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Metrological aspects of the certification of reference standards of the State Pharmacopoeia of Ukraine

Dmytro Leontiev, Natalia Volovyk, Oleksandr Gryzodub

State Enterprise "Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines"; volovyk@phukr.kharkov.ua

Introduction

Normally, a pharmacopoeial reference standard (RS) is certified for the use by the pharmacopoeial monograph, and uncertainty of the value assigned to the RS property is not provided. This creates difficulty ensuring the metrological traceability of the measurement results and using pharmacopoeial RS for non-pharmacopoeial applications (method validation, secondary RS certification, etc.).

This paper presents solutions adopted by the State Pharmacopoeia of Ukraine (SPhU) to address the issue.

Keywords: pharmacopeial reference standards; metrological traceability; measurement uncertainty

Combined uncertainty evaluation

A linear model is used for the evaluation of combined uncertainty:

$$y = f(x_1, x_2, \ldots x_n) \qquad \Delta_y^2 = \sum_{i=1}^{n} \left(\frac{\partial f}{\partial x_i} \right)^2 \times \Delta_{xi}^2$$

where y - measurand; x_i - independent random variable;

Δ - confidence intervals with the same probability.

Insignificance principle for intervals

$$\sqrt{\Delta_{pooled}^2 + \Delta_i^2} \le \left(1 + \frac{p}{100}\right) \times \Delta_{pooled}$$

where Δ_{pooled} – combined expanded uncertainty; Δ_i –component of Δ_{pooled}.

At a 95 % confidence level: $\Delta_i \le 0.32 \times \Delta_{pooled}$.

Hereinafter, we assume that a level of confidence is 95 % unless otherwise specified; under uncertainty we understand the expanded uncertainty.

Target measurement uncertainty (U^{tg})

Table 1. Recommendations for the target measurement uncertainty.

Application	Recommendation
Assay of pharmaceutical substances (two-sided specification limits)	$U^{tg} = B_{Upper} - 100$ %[1]
Assay of medicinal products (two-sided symmetric specification limits)	$U^{tg} = 0.32 \times (B_{Upper} - B_{Lower})/2$
Assay of medicinal products and pharmaceutical substances (one-sided upper specification limit)	U^{tg} = 6.4%
Uniformity of dosage units, Dissolution	U^{tg} = 3.0%
Related substances Limit tests Quantitative tests	 U^{tg} = 16% U^{tg} = 5%

[1] proposed by the European Pharmacopoeia; other recommendations were developed by the SPhU.
B_{Upper} - upper specification limit; B_{Lower} - lower specification limit.

RS property value uncertainty

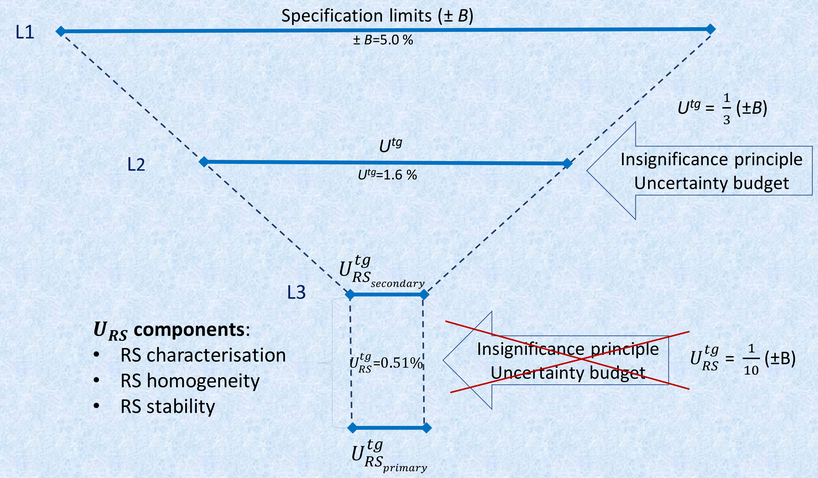
The maximum permissible uncertainty of the value assigned to an RS property (U_{RS}^{tg}) shall be negligible compared to U^{tg}:

$U_{RS}^{tg} = 0.32 \times U^{tg}$.

For SPhU RSs intended for assays of medicinal products with specification limits of 100 % ± 5 % (the most stringent requirements):

U_{RS}^{tg} = 0.51 %.

Uncertainty budget establishment



U_{RS} components:
- RS characterisation
- RS homogeneity
- RS stability

Fig. 1. The SPhU approach to the uncertainty budget establishment.

We consider U = 0.5 % the ultimate achievable value. If $U_{RS}^{tg} \le 0.51$ %, any U_{RS} component shall not exceed 0.51 %. If this is the case, the uncertainty budget is not established, and the insignificance principle is not applied.

RS property value assignment

The SPhU RS assigned value (X_{Char}) is established by mass balance and alternatively verified.

$$U_{RS_{alt}} \le U_{RS}^{tg}$$

$$|X_{Char} - X_{Char_{alt}}| \le \sqrt{2} \times U_{RS}^{tg}$$

where $U_{RS_{alt}}$ – uncertainty associated with the RS characterization and $X_{Char_{alt}}$ – value assigned to an RS property by an alternative method.

Homogeneity study

RS homogeneity is studied on data from at least ten determinations (X_i).

An RS is considered sufficiently homogeneous if both criteria are met:

1. A two-sided confidence interval for X_i at a 95% confidence level should not exceed U_{RS}^{tg}.

2. The difference between X_i and X_{Char} should not exceed U_{RS}^{tg} expressed at a 99 % confidence level ($U_{RS}^{tg(99)}$):

$$U_{RS}^{tg(99)} = (t_{95}/t_{99}) \times U_{RS}^{tg}$$

where t_{95} and t_{99} are two-sided critical values for Student's t for the confidence levels of 95 % and 99 %, respectively.

If $U_{RS}^{tg} = 0.51\%$, then $U_{RS}^{tg(99)} = 0.67$ %.

The approach is similar to the one used in pharmacy for standardization of the uniformity of dosage units.

If the first criterion is used alone, critical individual deviations from the assigned value may be erroneously considered acceptable.

Stability study

Continuous suitability for use is monitored. An RS is considered stable as long as the RS property value does not differ from the assigned value by more than U_{RS}^{tg}.

Certificate

The SPhU RS is accompanied by a certificate that states:

- intended use (tests and/or assays, and analytical methods),
- value assigned to the RS property and its maximum permissible uncertainty (for quantitative RS),
- minimum test portion that provides sufficient homogeneity of the RS (if necessary, for quantitative RS),
- expiration date under prescribed storage conditions.

Since 2002, about 900 SPhU RS have been established by the principles discussed above.

Conclusion

The approach employed by the State Pharmacopoeia of Ukraine to the certification of reference standards allows laboratories to apply the uncertainty concept and thereby comply with the requirements of ISO 17025. It enables users to make informed decisions about the fitness of SPhU RS for the intended purpose, including non-pharmacopoeial applications.