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EVALUATION OF MEASUREMENT UNCERTAINTY

CORE DOCUMENT

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Evaluation of Measurement Uncertainty

Note: Mandatory requirements in this guideline are defined using the terms «shall» or «must». The use of «should» indicates a recommendation. For these parts of the text, other appropriately justified approaches are acceptable. The term «can» indicates a possibility or an example with non-binding character.

1. INTRODUCTION

This document defines the basic principles and possible approaches for evaluation of measurement uncertainty for quantitative testing in OMCLs and is intended to give guidance for the interpretation of the requirements of ISO 17025 clause *7.6 "Evaluation of measurement uncertainty*" [1] and its applicability to the testing performed in Official Medicines Control Laboratories (OMCL). Measurement uncertainty is also referred in the following clauses: *6.4 Equipment, 6.5 Metrological traceability, 7.2 Selection, verification and validation of methods, 7.5 Technical records and 7.8 Reporting the results.*

According to ISO 17025, each laboratory performing testing shall identify the contributions to measurement uncertainty (clause 7.6.1) and shall evaluate measurement uncertainty (clause 7.6.3). If not already included in the specification limits, the uncertainty of measurement should be taken into account in the statement of conformity to a specification, according to the applied decision rules (7.8.6).

The core document is complemented with three annexes containing examples for calculation of the measurement uncertainty following different approaches. Annexes have non-binding character.

The content of this guideline is linked to the OMCL Guidelines "*Validation of analytical procedures"* and "*Evaluation and reporting of results"* [2, 3].

2. SCOPE

This guideline is applicable to all activities (compliance testing and other testing activities) within the OMCL Network related to quantitative testing of chemical and biological pharmaceutical substances and medicinal products for human and veterinary use and herbal products. Compliance testing includes: market surveillance studies (MSS), testing of centrally authorised products (CAP), testing of products authorized with mutual recognition procedure and decentralised procedure (MRP/DCP) or national authorisation, official control authority batch release (OCABR) and pre-licensing evaluation. It may also be applicable for testing of pharmaceutical preparations prepared in pharmacies, suspected and falsified products.

Calculation of uncertainty of measurement using dedicated software is out of the scope of this Guideline. However, CombiStats is commonly used by OMCLs and can provide an estimation of the uncertainty in biological assays in terms of confidence intervals, in cases where the bias component is considered negligible or in case the results are corrected when the bias is significant (an example is provided in Annex 3).

3. GLOSSARY AND DEFINITIONS

Analytical acceptance criteria: Performance criteria applied to results obtained from the analysis performed. These criteria are pre-defined and are dependent on the nature of the product, the analytical procedure and the specification limits given in the monograph or in the marketing authorisation.

Bias (measurement bias): estimate of a systematic measurement error [4].

Combined standard uncertainty: standard uncertainty of the result of a measurement when the result is obtained from the values of a number of other quantities, equal to the positive square root of a sum of terms, the terms being the variances or covariances of these other quantities weighted according to how the measurement result varies with these quantities [5].

Compliance testing: tests performed, using official or validated analytical procedures to verify that a pharmaceutical substance or medicinal product examined conforms with the specification limits given in the monograph or in the marketing authorisation.

Confidence interval: an interval obtained from repeated measurements on a sample using a specified method, which includes the true value of the parameter (e.g. mean, potency) with a probability i.e level of confidence, P. For example, for a P =95%, calculated confidence intervals include the true value of the parameter with a level of confidence of 95% [6,7].

Coverage factor, k: numerical factor used as a multiplier of the combined standard uncertainty in order to obtain an expanded uncertainty, which is typically in the range 2 to 3. The choice of the factor k is based on the level of confidence required and on the set of data available. At the approximate level of confidence of 95%, k value can be usually set to 2, for normally distributed data. However, a correction factor (i.e. t-Student value) should be applied in the calculation of the standard uncertainty depending on the number of measurements [5,7].

Decision rule: a rule that describes how measurement uncertainty will be accounted for when stating conformity with a specified requirement [1].

Error (of measurement): error is defined as the difference between a measured value (individual result) and the true value (reference value) of the measurand [8].

Estimation: the operation of assigning, from the observations in a sample, numerical values to the parameters of a distribution chosen as the statistical model of the population from which this sample is taken. A result of this operation may be expressed as a single value (point estimate) or as an interval estimate [6]

Expanded uncertainty, U: quantity defining an interval about the result of a measurement that may be expected to encompass a large fraction of the distribution of values that could reasonably be attributed to the measurand. It is calculated from a combined standard uncertainty and a coverage factor k [4, 5].

Level of confidence: a number expressing the degree of confidence in a quoted result, e.g. 95%. It represents the probability that the value of the measurand lies within the quoted range of uncertainty [6,7].

Measurand: quantity intended to be measured [8].

Method performance data: data obtained from method validation and quality control results (PTS, collaborative studies, use of certified reference materials, internal quality control criteria). The term “method” encompasses the operational steps, for example equipment set up, reference standards, samples and solutions preparation, data integration, etc.

Specification limits: appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug

product should conform to be considered acceptable for its intended use [9].

