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UNCERTAINTY OF MEASUREMENT - PART 2

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OMCL POLICY ON THE ESTIMATION AND APPLICATION OF UNCERTAINTY IN ANALYTICAL MEASUREMENT

To be used by OMCLs for activities other than compliance testing

1. INTRODUCTION

This document is intended to give guidance for the interpretation and application of ISO 17025 “General requirements for the testing and calibration laboratories”[1] and its pertinence to activities **other than** compliance testing performed in Official Medicines Control Laboratories (OMCL).

Measurement uncertainty is mentioned in ISO 17025 in several aspects and as described in a separate OMCL guidance [2].

The laboratory is to demonstrate that it has adequate knowledge of the contributions of all relevant aspects of the measurement process to the overall measurement uncertainty and that the laboratory has measures, in place, to keep these aspects under control as part of the quality policy. The laboratory may in this context be requested to give a quantitative indication of the uncertainty.

It should be noted that sampling, which may introduce a high degree of uncertainty, is not the responsibility of an OMCL and therefore results reported only relate to the specific sample.

2. OBJECTIVE

Investigation of suspicious samples is a statutory requirement in some countries and is performed in some OMCLs. The objective of this document is to give guidance on how to implement the ISO 17025 requirements dealing with the principles of measurement uncertainty for this type of testing.

3. SCOPE

This guidance is applicable to activities within the OMCL not related to compliance testing, such as investigation of suspicious samples. This includes testing of suspicious samples received for analysis by various clients (health authorities, customs, police, etc.). These samples are sometimes unique samples without indication of contents. Generally, testing which can be considered investigative and for which there are no pre-set performance characteristics or analytical acceptance criteria is covered by this guidance. Investigations based on the client's request are sometimes limited to determination of presence/absence and/or magnitude of a suspect ingredient rather than quantitative determination *strictu sensu*.

4. DEFINITION

The uncertainty of measurement “characterises the dispersion of the values that would be reasonably attributed to the measurand” [3].

5. ESTIMATION OF THE UNCERTAINTY OF MEASUREMENT

5.1. Introduction

This document relates to testing activities other than compliance testing. The extent of testing activities depends on the size of the sample, demand of the client - whether or not there is a need for a quantitative determination and, if so, the estimation of the measurement uncertainty of the results may or may not be required.

A number of steps in the analysis of the suspicious samples can be identified.

Step 1: Identification

Identification of component(s) of the sample using different methods (at least two independent methods).

Screening. A separation method like thin layer chromatography or liquid chromatography with DAD often gives an indication of what substance(s) may be present (tentative identification).

Confirmation. The presence of the substance(s) indicated during screening may be confirmed by a different chromatographic system. This might be thin layer chromatography, liquid chromatography or gradient liquid chromatography. Further information of the identity of the substance may be verified by a "spiking" experiment with DAD peak purity evaluation.

Specific test. When the presence of the substance(s) has been confirmed it may be necessary to perform a specific test like LC/MS for definitive identification.

Step 2a: Quantitative determination with authorised or other validated methods

The identified component (measurand) of the sample may be determined using an already validated method [2]. If there is no authorised method or validated method, which can be applied, then the procedure in Step 2b could be used.

Step 2b: Quantitative determination with methods adapted from authorised or other validated methods

The identified component in a pharmaceutical preparation, for which there is no authorised method or validated method, may be determined by a method described in the scientific literature or by modification of an authorised or validated method used for the determination of a similar compound.

-If sufficient amount of sample is available: A recovery experiment will be required and replicate determinations using a method where the standard uncertainty is estimated from the standard deviation.

-If not sufficient amount of sample is available: An approach based on historical data may be used (see 5.2.2).

5.2. Identification and quantification of Measurement uncertainties

The Eurachem/CITAC Guide [3] gives two possible approaches for estimation of measurement uncertainties:

5.2.1 Identifying and quantifying each component which contributes to the uncertainty and combining all contributions. This is referred to as a “step-by-step” approach.

