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Metrological Aspects of the State Pharmacopoeia of Ukraine Reference Standards Establishment

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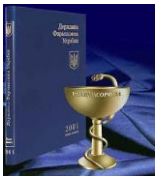

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Basis for the Pharmaceutical Reference Standards Establishment

Reference standards must be established taking into account that the risk of making a wrong decision about the quality of medicines should be acceptably low.

The uncertainty of RS assigned value (U_{RS}) is an integral characteristic of the quality of reference standards that allows evaluating the risk.

The requirement for U_{RS} depends on the target uncertainty of a measurement result (U_{Target}).

The requirement for U_{Target} is set considering the specifications for medicines.

Basis for the Pharmaceutical Reference Standards Establishment

Consequently,

If we know standardization rules for the whole chain – beginning with the specification and ending with U_{RS} – we can define what the fitness for use of RS is.

Most of the specifications for medicines are expressed as intervals.

As requirements for the uncertainty are associated with the specifications, further the term *uncertainty* refers to the *expanded uncertainty.*

Pharmacopoeial decision-making rule for specifications compliance

Requirements for the uncertainty of a measurement result (and for its sources of uncertainty) largely depend on the decision-making rule for compliance with specifications.

Although decision-making rules may vary, there is

the only specific approach used by *Ph. Int., USP, Ph.Eur.*:

- Specification limits for Assay include analytical variability;
- A decision about compliance with specifications should be made only on the basis of whether the measurement result lies within the specification range or not.

Note: It is reasonable to use this approach not only for Assay but also for other pharmaceutical tests.

Pharmacopoeial decision-making rule for specifications compliance

In terms of the uncertainty concept, a reliable conclusion about quality of medicines can be made if:

- ✓ U_{Target} established for measurement results, compared to specifications, is small enough to provide a reliable conclusion about quality of medicines;
- ✓ U_{Target} is generally accepted by all parties – industry, regulators, and consumers.

U_{Target} determines metrological requirements for all components of the analytical system:

- ✓ Analytical procedure (validation criteria);
- ✓ Laboratory equipment (criteria for equipment qualification);
- ✓ **Establishment of reference standards**;
- ✓ Others.

Recommendations for the target uncertainty of a measurement result (U_{Target})

TEST	RECOMMENDATIONS	STATUS
ASSAY (two-sided specification limits) for some **APIs**[1]:	$U_{Target} = B_{Upper} - 100\ \%$	**Ph. Eur.**
	$U_{Target} = 100\ \% - B_{Lower}$	**USP**[2]
for **Finished Drug Products (FDPs)** (for limits symmetrical around 100 %):	$U_{Target} = 0.32 \times (B_{Upper} - B_{Lower})/2$	**SPU**
	$U_{Target} = 0.33 \times (B_{Upper} - B_{Lower})/2$	**USP**[2]
ASSAY (one-sided specification limits) for **APIs** and **FDPs** (typically for Herbals):	$U_{Target} = 6.4\ \%$	**SPU**
UNIFORMITY of DOSAGE UNITS, DISSOLUTION:	$U_{Target} = 3\ \%$	**SPU**
RELATED SUBSTANCES **Limit tests**: **Quantitative tests**:	 $U_{Target} = 16\ \%$ $U_{Target} = 5\ \%$	 **SPU** **SPU**

[1] – in the case when an assigned limit is caused only by analytical variability
[2] – <1200> Requirements for Compendial Validation / Pharmacopeial Forum 39(6), http://www.usp.org
B_{Lower} – the lower content limit, B_{Upper} – the upper content limit, **SPU** – the State Pharmacopoeia of Ukraine

Interrelation between U_{RS} and U_{Target}

ISO guides do not indicate that U_{RS} must be insignificant in relation to U_{target}.

If U_{RS} is significant compared to U_{Target}, in the case when a lot of RS is replaced by a new one, the risk of making an opposite conclusion about quality of the same medicine becomes unacceptably high.

Conclusion:

In terms of the Pharmacopoeial decision-making rule,

U_{RS} must be insignificant compared to U_{Target}.

