TECHNICAL SPECIFICATION

ISO/TS 16393

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

Analyse de biomarqueurs moléculaires — Détermination des caractéristiques de performance des méthodes de mesure qualitatives et validation des méthodes

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Foreword

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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 %.