Secondary Standards – Considerations in Traceability to Pharmacopoeial Standards

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Outline

- ✓ Definitions
- ✓ Use of Pharmacopoeia Reference Standards
- ✓ Differences Pharmacopoeia RS to CRMs
- ✓ Secondary Standards and traceability
- ✓ Understanding uncertainty and risk
- ✓ Potential approach for secondary standard establishment
- ✓ Commercial secondary standards
- ✓ Conclusions

Definition Primary Standards

Reference Standard, Primary

A substance **that has been shown by an extensive set of analytical tests** to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognized source, (2) prepared by independent synthesis, (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

ICH Q7 and FDA GFI "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients"

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.

Definition Reference Standards in USP/Ph.Eur.

Ph.Eur. 5.12. Reference Standards

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

Definition Reference Standards in USP/Ph.Eur.

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USP General Notices 5.80. USP Reference Standards

- USP Reference Standards are authentic specimens that have been approved as suitable for use in USP or NF tests and assays (see USP Reference Standards ⟨11⟩).

USP General Chapter <11> USP REFERENCE STANDARDS

- When approved as suitable for use in USP or NF tests and assays, USP RS also assume official status and legal recognition in the United States and other jurisdictions that recognize the USP or NF (see GN, 2.30 Legal Recognition).
- USP RS, when they are physical materials, are Reference Materials as defined in the *International Vocabulary of Metrology—Basic and General Concepts and Associated Terms (VIM)*.

Use of Reference Standards in USP/Ph.Eur.

Ph.Eur. Chapter 5.12. – Reference Standards

- European Pharmacopoeia reference standards are shown to be suitable for their intended purpose; they are **not necessarily suitable for other purposes.**
- If a European Pharmacopoeia 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** and when applicable, to be described in the marketing authorisation application.
- Any **value assigned to a reference standard is valid for the intended use** and not necessarily for other uses.

Diapositive 5

C(1 Would like to replace with
"When approved as suitable for use in USP or NF tests and assays, USP RS also assume official status and legal recognition in the United States and other jurisdictions that recognize the USP or NF…"
Christian (Guest); 15/08/2023

Use of Reference Standards in USP/Ph.Eur.

USP General Notices 5.80. USP Reference Standards
Where USP or NF tests or assays call for the use of a USP Reference Standard, only those results obtained using the specified USP Reference Standard are conclusive.

USP General Chapter <11> USP REFERENCE STANDARDS
USP RS may also be used to support other measurements not necessarily prescribed in USP–NF. Assessment of the suitability for use in other applications is the responsibility of the user.

ICH Q7 and FDA GFI "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients", subclause 11.17
Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

Difference Pharmacopoeia Reference Standard - CRM

Certified Reference Material (ISO Guide 31:2015):
Reference material (RM) characterized by a metrologically valid procedure for one or more specified properties, accompanied by an RM certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability.

USP/Ph.Eur Reference Standards	Certified Reference Materials (CRMs)
✓ Suitability for method of intended use verified	○ Suitability for method of intended to be demonstrated by the user
✓ Uncertainty of assigned content compatible with testing procedure/limits	○ Compatibility of uncertainty with testing procedure/limits needs to be demonstrated
✓ Regulatory acceptance given	○ Regulatory acceptance required / suitability to be demonstrated

Pharmacop(o)eias– starting point for conclusive results

Pharmacopoeias establish public compendial standards

- Compendial standards developed in a transparent process
  - Types of standards
    - Documentary standards (DS, e.g. general chapters, monographs)
    - Physical reference standards (RS, CRS)
  - Pharmacopeia RS
    - Almost always primary RS
    - Established by a robust collaborative approach
    - Official status when connected to DS
      - As outlined in Ph.Eur. 5.12., USP GC <11> on slides above

Pharmacop(o)eias– starting point for conclusive results

- When assessing compliance with monographs: Only combination of DS/RS is conclusive/authoritative
  - Ph.Eur., General Text 5.12.
    - Where a European Pharmacopoeia reference standard is referred to in a monograph or general chapter, it represents the official standard that is alone authoritative in case of doubt or dispute.
  - USP General Notices 5.80.
    - Where USP or NF tests or assays call for the use of a USP Reference Standard, only those results obtained using the specified USP Reference Standard are conclusive.