Interrelation between U_{RS} and U_{Target}

An SPU approach – the Principle of Insignificance:

At the level of reliability of 95 %:

$$U_1 \leq 0.32 \times U_{2,}$$

U_1 – a source of uncertainty,

U_2 – a combined expanded uncertainty

For example,

$$U_{Target} \leq 0.32 \times (\pm B),$$

B – content limits for finished drug products.

$$U_{RS} \leq 0.32 \times U_{target.}$$

Note: The principle of insignificance is used in General Texts of SPU:

- *5.3.N.1. Statistical analysis of chemical experiment results;*
- *5.3.N.2. Validation of analytical procedures and tests;*
- *5.12. Reference Standards[N].*

Some consequences of using the SPU approach for Assay

THE MEASUREMENT HIERARCHY	
'THE CONFIRMING APPROACH', APIs	**'THE PROVING APPROACH', FDPs**
Specification limits *(± B)*	**Specification limits *(± B)***
Target measurement uncertainty (U_{Target})	**Target measurement uncertainty (U_{Target})**
$U_{Target} = B$	$U_{Target} = 0.32 \times B$
Reference standards uncertainty (U_{RS})	**Reference standards uncertainty (U_{RS})**
$U_{RS} \leq 0.32 \times B$	$U_{RS} \leq 0.1 \times B$

APIs: If impurities are properly controlled, an Assay Result **must lie within** the specification.

⇩

An Assay Result = The Confirmation of Identity

FDPs: Due to the presence of excipients, an Assay Result **can lie** either **within or beyond** the specification.

⇨ **The Role of Assay** is to determine, with high reliability, whether the true value lies within the specification or not.

If $U_{Target} > 0.32 \times (\pm B) \Rightarrow$ the Risk of making an Incorrect Decision on Compliance is High

The SPU approach to the U_{RS} evaluation

1. The well-known ***mass balance*** approach is used:

$$X_{Assigned_1} = 100\ \% - \Sigma Imp;$$

$$U_{RS_1} = U\,(X_{Assigned_1}).$$

Usually, $X_{Assigned_1}$ is given in a certificate.

But: this approach assumes that we are sure of the nature of impurities.

The lower an impurity content is, the lower U_{RS_1} is.

For synthetic APIs: $U_{RS_1} \approx 0.1\%$ is feasible.

2. If possible, the alternative method (*orthogonal*) for the verification of $X_{Assigned_1}$ is used to confirm the reliability of our knowledge of impurities.

$$U_{RS_2} = U\,(X_{Assigned_2})$$

The most used alternative methods: *Titrimetry, qNMR,* and *DSC*.

For alternative methods: $U_{RS_2} \approx 0.5\%$ is feasible.

The SPU approach to the U_{RS} evaluation

3. If we have an additional method to confirm $X_{Assigned}$, then:

$$U_{RS3} = \left| X_{Assigned1} - X_{Assigned2} \right|$$

Alternative methods can have notable bias concerning the *mass balance* approach. Therefore,

$$U_{RS3} \approx 0.5\% \text{ is feasible.}$$

4. It is very valuable to verify $X_{Assigned_1}$ by comparison with:
   - the previous batch of RS,
   - any other authentic substance.

Therefore,

$$U_{RS4} = U\,(X_{Assigned3})$$

The approach (4) is the same as for the calibration of secondary RS.

Since we determine the principal component in a very pure substance, it may be difficult to achieve $U_{RS4} \approx 0.5\%$.

Any of the described evaluations of U_{RS} is essential for assessing the RS quality.

The SPU approach to the U_{RS} evaluation

CONCLUSION:

1. The use of additional evaluation(s) of $X_{Assigned}$ is very valuable.
2. If an additional evaluation of U_{RS} is used (not only by the mass balance method):
   - $maxU_{RS} \leq 0.5\% \Rightarrow$ a feasible but limit value;
   - $maxU_{RS} \approx 0.1\% \Rightarrow$ **a myth!**
   - It is unclear **which U_{RS} should be given to a user**.

The SPU approach to the U_{RS} evaluation

The SPU approach:

- To use verification of $X_{Assigned}$ with additional method(s) (compulsorily);
- To use the evaluation of U_{RS} for the alternative method(s) and the difference between the two $X_{Assigned}$ (compulsorily);
- Any of U_{RS} evaluations must not exceed the $maxU_{RS}$;
- $maxU_{RS}$ must be insignificant in relation to the most stringent requirements for U_{Target};
- A user is provided with information only about $maxU_{RS}$ but not about any result of U_{RSi} *assessment*.

The metrological consistency of specifications and analytical methods

Specificity of pharmaceutical analysis is that the analysis and RS establishment are carried out at the limit capability of analytical methods.

Ph. Eur.: in an inter-laboratory experiment studied an analytical variability for some analytical methods. As a result, specifications for assay were adjusted to capability of analytical methods (expanded for some cases).

Issues that had not been taken into account:

- The correctness of setting the specifications range and the choice of the analytical method should be considered given the feasibility of RS establishment (requirements for $maxU_{RS}$).
- The problem is also an issue of great importance for **FDPs**.

