laboratory study
σ_w = standard deviation water
σ_{LC} = standard deviation LC
n = number of participants

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

$U_{exp.}$ = expanded uncertainty
u_{IS} = standard uncertainty of inter-laboratory study
u_{hom} = standard uncertainty homogeneity
k = coverage factor

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

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For any questions: www.edqm.eu (HelpDesk)

INFORMATION LEAFLET Ph. Eur. Reference Standard

Raltegravir potassium CRS batch 1

1. **Identification**

Catalogue code: Y0001943 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**

ASSIGNED CONTENT

Powder-filled CRS

Content (m/m) assigned on an " as is " basis.

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

PH.EUR. REFERENCE STANDARDS

→not necessarily suitable for other purposes.

If a reference standard 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.

Any value assigned to a reference standard is valid for the intended use and not necessarily for other uses.
[Ph.Eur. Chapter 5.12.]

Ph.Eur. Chapter 5.12. Reference Standards

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.

Risks related to off-label use: Artemisinin RS established for LC assay

LC-UV assay method: RP C18 column – Isocratic elution
Detection wavelength: 210 nm

Limits: 97.0 to 102.0%

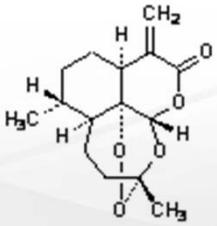
Content of the reference standard for assay:
mass balance: 99.9%
by qNMR: 99.9%

CAN THE STANDARD BE USED IN A DIRECT UV ASSAY METHOD AT 210 nm??

Risks related to off-label use :
LC vs direct UV assay of Artemisinin

Artemisinin

Impurity A
(Artemisitene)



At 210 nm impurity A needs a correction factor of 0.027 corresponding to a response factor of **37!**

Risks related to off-label use :
LC vs direct UV assay of Artemisinin

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

REFERENCE STANDARDS USED AS EXTERNAL STANDARDS IN THE RELATED SUBSTANCES TEST (IMPURITIES)

ESTABLISHMENT OF IMPURITY RS

A candidate impurity RS used as external standard is characterised for:

- identity (structure elucidation)
- identity of / screening for counter-ion
- purity (method of intended use)
- loss on drying / TGA or water (+ residual solvents)
- homogeneity
- confirmation of assigned content / purity by orthogonal methods.

Note: A content is assigned only if below 95.0%.

ESTABLISHMENT OF IMPURITY RS COUNTER-ION

Example: *Phenobarbital impurity A*

Analytical results:

- Loss on drying: below **0.1%**
- LC-purity: **99.7%**

But:

- Content by qNMR: **79%**
- Elemental analysis: does not match the theoretical composition
- **Identification of nitrate as the counter ion**
- Quantification of nitrate by ion-exchange chromatography: 20.6%

Content assignment: 79.1%

ESTABLISHMENT OF IMPURITY RS

Stoichiometric Conversion Factor

Applied for new impurity RS to be used as external standards provided the RS is supplied in a different salt form than the substance to be examined.

If required, a stoichiometric conversion factor will be provided in the leaflet accompanying the RS.

The stoichiometric conversion factor will in any case be given separate from the assigned content.

ESTABLISHMENT OF IMPURITY RS

Stoichiometric Conversion Factor - Example

- Impurity A CRS is used in the monographs of the base and the sulfate salt of the same API.
- Impurity A CRS 1 is supplied as sulfate salt.
- The sulfate salt of impurity A has a molecular mass (M_r) of 400.0, impurity A as a base has a M_r of 302.0.
- The calculated stoichiometric conversion factor for use in the API base monograph is: 400/302 = 1.324

ESTABLISHMENT OF IMPURITY RS

Stoichiometric Conversion Factor - Example

Information provided with the CRS:

" XXXX impurity A CRS 1 is provided as a sulfate salt.

For the calculation of the amount of impurity A in monograph xxxx (base), multiply the peak area of impurity A obtained with reference solution (b) by a stoichiometric conversion factor of M_r 400.0 / M_r 302.0 = 1.3.

For the calculation of the amount of impurity A in monograph xxxx (sulfate), no stoichiometric conversion is required.