Consequently, other combinations of DS/RS are NOT conclusive and may potentially increase RISK.

Secondary Standards – Definitions and Requirements

ICH Q7 and FDA GFI "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients":

- A substance of established quality and purity, **as shown by comparison to a primary reference standard**, used as a reference standard for routine laboratory analysis.

ICH Q7 and corresponding FDA GFI , 11.19:

- The suitability of each batch of secondary reference standard should be determined prior to first use by **comparing against a primary reference standard**. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

Secondary Standards – Definitions and Requirements

European Union, GMP Guideline, Part 1, Chapter 6, 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.

Ph.Eur. Chapter 5.12. – Secondary Reference 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 secondary standard is established by **comparison with the primary standard to which it is traceable**.

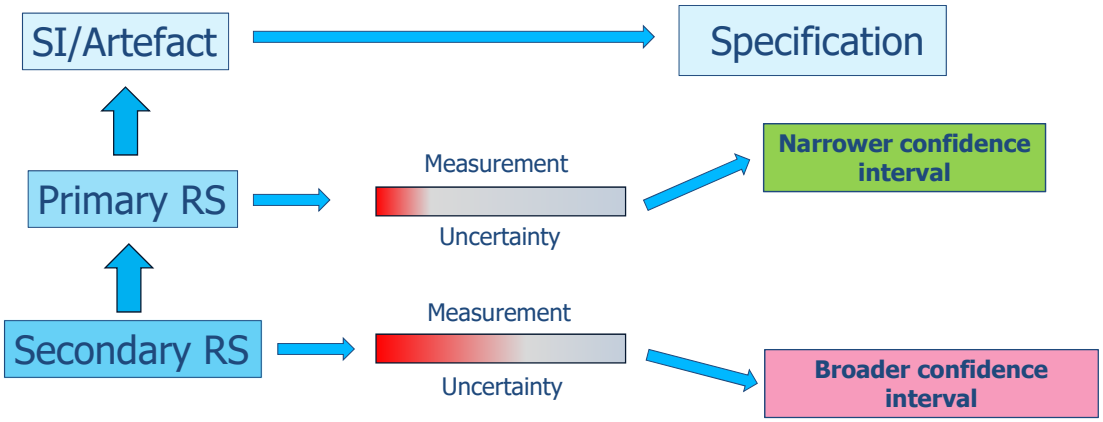
Secondary Standards – Requirements and Traceability

ISO/CEI Guide 99:2007 (VIM)

Metrological traceability (2.41)

Property of a **measurement result** whereby the result can be related to a reference through a documented unbroken chain of calibrations, **each contributing to the measurement uncertainty.**

