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UNCERTAINTY OF MEASUREMENT - PART 1

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GENERAL OMCL POLICY FOR IMPLEMENTATION OF MEASUREMENT UNCERTAINTY IN 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 compliance testing performed in Official Medicines Control Laboratories (OMCL).

Measurement uncertainty is mentioned in the ISO 17025 standard in several sections, e.g. the following sections relevant for this document:

5.4.1 Test and calibration methods and method validation – General
5.4.6. Estimation of uncertainty of measurement
5.10.3 Reporting the results – Test reports

The laboratory is to demonstrate that it has adequate knowledge of all aspects of the analytical procedure relevant to the measurement process, contributing to the overall measurement uncertainty and that the laboratory has procedures in place to keep these aspects under control as part of its quality policy. The OMCL should therefore be able, where appropriate, to report on this issue.

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

2. OBJECTIVE

Compliance testing of pharmaceutical substances and medicinal products is a statuary requirement and is performed by OMCLs. The objective of this document is to give the policy on how to implement the ISO 17025 requirements dealing with the principles of measurement uncertainty.

3. SCOPE

In the field of pharmaceuticals, the legal framework is enforced by the application of requirements set by "The Rules Governing Medicinal Products in the European Union", including "Good Manufacturing Practices", the European Pharmacopoeia and guidelines adopted by the "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use". This document is applicable to all activities related to compliance testing in this field for chemical and biological pharmaceutical substances and medicinal products for human and veterinary use, within the OMCL Network.

4. DEFINITION

The uncertainty of measurement “characterises the dispersion of the values that would be reasonably attributed to the measurand” [2].

5. ESTIMATION OF THE UNCERTAINITY OF MEASUREMENTS

5.1 Introduction

The OMCL activities can be divided into two types:

1. Compliance testing
2. Other testing activities

This document only relates to the compliance testing which comprises testing towards previously defined specifications. In case of compliance testing, validated or official methods are used, the uncertainty aspects of which are well known and can be demonstrated to be under control. Other testing activities are treated in a separate OMCL guidance [3].

5.2 Measurement uncertainties

Both the Eurachem/CITAC Guide [2] and EA guidelines EA 4/16 [12] give two possible approaches for estimation of measurement uncertainties:

1. Identifying and quantifying each component which contributes to the overall uncertainty and combining all contributions. This is referred to as a "step-by-step" approach (combined uncertainty).

2. Data from prior studies originating from defined internal quality control procedures, from method validation, from collaborative studies or from proficiency tests. These data are combinations of uncertainty components. This is referred to as the "overall" approach (overall uncertainty).

5.3 Application to compliance testing (see Appendix 1)

ISO 17025 states that “The laboratory shall use test and/or calibration methods, including methods for sampling, which meet the needs of the client and which are appropriate for the tests and/or calibrations it undertakes. Methods published in international, regional or national standards shall preferably be used”.

In compliance testing analytical procedures can be used from three different origins:

- Official methods (e.g. compendial)
- Methods described in the marketing authorisation
- Internal methods developed in the OMCL.

5.3.1 Official methods (e.g. compendial)

The precision of the method is known and the limits have been set accordingly. The General Notices of the European Pharmacopoeia [4] states that the limits described are based on data obtained in normal analytical practice, they take account of normal analytical errors, of acceptable variations in manufacture and compounding and of deterioration to an extent considered acceptable. No further tolerances are to be applied to the limits prescribed to determine whether the article being examined complies with the requirements of the monograph and “The procedures for the tests and assays published in the individual

monographs have been validated according to the current practice at the time of their elaboration for the purpose for which they are intended" [5].

5.3.2 Methods described in the marketing authorisation

These methods are fully validated [6] and have been assessed during the licensing procedure and officially approved by the competent authority.

The precision of the method is known and the limits are set based on validation that has been assessed and authorised by the competent authority. When the required conditions are met (i.e. the system suitability or method transfer checks are fulfilled) when applying the method as prescribed and using appropriate reference substances, the experimental precision is used to indicate the uncertainty.

5.3.3 Internally developed methods

These methods are validated [7] for the purpose for which they are used and can therefore be treated as the former cases.

5.4 The overall uncertainty

In all the above approaches the overall uncertainty of the result is expressed by the relative standard deviation. The methods have been validated and hence the precision of the method is known which is taken into account when setting the limits of content. Thus, the relative standard deviation of the result must be below a pre-determined maximal permitted relative standard deviation that depends on the precision of the method [8]. The data are thus statistically assessed and the uncertainty of the measurement (estimated by the relative standard deviation) is taken into account when taking a decision on the acceptability of the result.

It is recalled that the tests are performed under a properly functioning quality system, which means that:

1. all balances and volumetric glassware are under regular control
2. official reference substances [9] or in house reference substances are properly qualified and stored
3. instruments are regularly calibrated
4. equipment is regularly re-qualified
5. laboratory technicians are (re-)qualified

and the uncertainties due to these sources are under control and contribute little to the total uncertainty of the test result.

It should also be recalled that it is state of the art in pharmaceutical analysis to use pre-defined system suitability test criteria for the test procedures and analytical acceptance criteria for the results. These are to be fulfilled to assure good performance [10, 11]. The system suitability test criteria in many cases are integral part of the method whereas analytical acceptance criteria of the results are pre-defined by the individual OMCL based on sound statistical principles.

The application of the above procedure avoids the use of the “step-by-step” approach where the laboratory calculates the uncertainty by summation of each step or series of steps. However, such an approach may be usefully employed by an OMCL to identify and estimate the uncertainty at each stage of the procedure when considered necessary. It is particularly useful for the investigation of out-of-specification results and for setting limits for performance tests of measurement apparatus and critical parameters of methods. The expression of measurement uncertainty is described in the OMCL guideline "Evaluation and reporting of results” [8];other examples are given in the Eurachem / CITAC Guide [2] and in the EA guideline on “Expression of uncertainty in quantitative testing” [12].

6. CONCLUSION

The confidence in the result obtained by the OMCLs for compliance testing can be assured by the ‘overall’ approach for the estimation of the uncertainty, by the application of the system suitability criteria and by adherence to pre-defined analytical acceptance criteria, provided that a well-functioning quality system is in place.

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. Quantifying Uncertainty in Analytical Measurements, Eurachem / CITAC Guide CG 4.

3. OMCL Policy on the Establishment and Application of Uncertainty in Analytical Measurements: to be used by OMCLs for activities other than compliance testing.

4. General Notices, 1.4 Monographs, Limits, European Pharmacopoeia.

5. II. Introduction, General Principles, European Pharmacopoeia.

6. Validation of Analytical Procedures – Text and Methodology. ICH Guideline. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

7. OMCL Guideline "Validation of Analytical Procedures".

8. OMCL Guideline "Evaluation and Reporting of Results”.

9. OMCL Guideline "Chemical Reference Substances used as Assay Standards".

10. Chromatographic Separation Techniques (2.2.46), European Pharmacopoeia.

11. Statistical Analysis of Results, Biological Assays and Tests (5.3), European Pharmacopoeia.

12. EA guidelines on the expression of uncertainty in quantitative testing, EA-4/16.

APPENDIX

Flow chart for evaluation of measurement uncertainty in compliance testing