Standard uncertainty: uncertainty of the result of a measurement, expressed as a standard deviation [5].

System suitability criteria: performance limits designed to ensure the adequate performance of the analytical procedure. These criteria are to be fulfilled before proceeding to the analysis of the sample.

Systematic error (**Systematic measurement error)**: component of measurement error that in replicate measurements remains constant or varies in a predictable manner [4].

Type A evaluation (of uncertainty): method of evaluation of uncertainty by the statistical analysis of series of observations [5].

Type B evaluation (of uncertainty): method of evaluation of uncertainty by means other than the statistical analysis of series of observations [5].

Measurement uncertainty (MU): a parameter associated with the result of a measurement that characterises the dispersion of the values that could be reasonably attributed to the measurand [8].

Uncertainty evaluation procedure: the procedure used for estimating the overall uncertainty [8].

4. GENERAL OMCL POLICY FOR EVALUATION OF MEASUREMENT UNCERTAINTY

The OMCL activities can be divided into two types i.e. compliance testing and other testing activities. Compliance testing comprises testing towards previously defined specification limits using official and/or properly validated methods (e.g. compendial methods, methods described in the marketing authorization documentation or internally developed methods).

The compendial methods and methods described in the marketing authorization documentation are well-recognized methods, which have been properly validated in accordance with the accepted scientific practice and current recommendations on analytical method validation. The precision (as intermediate precision or reproducibility) of these methods is known and reflected in method performance limits setting. For these methods, the uncertainty sources are well known and are taken into account while setting the specification limits.

Therefore, for compliance testing activities employing well-recognised methods, the ISO 17025 requirements for evaluation of measurement uncertainty are fulfilled if the results are obtained by following the described analytical procedure and reporting instructions, provided that all uncertainty contributors are under control (i.e.: testing is performed by qualified personnel using suitable reference standards and calibrated/qualified equipment, system suitability criteria are satisfied and the repeatability is evaluated against pre-defined acceptance criteria).

For compendial methods, no further tolerances (e.g. obtained by estimation of measurement uncertainty, by the establishment of acceptance and rejection zones) are to be applied to the limits prescribed to determine whether the article being examined complies with the requirements of the monograph [10]. The same is applicable to the methods described in marketing authorization documentation.

For compendial and marketing authorization methods, the laboratory may decide in which cases the uncertainty of measurement will be estimated and taken into account in the statement of conformity to a specification limit.

Alternatively, in house developed methods of analysis may be used in compliance testing, provided that the methods used are properly validated for the purpose for which they are used and enable unambiguous decision on the compliance with the specification limits, taking into account the estimated uncertainty of measurement. In these cases, the decision rule shall be applied and documented, taking into account the level of risk of the decision rule employed, and therefore the level of risk of making a wrong decision.

There are certain cases where it should be necessary to perform more rigorous evaluation of the measurement uncertainty, for example when:

- using *ad-hoc* methods (e.g. screening, analysis of unknown products, trace analysis);
- using methods with unknown or incomplete information regarding uncertainty;
- confirming out-of-specification results, especially in case when the test could not be repeated;
- setting limits for performance tests of measurement apparatus and critical parameters of methods.

The degree of knowledge of the analytical method is important for the identification of the relevant contributors of the measurement uncertainty and for the selection of the best suited evaluation approach. Examples are provided in Annexes to this guideline.

For a particular method that is repeatedly used in the laboratory, for which the measurement uncertainty of the results has already been established and verified, there is no need to evaluate measurement uncertainty for each result, if the laboratory can demonstrate that the identified critical influencing factors are under control (ISO 17025 clause 7.6 Note 2) (such as: testing is performed by qualified personnel, using suitable reference standards and calibrated/qualified equipment, system suitability criteria are satisfied and the repeatability is evaluated against pre-defined acceptance criteria) [1].

The laboratory can decide to perform evaluation of the uncertainty of measurement as an internal quality control indicator, whenever considers it necessary.

5. GENERAL APPROACH FOR EVALUATION OF THE UNCERTAINTY OF MEASUREMENT

The process of measurement uncertainty evaluation comprises four steps (APPENDIX 1):

5.1. First step: Identification of the measurand.

The measurand shall be clearly and unambiguously defined. The quantitative expression relating to the value of the measurand, the procedure for the determination of its value (analytical method used) and, if found necessary, the basis for the calculation of the quantity should also be defined.

5.2. Second step: Identification of uncertainty contributors.

All relevant sources of uncertainty shall be listed and documented for example using a cause and effect diagram (e.g. Ishikawa diagram). The individual components are not to be quantified at this stage.

5.3. Third step: Quantification of uncertainty.

According to Eurachem/CITAC Guide [8] and EA guidelines EA 4/16 [11], quantification of uncertainty should be done by one of the following approaches:

- *Bottom-up approach:* It is applicable to the cases where limited or no method performance data is available. The uncertainty arising from each individual source is evaluated by replicate measurements and then combined using statistical processes. Examples are given in Annex 1.
- *Top-down approach:* It is applicable to the cases where method performance data are available. The combined contribution to the uncertainty is estimated using method performance data:
  - *Certified reference materials,*
  - *Validation study data,*
  - *Collaborative study data (e.g. establishment of chemical reference standards or validation of new test method)*
  - *PTS study data*
  - *Control charts*

  providing that the available performance data are used for the estimation of MU of the selected test/method, namely:
  - comparable precision,
  - satisfactory performance (*i.e.* system suitability) and
  - quality control results compliant with the established analytical acceptance criteria.