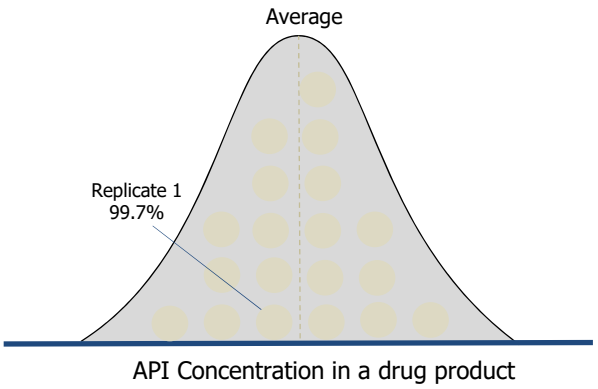
Secondary standards and traceability



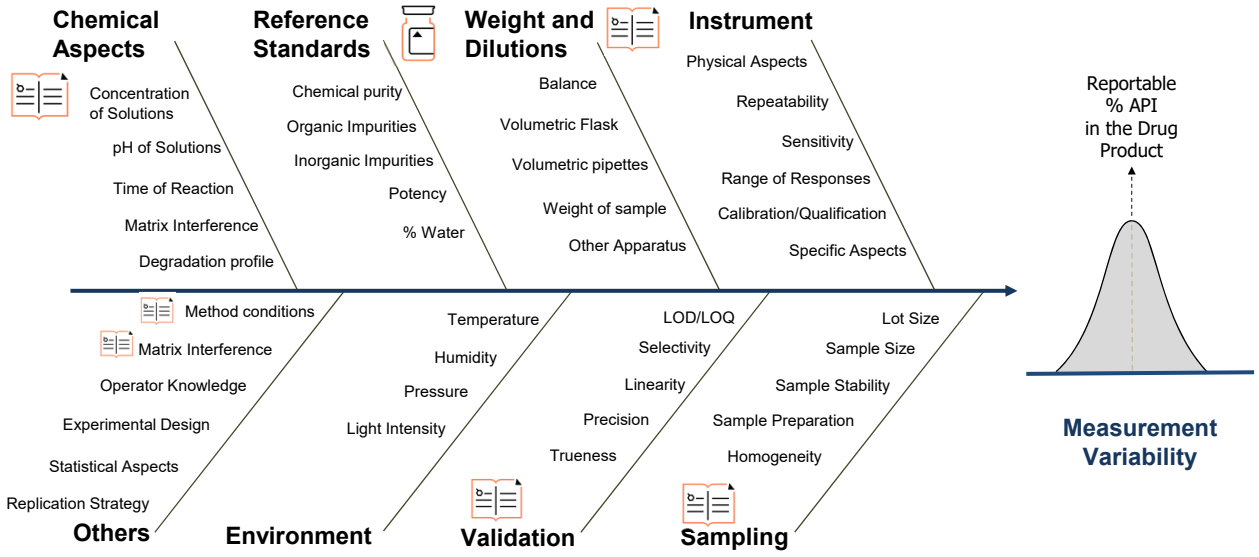
Understanding uncertainty and risk

- All measurements have many potential sources of variation
- Leading to measurement uncertainty, which can lead in turn to a confidence interval of the measurement result, the interval including the true value at a certain level of confidence (often 95%)

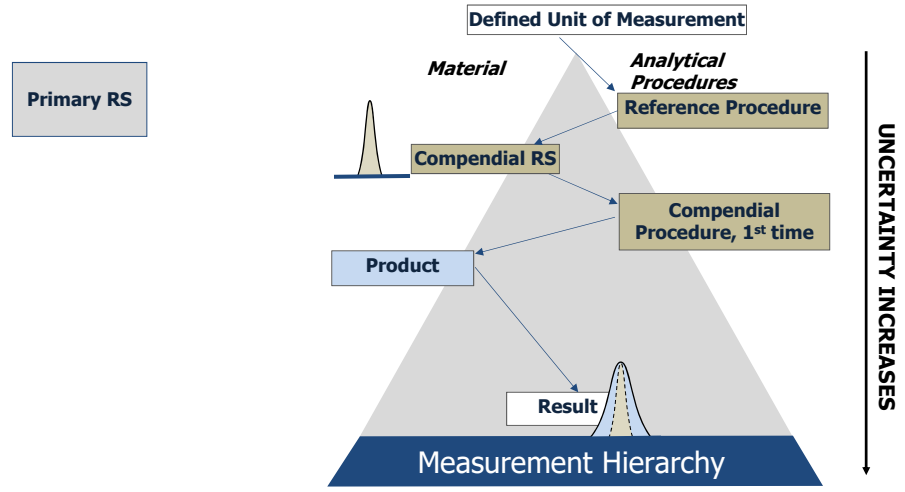
Measuring the API assay for batch release