The SPU approach to the metrological consistency

TESTS		REQUIREMENTS for U_{Target}	REQUIREMENTS for $maxU_{RS}$	ASSESSMENT OF POSSIBILITIES OF USING RS
ASSAY	APIs (B_{Upper} =100.5%):	0.5 %	0.16 %[1]	[1] – cannot be set as a requirement for RS; [2] – achievable in certain favorable cases; [3] – usually does not cause problems; [4,5] – a substance (reagent) with the content taken as 100 % can be used instead of RS (with the purity of [4] ≥ 98 % or [5] ≥ 95 %, respectively).
	APIs(B_{Upper} = 101%):	1 %	0.32 %[2]	
	APIs (B_{Upper}= 102%):	2 %	0.64 %[3]	
	FDPs (± B = 5%):	1,6 %	0.51 %[3]	
	FDPs, one-sided limit (± B = 20%):	6,4 %	2.0 %[4]	
UNIFORMITY of DOSAGE UNITS, DISSOLUTION		3.0 %	0.96 %[3]	
RELATED SUBSTANCES	Quantitative tests	5.0 %	1.6 %[4]	
	Limit tests	16 %	5.1 %[5]	
RESIDUAL SOLVENTS		16.0 %	5.1 %[5]	

The SPU approach to the metrological consistency

CAPABILITY of USING ANALYTICAL METHODS	THE NARROWEST CONTENT LIMITS	
	APIs	FDPs
TITRIMETRY (the use of RS is not required)	$B_{Upper} \geq 101$ %	$\pm B = 3$ %
CHROMATOGRAPHY	$B_{Upper} \geq 101.5$ %	$\pm B = 5$ %
SPECTROPHOTOMETRY (the use of RS is required)	$B_{Upper} \geq 101.5$ %	$\pm B = 5$ %
SPECTROPHOTOMETRY (specific absorbance)	$B_{Upper} \geq 103$ %	$\pm B = 10$ %

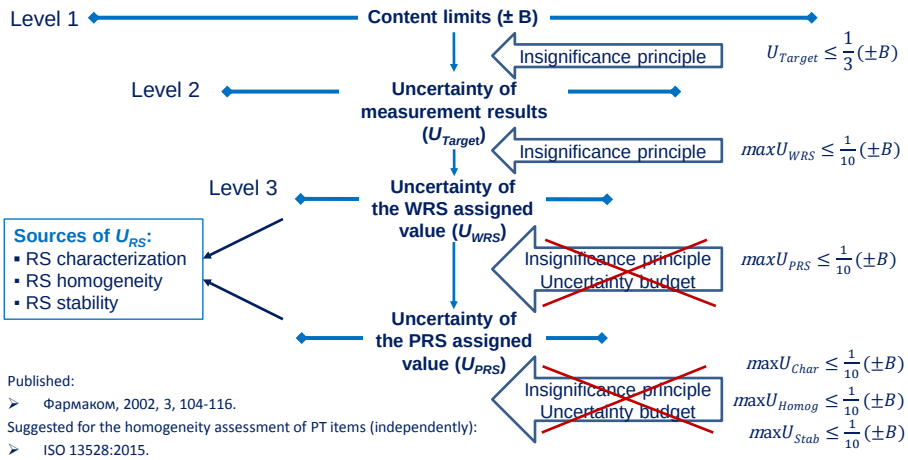
The problem: metrological inconsistency of analytical procedures

An RS cannot be suitable if it is intended for use in a metrologically incorrect analytical procedure.

Typical problems for Assay:

- ✓ The interrelation between the requirement for analytical variability and the capability of an analytical method are not taken into account;
- ✓ The difference between requirements for APIs and FDPs is not taken into account;
- ✓ The dependency of requirements for U_{Target} on the specifications range is not taken into account.

The SPU approach to the evaluation of uncertainty sources



Published:

- Фармаком, 2002, 3, 104-116.

Suggested for the homogeneity assessment of PT items (independently):

- ISO 13528:2015.
- IUPAC Technical report, 2006, doi:10.1351/pac200678010145.

Summary

The State Pharmacopoeia of Ukraine applies metrological approaches discussed above, in particular, for:

- ✓ Validation of Analytical Procedures;
- ✓ Qualification of Laboratory Equipment;
- ✓ Establishment of Reference Standards.

Currently, the nomenclature of reference standards of the State Pharmacopoeia of Ukraine established under the present approaches comprises around 700 items.

Thank You for Your Attention!