Note: Molecular masses used for the calculation of the stoichiometric correction factor in this leaflet:
xxxx impurity A sulfate: ($C_xH_yN_z$ * H_2SO_4) 400.0 g/mol
xxxx impurity A base: ($C_xH_yN_z$) 302.0 g/mol"

REFERENCE STANDARDS USED AS REFERENCE MATERIAL

NEW: Ph.Eur. ELEMENTAL IMPURITY CRS

Four new elemental impurity CRS are available in the Ph.Eur. catalogue:

- Lead solution CRS (1.00 mg/g)
- Cadmium solution CRS (1.00 mg/g)
- Mercury solution CRS (1.00 mg/g)
- Arsenic solution CRS (1.00 mg/g)

NEW:
Ph.Eur. ELEMENTAL IMPURITY CRS

These elements occurring in nature are amongst the greatest potential sources of elemental contamination in medicinal products and substances for pharmaceutical use; the new reference standards are **traceable to the SI** (International System of units of measurements) and enable metrologically sound determination of lead, cadmium, mercury and arsenic as elemental impurities in medicinal products and substances for pharmaceutical use in relation with Ph.Eur. Chapter 2.4.20. describing the determination of elemental impurities.

New: Sodium aminosalicylate dihydrate for equipment qualification CRS

Sodium aminosalicylate dihydrate for equipment qualification CRS 1 replaces the former ***Amoxicillin trihydrate for performance verification CRS***, which has been discontinued since 1 April 2018 in the Ph.Eur.

The new reference standard (RS) comes with enhanced features compared to the former beta-lactam based RS.

In addition to simpler and faster sample preparation, the *new CRS* allows for a broader spectrum of applications as, unlike the previous RS, it can be used for all applications described in the Ph. Eur. chapter on micro determination of water (2.5.32) and not only the oven technique.

Sodium aminosalicylate dihydrate for equipment qualification CRS

2.2.32. LOSS ON DRYING

Method. Place the prescribed quantity of the substance to be examined in a weighing bottle previously dried under the conditions prescribed for the substance to be examined. Dry the substance to constant mass or for the prescribed time by one of the following procedures. Where the drying temperature is indicated by a single value rather than a range, drying is carried out at the prescribed temperature ± 2 °C.

...

d) "in an oven within a specified temperature range": the drying is carried out in an oven within the temperature range prescribed in the monograph; 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**); **...**

Sodium aminosalicylate dihydrate for equipment qualification CRS

RS leaflet – 2.2 analytical information:

... **2.2.32. – Loss on drying**

Certified loss on drying value: 169.6 mg/g

Uncertainty: 0.4 mg/g

Test procedure:
Determine the loss on drying in triplicate using 1000 mg of substance per determination. Drying conditions: 105 °C until constant mass (Ph. Eur. method 2.2.32. d)).

Container dimensions (recommended): diameter about 50 mm; height about 30 mm. ...

Sodium aminosalicylate dihydrate for equipment qualification CRS

Determination of the suggested acceptance criteria (1):

According to ISO Guide 33 two factors contribute to the difference between the certified value and the measurement result:

- the uncertainty of the certified value.
- the uncertainty of the results of the measurement process being assessed expressed by its standard deviation (σ_D).

Sodium aminosalicylate dihydrate for equipment qualification CRS

Determination of the suggested acceptance criteria (2):

The standard deviation of a measurement process (σ_D), which is caused by an unavoidable random error inherent in every measurement process is composed of:

- within-laboratory variability (short term fluctuation), expressed as repeatability standard deviation (s_w)
- between laboratory fluctuation, expressed as intermediate precision or reproducibility standard deviation (σ_{Lm}),

Consequently, the uncertainty of a measurement process (σ_D^2) can be calculated as follows:

$$\sigma_D^2 = \sigma_{Lm}^2 + \frac{s_w^2}{n}$$

Sodium aminosalicylate dihydrate for equipment qualification CRS

RS leaflet – 2.4 instructions for use:

Taking into account the inter-laboratory standard deviation as well as the mean intra-laboratory standard deviation obtained in the inter-laboratory study for the value assignment, the result of a measurement (following the indicated experimental conditions) may be 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

…

REFERENCE STANDARDS FOR QUALITATIVE USE

RS FOR QUALITATIVE USE

Purpose

Identification of monograph substance (not further discussed).