Measured value and potential sources of variation

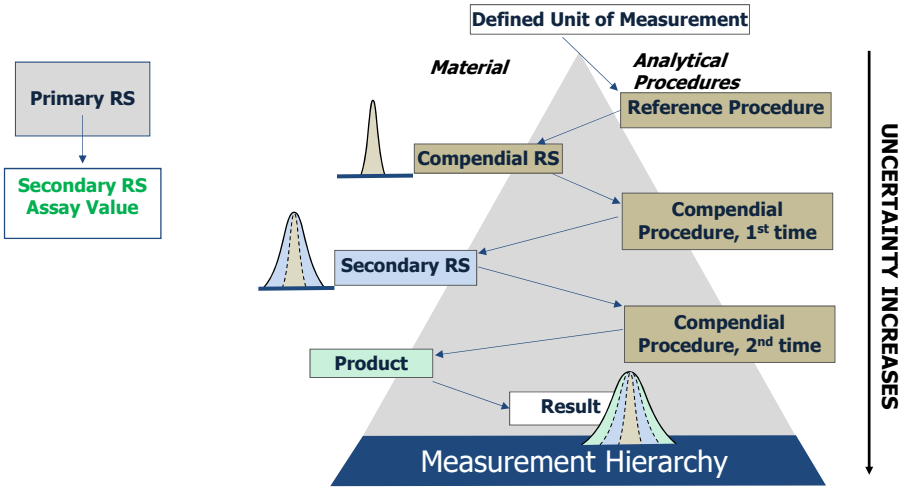


Understanding uncertainty and risk



Principle adopted from ISO 17511, 2003/2020.

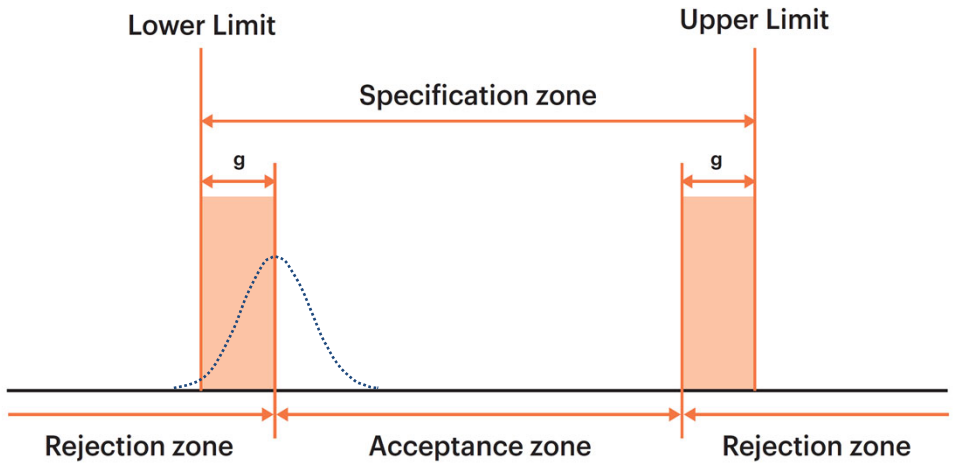
Understanding uncertainty and risk



Principle adopted from ISO 17511, 2003/2020.

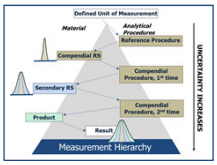
Understanding uncertainty and risk

Guard bands

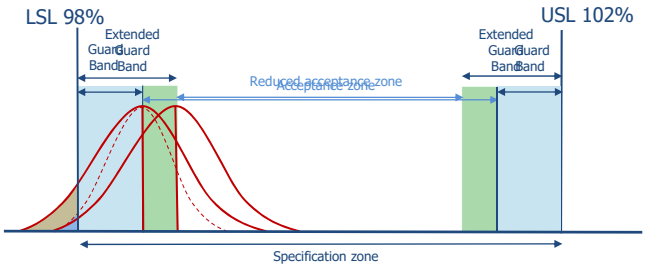


Understanding uncertainty and risk

Secondary standards – imprecision at work



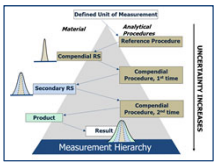
- Secondary standard: “A standard whose property value is assigned by comparison with a primary standard of the same property or quantity” (Ph.Eur., General Text 5.12.)
- Additional measurement step – additional uncertainty