  Examples are given in Annex 2.

In practice, a combination of these approaches (i.e. bottom-up and top-down) could be necessary and convenient.

5.4. Fourth step: Calculation of combined uncertainty and expanded uncertainty.

Calculation of combined uncertainty from all uncertainty components expressed as standard deviations and multiplying the combined standard uncertainty by the chosen coverage factor in order to obtain an expanded uncertainty. The expanded uncertainty is required to provide an interval which may be expected to encompass a large fraction of the distribution of values which could reasonably be attributed to the measurand [11].

6. DECISION ON COMPLIANCE OF THE TEST RESULT TAKING INTO ACCOUNT THE UNCERTAINTY OF MEASUREMENTS

According to ISO 17025:2017, the laboratory shall clearly define the decision rule describing how the measurement uncertainty will be taken into account when stating conformity with a specified requirement. In the case where the decision rule is not prescribed by the authority, manufacturer, regulations, standards or guidelines, the level of risk for acceptance or rejection (including statistical assumptions) should be evaluated. The decision rule shall be communicated and agreed with the customer, unless inherent in the specification limits.

Approaches for setting up the decision rules given in the Eurachem / CITAG Guide “Use of uncertainty information in compliance assessment”, 1st Ed (2007) and/or Eurolab technical report “Decision rules applied to conformity assessment” (2017) can be used [12, 13].

7. REPORTING THE RESULT WITH UNCERTAINTY OF MEASURMENT

The measurement uncertainty shall be reported in the test report when it is relevant to the validity of the test result or affects the conformity to a specification limit, or when it is required by the customer [1]. However, the estimated measurement uncertainty shall be kept available for information with the raw data.

The result should be reported together with the value of measurement uncertainty expressed as *Expanded uncertainty U*, presented in the same unit as the measurand or as a relative value to the measurand:

"Result: $x \pm U$ (units) for k (value) and level of confidence (value)"

e.g. for k = 2, the level of confidence is approximately 95%.

Alternatively, the uncertainty of measurement of the result can be expressed as *Combined standard uncertainty*:

"Result: x (units) [with a] standard uncertainty of u_c (units)"

The use of the symbol ± is not recommended for expression of uncertainty of measurement when using standard uncertainty, as this symbol is commonly associated with intervals corresponding to high levels of confidence (e.g. 95%) [8].

Examples of reporting the results with measurement uncertainty are given in Annexes to this guideline.

8. ANNEXES

Annex 1: Estimation of measurement uncertainty using Bottom-up approach

Annex 2: Estimation of measurement uncertainty using Top-down approach:

- 2.1 Use of data from validation studies for the estimation of measurement uncertainty;
- 2.2 Use of data from control charts for the estimation of measurement uncertainty;
- 2.3 Use of certified reference materials for the estimation of measurement uncertainty;
- 2.4 Use of data from collaborative studies for the estimation of measurement uncertainty;
- 2.5 Use of data from PTS for the estimation of measurement uncertainty.

Annex 3: Estimation of measurement uncertainty expressed as confidence interval using standard deviation from testing results

9. REFERENCES

(For all references, the latest version applies)

1. ISO/IEC 17025 “General requirements for the competence of testing and calibration laboratories”

2. OMCL Guideline "Validation of Analytical Procedures"

3. OMCL Guideline "Evaluation and Reporting of Results”

4. International Vocabulary of Metrology - Basic and General Concepts and Associated Terms (VIM 3rd edition - 2008 edition with minor corrections) [JCGM 200:2012]

5. ISO Guide 98-3, Uncertainty of measurement - Part 3: Guide to the expression of uncertainty in measurement (GUM)

6. Evaluation of measurement data - Guide to the expression of uncertainty in measurement, JCGM 100:2008

7. Keith Birch, British Measurement and Testing Association: Measurement Good Practice Guide No. 36, Estimating Uncertainties in Testing, An Intermediate Guide to Estimating and Reporting, Uncertainty of Measurement in Testing, 2003

8. S L R Ellison and A Williams (Eds). Eurachem/CITAC guide: Quantifying Uncertainty in Analytical Measurement, Third edition, (2012) ISBN 978-0-948926-30-3.

9. Q6A Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, ICH Harmonised tripartite Guideline

10. European Pharmacopoeia, General Notices

11. EA-4/16 G:2003, EA guidelines on the expression of uncertainty in quantitative testing

12. S L R Ellison and A Williams (Eds). Eurachem/CITAC guide: Use of uncertainty information in compliance assessment. (First Edition (2007).

13. Eurolab Technical report No1/2017: Decision rules applied to conformity assessment, (2017)

APPENDIX 1

General approach for Evaluation of uncertainty of measurement