Identification of impurities of the monograph substance, often in a test for related substances using a chromatographic method (LC, GC or TLC), e.g. because of specific limit for impurity, correction factor for impurity…

System suitability test of an analytical method, e.g.:

- selectivity: resolution, peak-to-valley ratio;
- sensitivity.

→ **Individual substance ("impurity") or mixture RS**

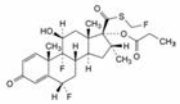
'SINGLE COMPOUNDS – IMPURITY'

Example

01/2016:1750

FLUTICASONE PROPIONATE

Fluticasoni propionas



$C_{25}H_{31}F_3O_5S$ M_r 500.6
[80474-14-2]

Related substances. Liquid chromatography (*2.2.29*).

Reference solution (a). Dissolve 1 mg of *fluticasone impurity D CRS* in the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 25.0 mL with the test solution.

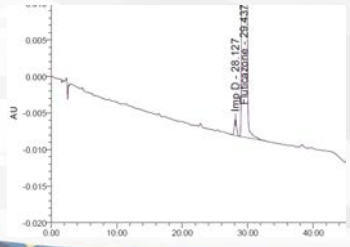
Identification of impurities: use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D; use the chromatogram supplied with *fluticasone*

System suitability: reference solution (a):

- *resolution*: minimum 1.5 between the peaks due to impurity D and fluticasone propionate.

Limits:

- *impurities D, G*: for each impurity, maximum 0.3 per cent;



'SINGLE COMPOUNDS – IMPURITY'

Establishment

Key quality attribute = identity.

Verification of the identity and intended use.

Overall, less elaborate than for impurities used quantitatively.

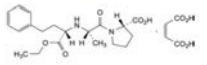
'MIXTURES'

Example

07/2010:1420

ENALAPRIL MALEATE

Enalaprili maleas



$C_{20}H_{28}N_2O_5$ [76095-16-4] M_r 492.5

Related substances. Liquid chromatography (*2.2.29*).

Reference solution (b). Dissolve 3 mg of *enalapril for system suitability CRS* (containing impurity A) in the dissolution mixture and dilute to 10.0 mL with the dissolution mixture.

Reference solution (c). Dissolve the contents of a vial of *enalapril impurity mixture CRS* (impurities B, C, D, E and H) in 1.0 mL of the dissolution mixture.

Identification of impurities:

- use the chromatogram supplied with *enalapril impurity mixture CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities B, C, D, E and H;
- use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

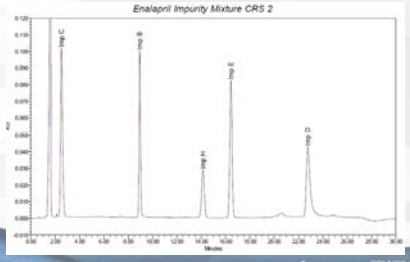
System suitability: reference solution (b):

- *peak-to-valley ratio*: minimum 10, 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 enalapril.

Limits:

- *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);
- *impurities B, C, D, E, H*: for each impurity, not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);

Enalapril Impurity Mixture CRS 2



'MIXTURES'

Composition (see monograph): several impurities with/without main compound

Name: for system suitability CRS, for peak identification CRS, impurity mixture CRS, ...

Establishment

Identity of impurities:	normally confirmed by spiking with individual impurity samples.
Fitness for purpose:	using method of intended use
	impurities present in sufficient amount for peak identification
	system suitability assessment.
Homogeneity:	for compounded mixtures.

LABELLING AND USE

Labelling

Includes:

- name of the reference standard;
- name of the supplier;
- batch number;
- any other information necessary to the proper use of the reference standard.

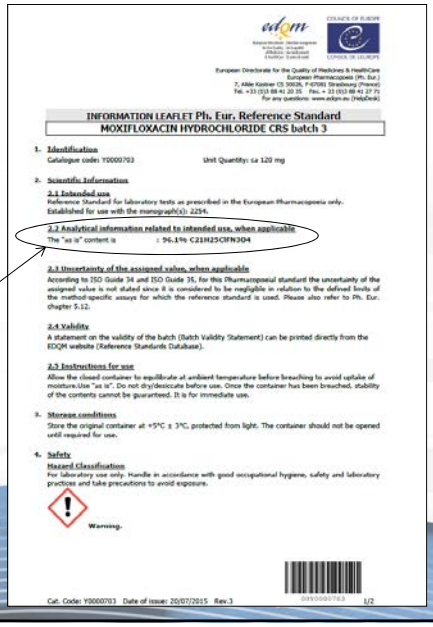
Labelling

If used as an assay standard the following information is also given:

- the assigned percentage content;
- or, the content in mg or mL of the chemical entity in the container;
- or, the assigned potency (for biological assays or microbiological assays) in units either per mg or per vial.