When a single determination is made the uncertainty of the measurement can be made taking into account the variance of each step of the analysis sequence and guidance on such calculation for different types of analysis have been published [3]. In these examples the contribution of each step is taken into account for the calculation of the expanded uncertainty with a coverage probability of 95 per cent. Each uncertainty component should be considered. Nevertheless, it is obvious that their importance varies and some contributions to the uncertainty budget e.g. molecular weight, is insignificant compared to other possible contributions.

Much of this information is already available and may be obtained from certificates or published tables but some must be experimentally determined. Information regarding weighing errors and dilution sequences is given in the Technical Guide for the Elaboration of Monographs [4].

The client may require the identification of a component but also a quantification of the identified component. If there is insufficient sample or if experimental determination is not possible then the uncertainty, if required, can be estimated using the step-by-step approach when a single determination of the analyte is made or use data from other sources or from theoretical considerations (see Appendix).

5.2.2 However, data from prior studies originating from defined internal quality control procedures, from method validation, from collaborative studies or from proficiency tests may be used. These data are combinations of uncertainty components. This is referred to as the "overall" approach.

The determination of the uncertainty associated with each individual step in the procedure is, in most instances, unnecessary in the context of the work of the OMCLs. When such methods are employed they are derived from methods published in the scientific literature, adapted from authorised methods or developed from the experience of the analyst and if an estimation of uncertainty is required then the “overall” approach can be applied.

Confirmation of the result obtained with one method or by an alternative, independent method may be all that is required (e.g. HPLC and titration).

If there is sufficient sample available, and an estimate of uncertainty of the result is required, then it is adequate to determine:

- the precision of the method (includes the major uncertainty components)
- the bias (recovery experiment)

The precision of the method is calculated by performing the procedure several times and calculating the relative standard deviation.

A number of recovery experiments, at least three, should be performed using 'spiked' samples. Both the recovery of the 'spike' and its standard deviation are determined.

6. CONCLUSION

For the most part, the confidence in the result obtained by the OMCLs for investigative studies can, when required, be covered by the "overall" approach for the estimation of the uncertainty, although the "step-by-step" approach may be necessary in certain cases.

7. GLOSSARY

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

Measurand – A particular quantity subject to measurement, the parameter to be determined.

System suitability criteria – Performance limits applied to various tests which are designed to ensure the adequate performance of the analytical procedure. These criteria are to be fulfilled before proceeding to the analysis of the sample.

Analytical acceptance criteria – Performance limits 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 limits given in the monograph or in the marketing authorisation specifications.

8. REFERENCES

(For all references, the latest version applies)

- 1 ISO/IEC 17025 “General requirements for the competence of testing and calibration laboratories”.
- 2 OMCL Policy on the establishment and application of uncertainty in analytical measurements: to be used by OMCLs for compliance testing.
- 3 Quantifying Uncertainty in Analytical Measurements, Eurachem / CITAC Guide CG 4.
- 4 Technical guide for the elaboration of monographs. European Pharmacopoeia.

APPENDIX

Identification and quantification of measurement uncertainty

1

Specify measurand (parameter to be determined)

2

Identify the relevant uncertainty components of the test (individually or grouped). Be pragmatic!

3

Estimate the size of these uncertainty components (either experimentally or use former results such as validation data if available)

E.g. : - repeatability of your experiments

- performance criteria of your equipment
- specifications of the supplies used
- environmental effects (such as temperature)
- validation data (former results)
- performance results of PTS and collaborative studies
- theoretical considerations
- experience and professional judgement
- recovery experiments (or others)

4

Consider if all relevant contributions are taken into account and covered.
Also consider which components (individually or grouped) established under **3**:

- have a major effect (so that minor effects can be ignored)
- include (most of) the other aspects (e.g. PTS results)

5

Calculate or estimate the combined and expanded uncertainty according to the Eurachem/CITAC Guide [3] if necessary (see step 2b in chapter 5.1) or use the established major effects as uncertainty value.
If the calculated combined uncertainty and the performance of PTS results, or a specific collaborative study, are independent of each other, these results may be used to verify the calculated or estimated uncertainty.