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Reproducibility of the level of detection (LOD) of binary methods in collaborative and in-house validation studies

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Reproductibilité de la limite de détection (LD) des méthodes binaires pour des études de validation internes et collaboratives

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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This document was prepared by Technical Committee ISO/TC 69, *Applications of statistical methods*, Subcommittee SC 6, *Measurement methods and results*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

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Introduction

An appropriate approach for the validation of binary methods will often differ considerably from that of quantitative methods. Nevertheless, core concepts from the validation of quantitative methods can be successfully carried over to binary methods. In particular, the precision of a method – a performance characteristic usually associated with quantitative methods – can be determined for the level of detection (LOD) of binary methods.

In analytical chemistry, one of the fundamental indicators of method performance is the reproducibility of quantitative test results as described in ISO 5725 (all parts)[1]. This aspect of method performance is not usually taken into consideration in the validation of binary methods. However, in the last few years, novel validation approaches have been proposed in which the reproducibility of a binary method can be determined and meaningfully interpreted.

Why is it important to determine a method's reproducibility? In order to answer this question, consider an example from the field of microbiology. Take the case that, in the validation study, a method's LOD is determined as 3 CFU/ml (CFU = colony forming unit), but that the LOD is sometimes much higher depending on the laboratory or on the test conditions. Failing to detect the occasional unreliability of the method could lead to mistakes in routine laboratory determinations. On the other hand, if an LOD of 300 CFU/ml is obtained in the validation study, the method will not be validated even though this excessive LOD is not representative of its average performance. Accordingly, both the average LOD value and the reproducibility parameter – describing the variability of the LOD across laboratories or test conditions – capture important information about the performance of the method and should be determined in the course of the validation process.

In order to accomplish this, a suitable approach should be identified for the conversion of the binary results into quantitative ones. In this standard, two parametric models for the calculation of the LOD will be used: one model for methods for discrete measurands, e.g. microbiological and Polymerase Chain Reaction (PCR) methods, and one model for methods for continuous measurands, e.g. chemical methods.

Two different study designs will be applied. In the conventional approach, test conditions vary randomly from one laboratory to the other, whereas in the factorial approach, at least to some extent, test conditions are controlled. The factorial approach makes it possible to assess different sources of errors such as the variability arising in connection with different analysts, different instruments, different lots of reagents, different elapsed assay times, different assay temperatures etc. Such an approach also allows a reduction in workload and fewer participating laboratories.

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Reproducibility of the level of detection (LOD) of binary methods in collaborative and in-house validation studies

1 Scope

This document provides statistical techniques for the determination of the reproducibility of the level of detection for

a) binary (qualitative) test methods for continuous measurands, e.g. the content of a chemical substance, and

b) binary (qualitative) test methods for discrete measurands, e.g. the number of RNA copies in a sample.

The reproducibility precision is determined according to ISO 5725 (all parts).

Precision estimates are subject to random variability. Accordingly, it is important to determine the uncertainty associated with each estimate, and to understand the relationship between this uncertainty, the number of participants and the experimental design. This document thus provides not only a description of statistical tools for the calculation of the LOD reproducibility precision, but also for the standard error of the estimates.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 3534-1, *Statistics — Vocabulary and symbols — Part 1: General statistical terms and terms used in probability*

ISO 5725-1, *Accuracy (trueness and precision) of measurement methods and results — Part 1: General principles and definitions*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 3534-1 and ISO 5725-1 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
factor
binary or quantitative parameter within the method that can be varied at two or more levels within the limits of the specified method

EXAMPLE Technician.

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