An explanatory leaflet is considered as part of the labelling.

Reference Standard Leaflets



INFORMATION LEAFLET Ph. Eur. Reference Standard
MOXIFLOXACIN HYDROCHLORIDE CRS batch 3

1. Identification
Catalogue code: Y0000703 Unit Quantity: ca 120 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): 2254.

2.2 Analytical information related to intended use, when applicable
The "as is" content is : 96.1% $C_{21}H_{25}ClFN_3O_4$

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

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

2.5 Instructions for use
Allow the closed container to equilibrate at ambient temperature before breaching to avoid uptake of moisture.Use "as is". Do not dry/desiccate before use. Once the container has been breached, stability of the contents cannot be guaranteed. It is for immediate use.

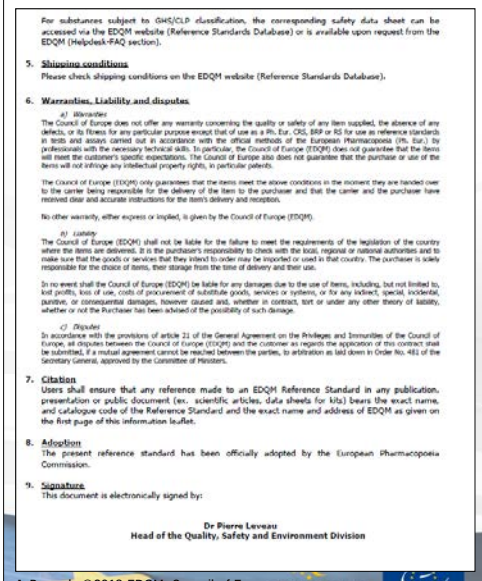
3. Storage conditions
Store the original container at +5°C ± 3°C, protected from light. The container should not be opened until required for use.

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

Warning.

Cat. Code: Y0000703 Date of issue: 20/07/2015 Rev.3 1/2

Assigned content value



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

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

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

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

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

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

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

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

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

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

9. Signature
This document is electronically signed by:

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

WHAT IS EXPECTED FROM THE USER

Immediately before using a Ph.Eur. Reference Standard, the following shall be checked:

- that the reference standard batch number be current at the time of use. A real-time batch validity statement is available online;
- that the container/closure system integrity be kept, i.e. absence of visible defects originating from shipping;
- that the reference standard after receipt has been stored at the conditions prescribed in the Ph.Eur. RS catalogue;

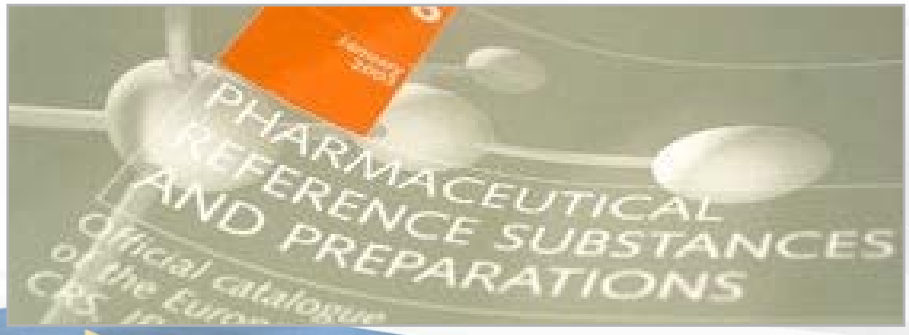
Moreover, allow the RS to equilibrate to lab temperature before opening.

