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Molecular biomarker analysis - Determination of the performance characteristics of qualitative measurement methods and validation of methods

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National foreword

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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 34, *Food products*, Subcommittee SC 16, *Horizontal methods for molecular biomarker analysis*.

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.

Introduction

Qualitative (binary) analytical methods (e.g. applied to screening tests) for use in the analysis of food or food products (including seeds of food crops) with the purpose of demonstrating the presence/absence of a given measurand in a sample should provide objective evidence that they are adequate for their intended use. A validated test method is much preferred over one that has not undergone studies to determine its accuracy and reliability for its specific purpose. These methods that yield a binary result (yes/no, positive/negative, etc.) are referred to as "qualitative" or "binary" methods.

As with quantitative methods, qualitative method performance has to be characterized with respect to the concentration of the measurand. However, only two conditions are indicated in the result: either the measurand is detected (a positive result) or it is not detected (a negative result). While internationally recognized guidelines (e.g. ISO 5725-2, References [7] and [16]) have been produced over the years to harmonize the validation of quantitative analytical methods, no consensus is yet available among stakeholders on a practical implementation of the performance criteria approach to the validation of qualitative methods for use in food and food products.

Conceptual approaches for validating qualitative methods classically focused on parameters such as sensitivity, selectivity, false positive rate and false negative rate, based on detection/non-detection of the measurand in the test sample. The limitation of this approach was the underlying assumption that the method had a predictable response to the presence of a measurand present at a non-zero concentration. In practice, however, a non-zero concentration can result in a variable probability of a positive result in the assay. Treating the concentration of measurand as a continuous variable with reasonable and/or previously determined confidence in a defined matrix using a specific analytical method is a better predictor of measurement response than a two-state, zero/non-zero variable.

This document describes the assessment of probability of detection (POD). This approach allows for comparison of probabilities across concentrations and further allows for a simple graphical representation of validation data as a POD response curve graphed by concentration with associated error bars of the mean POD value. This approach expresses the POD as dependent on concentration; the goal of validation is to characterize the response probability curve as a function of measurand mass or concentration.

A number of models have been described in the literature for the calculations of the confidence intervals of the POD and confidence intervals or predictive ranges for concentrations in case of a positive or negative result, e.g. References [4], [8], [9], [11], [17], [19] and [20]. Whereas qualitative methods are often evaluated at 50 %, they are used close to 100 %, or at levels where the sample size is adjusted so as to always obtain a clear positive or negative result. The present specification is therefore the result of an extensive discussion of the possible improved models for characterization of qualitative methods, particularly focused on the characterization of the methods close to the 0 and 100 % POD cases. The performance characteristics include:

a) the mean POD across laboratories (LPOD);

b) the corresponding confidence interval of the LPOD, which is the interval estimate of the mean POD;

c) the prediction interval for future observations of laboratory specific PODs.

An advanced statistical method allows the user to calculate confidence and/or prediction intervals for the concentrations where the user would expect positive or negative results. To do so is particularly challenging where the POD is close to 0 % or 100 %.

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1 Scope

This document specifies methods that yield a binary result and are used for the determination in food or food products (including seeds of food crops) of the presence of molecular biomarkers. These methods are typically used where the measurand is expected to be present in very small amounts and concentrations at the limit of detection (LOD).

Methods are validated in terms of the probability of detection (POD) and of the precision of the POD. They do not rely on the concept of false positive/false-negative results, or the concept of LOD. However, inferences about the precision of the classical LOD can be made.

This document describes the extent of method validation. The annexes provide different statistical models that can be considered depending on the analytical method, structure of data and statistical experience.

This document does not apply to quantitative methods that are used to make a detection decision by comparing the value of a response to a cut-off value using a quantitative method, where the methods are validated by using quantitative statistics on the responses. This document also does not apply to microbiological test methods, starch, essential oils or quantitative methods.

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 5725-1:1994, *Accuracy (trueness and precision) of measurement methods and results — Part 1: General principles and definitions*

ISO 5725-2:1994, *Accuracy (trueness and precision) of measurement methods and results — Part 2: Basic method for the determination of repeatability and reproducibility of a standard measurement method*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

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

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

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

3.1
binary result
result from a *method* (3.6) of analysis where there are only two possible outcomes