Translation from Ukrainian into English

5.12. REFERENCE STANDARDS

The National part to the General texts of the State Pharmacopoeia of Ukraine 2.1

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Pharmacopoeial reference standards of the State Pharmacopoeia of Ukraine (SPU RS) — reference standards certified by the authorized pharmacopoeial body of Ukraine. In this chapter, SPU RS is a general term for standardized chemical substances, herbal reference standards[1], biological reference preparations and reference spectra. SPU RS are certified for use in tests in accordance with monographs or general chapters of Pharmacopoeia and according to the manufacturer's specifications.

Pharmacopoeial reference standards (PhRS) — reference standards of the European Pharmacopoeia or the State Pharmacopoeia of Ukraine. It can be standardized chemical substances (EP CRS or SPU RS) or herbal reference standards (EP HRS or SPU RS).

Biological reference preparations (BRP) - biological reference preparations of the European Pharmacopoeia (EP BRP) or the State Pharmacopoeia of Ukraine (SPU BRP).

Reference standards of the European Pharmacopoeia are official for quality control of medicines described in the European Pharmacopoeia. In all other cases, SPU RS are official.

If a national SPU monograph exercises texts retrieved from the monographs of United States Pharmacopoeia or British Pharmacopoeia, reference standards of corresponding pharmacopoeias (USP RS or BP CRS) are used as official along with SPU RS; in this case a link to the corresponding reference standard is given in the monograph.

[1] Herbal reference standards of the State Pharmacopoeia of Ukraine are medicinal herbs or medicinal herbal products (usually extracts) certified as reference standards.

Metrological aspects of certification and use of SPU RS. SPU RS are certified using the concept of uncertainty. The uncertainty of certified value of SPU RS (Δ_{RS}) matches the ratio (the principle of insignificance — see Chapter 5.3.N.2. *Validation of analytical procedures and tests*):

$$\Delta_{RS} \leq 0.32 \times \Delta_{As}, \quad (1)$$

Δ_{As} — the maximum permissible uncertainty (target uncertainty) of test results of a substance or finished drug product.

The uncertainty is considered to be the one-tailed confidence interval for the probability of 95 % (see Chapter 5.3.N.1. *Statistical analysis of chemical experiment results*).

When confirming homogeneity and stability of a reference standard, these requirements are also applied.

The uncertainty of certified value of a reference standard is set to meet the requirement (1); therefore Δ_{RS} is insignificant compared to Δ_{As}, and Δ_{RS} can be neglected when assessing the value Δ_{As}. Other science-based approaches can be used when assessing the value Δ_{As}.

Since Δ_{RS} is insignificant in relation to Δ_{As} for all SPU RS, the use of SPU RS lead, with high reliability, to an equivalent conclusion on the quality of the analyzed medicinal product when SPU RS are used in place of reference standards of other pharmacopoeias. Given this, SPU RS can be used instead of reference standards of other pharmacopoeias. However, in case of doubt about the test results or dispute between the parties, the official reference standard should be used.

Accompanying documentation. SPU RS are accompanied by a certificate. Information provided in the certificate enables a user to make a well-founded decision about the correct use of the SPU RS for quality control of a medicinal product if the procedure used for the test is not pharmacopeial.

In addition to general information, the certificate includes:

- Intended use of SPU RS: tests (e.g., identification, purity tests, assay, dissolution for solid dosage forms, uniformity of dosage units, etc.) and methods of analysis for which the reference standards are applicable;

- Shelf life of SPU RS.

For SPU RS intended for quantitative tests, the certificate includes:

- Assigned content (certified value) of the measurand;

- Maximum permissible uncertainty of certified value (Δ_{RS}) and its estimation procedure;

- Procedures for assignment of the certified value and details of certification necessary for a user;

- Minimum sample weight for which homogeneity has been confirmed (if necessary);

- The most narrow content limits for the assay for which the use of SPU RS is correct.

If SPU RS is intended to determine the content of impurities and the certified value is not specified, then content for SPU RS is:

- No less than 98 % for SPU RS intended for the quantitative purity tests;

- No less than 95 % for SPU RS intended for the limit purity tests.

In such cases, the content of SPU RS is considered to be equal to 100%.

If the content of SPU RS is less than the limit value, a certified value is specified in the certificate of SPU RS. This content is used for correcting the sample weight of SPU RS or performing calculations of impurity content.

Information about SPU RS in stock can be found on the site of the authorized pharmacopoeial body of Ukraine.

Working reference standards. A working reference standard (WRS) is a secondary reference standard that is calibrated by comparison with a primary reference standard (PhRS or non-pharmacopoeial official reference standards specified in the manufacturer's specification).

WRS are used for routine tests to reduce the amount of use of PhRS. In case of any doubt about the analysis result, the tests are repeated using official reference standards.

WRS are calibrated under analytical procedure conditions for which a reference standard is intended to use. WRS certification procedure should be statistically justified and documented. The assigned value of the certified characteristic of WRS should be traceable to the same characteristic of the official reference standard.

Metrological requirements accepted for SPU RS can be used for WRS certification. If the uncertainty of certified value of WRS meets the requirement (1), it can be neglected when assessing the value Δ_{As}. Other science-based approaches can be used.