REFERENCE STANDARDS CATALOGUE

Available online. Updated daily. English only.

http://crs.edqm.eu/db/4DCGI/web_catalog_CRS

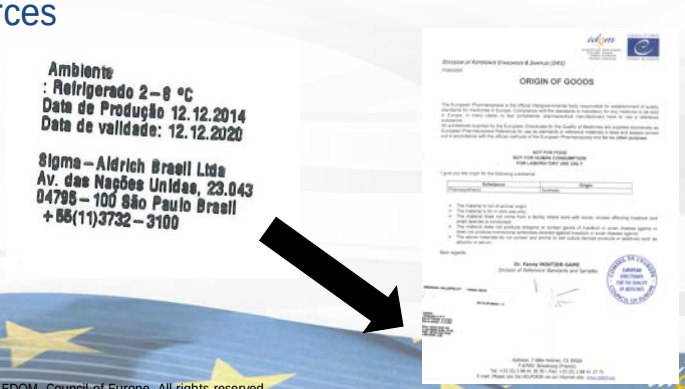
(for searching database: https://crs.edqm.eu)



ORDERING

- Ph.Eur. RS can be ordered directly from EDQM:
  https://www.edqm.eu/en/ph-eur-reference-standards-orders-catalogue

- Care should be taken when ordering from other sources



REFERENCE STANDARDS ONLINE INFORMATION

- Terms and conditions of supply
  http://www.edqm.eu/medias/fichiers/CRS.pdf
- List of new batches and new products
  http://crs.edqm.eu/db/4DCGI/web_catalog_news
- RS withdrawn from sale in the past 12 months
  http://crs.edqm.eu/db/4DCGI/web_catalog_olds

http://www.edqm.eu → Databases

Online Ph.Eur. Reference Standards Database

Search European Pharmacopoeia Reference Standards

THE DATABASE PROVIDES SPECIFIC INFORMATION INCLUDING

Availability
Origin
Storage and dispatching conditions
Presentation
Assigned Content
Batch Validity Statement
Complementary information (for ex. chromatogram)
Safety Data Sheet

Catalogue Code	Y0000703
Name	Moxifloxacin hydrochloride
Current batch number	3
Unit quantity	120 mg
Sale unit	1
Used in monograph(s)	2254
Assigned content	See leaflet
Additional information	
Leaflet	click to download the leaflet
SDS	Click to download SDS
CAS Registry Number	186826-86-8
Presentation	
Origin	click to download Origin Of Goods.pdf
Proposed Import HS code	293349
EDQM long term storage conditions	+5°C ± 3°C
Dispatching conditions	Ambient temp.
UN Code	3077
Shipping group	A1A
Price	79 EUR
Availability	Available
Sales restriction	No

Batches

batch 3 is valid at this date

Print BVS

Print the «Batch Validity Statement»

BATCH VALIDITY STATEMENT
EUROPEAN PHARMACOPOEIA REFERENCE STANDARDS (CRS) & (BRP)
This Batch Validity Statement has to be used in conjunction with Ph. Eur. general chapter 04/2015:51200 Reference Standards.

European Directorate for the Quality of Medicines & HealthCare (EDQM) – Council of Europe
Postal address: 7 Allée Kastner CS 30026 F - 67081 STRASBOURG (France)
Phone: +33 (0)3 88 41 30 30
Fax: +33 (0)3 88 41 27 71
Internet : http://www.edqm.eu

Batch 3 is official at the time of printing

Name	Moxifloxacin hydrochloride
Catalogue code	Y0000703
Batch number*	3
Assigned value	See leaflet
Validity	Batch 3 is valid at the printing date: 2017-5-19
Additional information	
Storage conditions	The standard is intended for immediate use. Recommended EDQM storage conditions for unopened containers : +5°C ± 3°C
Safety data	Safety Data Sheet is available from the detailed view or upon request.
Leaflet	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) click to download the leaflet

SECONDARY STANDARDS

WORKING STANDARDS

Ph.Eur. Chapter 5.12. Reference Standards

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

4-5. SECONDARY STANDARDS

A secondary standard should exhibit the **same property** or properties **as the primary standard**, relevant for the test(s) for which it is established. The extent of testing may not be as comprehensive as is required for the establishment of a primary standard. The secondary standard is established by comparison with the primary standard to which it is traceable. **An official primary standard is used wherever possible for establishment of secondary standards.**

EU GMP
Annex VI - 6.20

Whenever compendial reference standards from an official source exist, these should preferably be used as primary reference standards unless fully justified.