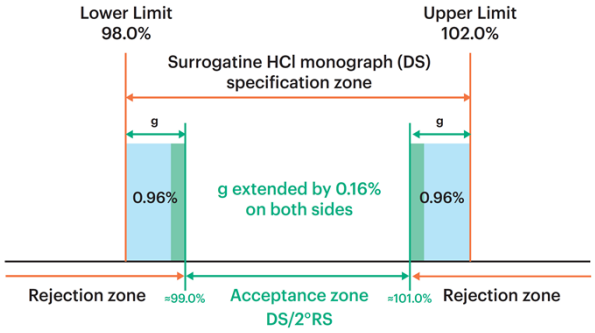


Uncertainty and risk: Surrogatine HCl

Using secondary RS

- Additional measurement step – additional uncertainty
- Means extension of guard band – narrowing down acceptance zone to avoid risk of unknown OOS
- In theory, the "full" uncertainty of 0.96% would apply as guard band
- Not really possible for users to estimate adequate narrowing of acceptance zone





C. Zeine et al., Pharm. Tech. 45 (2) 52–58 (2021). https://www.pharmtech.com/view/the-value-of-pharmacopeial-reference-standards

Potential approach for secondary standard establishment

- The identity of the secondary standard may be established against the pharmacopeial RS. Additional analytical techniques should be considered.
- It may be considered to determine the assigned property value and associated MU by mass balance.
- "Traceability" to primary standard may be demonstrated by showing equivalence of results obtained with both primary and secondary standard, by means of statistical tests.
- MU of the assigned property values shall be negligible with regards to the specification and/or release limits.
- Regular checks should be considered if relation pharmacopoeial to secondary RS still valid (incl. when lot changes of pharmacopoeial RS occur).

Commercial Secondary Standards – case study

Primary standard: Ph.Eur. Ibuprofen CRS

Intended use:

- **For identification by IR spectrophotometry**

Characterisation	NMR / MS / IR / monograph testing
Qualified property	Identity

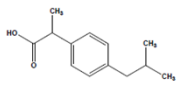
Primary standard established for quantification? **NO**

Commercial Secondary Standards – case study

Certificate of Analysis – Certified Reference Material

IBUPROFEN

Product no.:	PHR1004-1G
Lot no.:	LRAD4442
Description of CRM:	White Powder
Expiry date:	30 June 2027
Storage:	2-30°C



Analyte	Certified Purity ± associated uncertainty *U*, $U = k \cdot u$ (*k*=) (Mass Balance/ basis)
Ibuprofen	99.6 % Ucrm = ± 0.7 %, k = 2.0 (as is basis)

Metrological traceability:	Traceable to the SI and higher order standards from NIST through an unbroken chain of comparisons. Additional traceability to Primary Standards is established through comparative assay determinations. See "Details on metrological traceability" on page 2.
Measurement method:	Where applicable, the certified value is based on a purity determination by mass balance. See "Certification process details" on page 3.
Intended use:	Intended for R&D and Analytical Use only. Not for drug, household or other uses.
Minimum sample size:	40 mg
Instructions for handling and correct use:	Do not dry, use on the as is basis. The internal pressure of the container may be slightly different from the atmospheric pressure at the user's location. Open slowly and carefully to avoid dispersion of the material. Attachment of a 20 mm aluminum crimp seal recommended for unused portions.

Commercial Secondary Standards – case study

Metrological traceability statement page 2

Traceability Assay:
Comparative assay demonstrates direct traceability to Pharmacopeial Standards

ASSAY vs. USP REFERENCE STANDARD (1335508) (as is basis)

ASSAY VALUE	vs. USP LOT
100.5 %	R13060
	Labeled Content = 0.998 mg/mg

ASSAY vs. EP CRS (I0020000) (as is basis)

ASSAY VALUE	vs. EP BATCH
100.1 %	6.0
	Labeled Content = None
	Assigned Content = 100.6 % *

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

?

Conclusions

- Secondary standards / in-house standards may be used in routine test.
- Establishment of secondary RS for quantitative standards requires careful consideration.
- Traceabilility to the USP/Ph.Eur. primary standard must be demonstrated.
- Assigned property values of primary and secondary standards shall be the same.
- Propagation of uncertainty must be assessed and incorporated in the overall uncertainty.
- Suitability for intended use shall be demonstrated (compatibility with specification limits).
- Establishment strategy of the secondary standard should be carefully chosen.
- Special care should be taken when relying on commercial standards.

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Ph. Eur.

Andrea Lodi

EDQM Public Relations team

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Questions?