The use of secondary standards is permitted once their **traceability to primary standards** has been demonstrated and is documented.

Case 1: Secondary standard for assay

Primary standard Ibuprofen CRS
Intended use: for identification

Characterisation	NMR / MS / CHN IR / monograph testing
Traceability	Measurement → Identity

Primary standard established for quantification? NO

Case 1

Certificate of Analysis

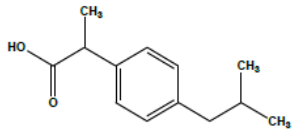
RTC

ISO GUIDE 34
ACLASS Cert# AR-1470

ISO/IEC 17025
ACLASS Cert# AT-1467

IBUPROFEN

CERTIFIED REFERENCE MATERIAL



CERTIFIED PURITY: 99.9%, U_{crm} = ±0.1% k = 2
(Mass Balance/as is basis)

NOMINAL PACKAGE SIZE: 1g

Case 1

1. Method: not the Ph.Eur. (UV assay)
2. No assigned content
3. No uncertainty

...no documented traceability to Ph.Eur.

Fluka Analytical

RTC

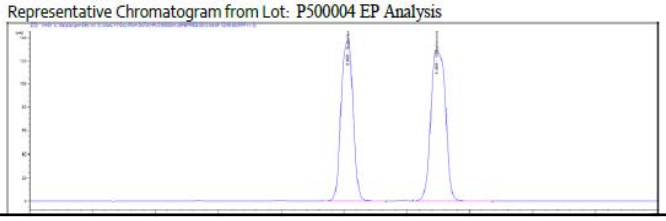
ASSAY vs. EP CRS (as is basis)

ASSAY VALUE	vs. EP BATCH
99.8%	5.0 Labeled Content = None Assigned Content = 99.8% *

METHOD: HPLC (ref.: Ibuprofen; USP34)
Column: Ascentis C18, 4.6 x 250mm, 5µm
Mobile Phase: Acetonitrile/Water/chloroacetic acid (600:400:4)
Column Temperature: 30°C
Flow Rate: 2 mL/min
Injection: 10µl
Detector Wavelength: 254 nm

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

Representative Chromatogram from Lot: P500004 EP Analysis



Properties

Related Categories	APIs & Metabolites, APIs (Active Pharmaceutical Ingredients) & Metabolites, Additional Standards, Analytical Standards, Analytical/Chromatography, Plus...
grade	**certified reference material**
	pharmaceutical secondary standard
form	**neat**
format	**neat**
pharmacopeia traceability	**traceable to BP 539**
	traceable to PhEur l0020000
	traceable to USP 1335508

Description

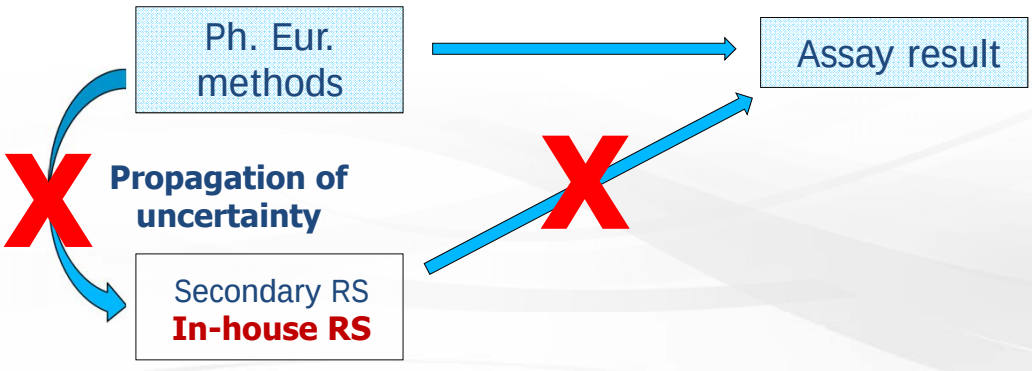
Analysis Note
These secondary standards offer multi-traceability to the USP, EP (PhEur) and BP primary standards, where they are available.

Biochem/physiol Actions
Cyclooxygenase (COX) inhibitor that has greater activity against COX-1 than against

Case 1

Is this statement of traceability correct?

Case 1 - Traceability chain

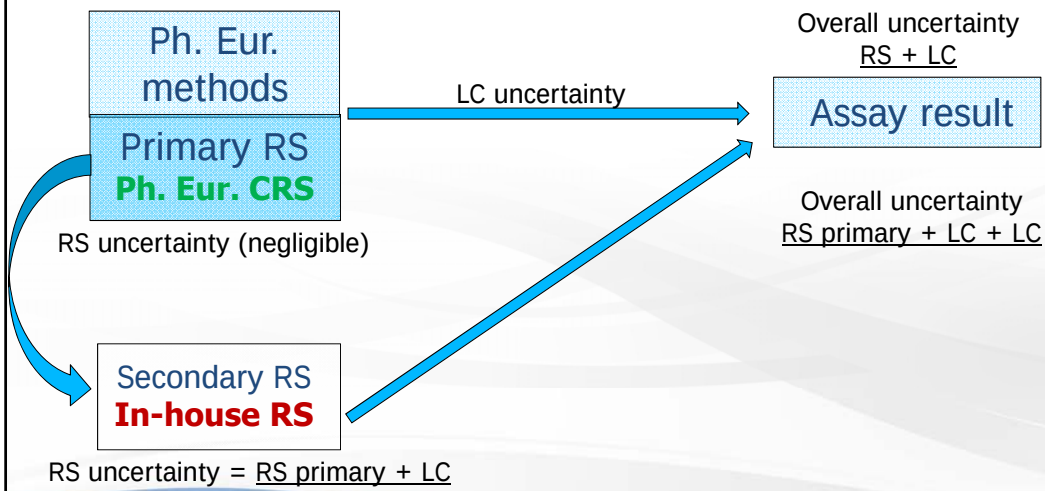


Case 2 Secondary standard for assay

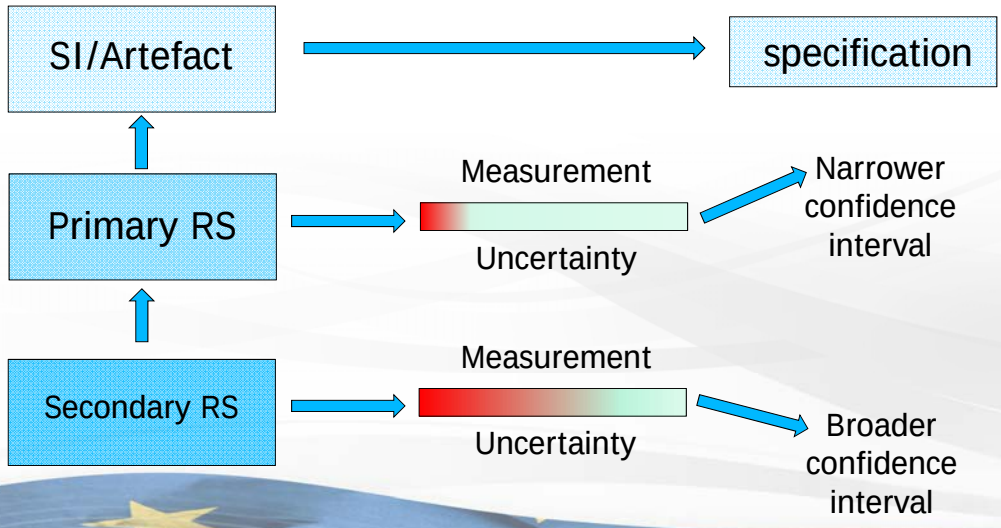
Primary standard Lamivudine CRS
Intended use: assay (monograph 2217)

Primary standard established for quantification? YES

Case 2 - Traceability chain



Case 2 - Traceability chain



Case 2: Traceability can be established but

RS characterised using the Ph. Eur. methods (i.e. related substances, water, residual solvents etc.), value assigned based on mass balance:

→ **propagation of uncertainty** must be assessed and incorporated in the overall uncertainty;

→ **fitness for purpose** (secondary standard) must be demonstrated by the user, which may be a challenge if you want to argue that with the secondary standard the same pass/fail decision criteria apply.

Thank you very much for your attention.