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NATIONAL STANDARD OF THE
PEOPLE'S REPUBLIC OF CHINA

GB 5009.295-2023

**National Food Safety Standard -- General Principles for
Validation of Chemical Analysis Methods**

食品安全国家标准 化学分析方法验证通则

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National Food Safety Standard -- General Principles for Validation of Chemical Analysis Methods

1 Scope

This Standard specifies the general requirements for the validation of national food safety standard -- chemical analysis methods.

This Standard is applicable to the validation process during the development and revision of national food safety standard -- chemical analysis methods.

2 Terms and definitions

2.1 Method validation

Test activities that provide objective and valid evidence to confirm that the performance parameters of an analytical method meet the intended use of the method.

2.2 Qualitative method

An analytical method that identifies the presence or absence of a target analyte in a sample based on its specific properties.

2.3 Quantitative method

An analytical method that determines the concentration or amount of target analytes under conditions that meet specified precision and accuracy.

2.4 Concentration paid attention to

The concentration that is decisive for determining whether the target analyte in the sample meets the requirements of regulations or standards.

2.5 Specificity

The ability of an analytical method to distinguish between target analytes and interfering substances.

2.14 Intermediate precision

In the same laboratory, over a long period of time (pay attention to small changes in test conditions, such as temperature, humidity, light, etc.), the precision of independent measurement results obtained by using the same method to test the same sample.

2.15 Linear range

Under a certain level of significance, a linear calculation model is used to define the relationship between instrument response and concentration (or amount), which conforms to the interval between the lowest concentration (or amount) and the highest concentration (or amount) of the calculation model.

2.16 Detection probability

The probability that an analytical method will detect the target analyte at a specified concentration and confidence level.

3 General requirements for validation of chemical analysis methods

3.1 Selection of performance parameters

3.1.1 For qualitative methods, intra-laboratory and inter-laboratory validation parameters shall include method specificity and detection limit.

3.1.2 For quantitative methods, laboratory validation parameters shall include method specificity, detection limit, quantitation limit, measurement range, accuracy, and repeatability. Interlaboratory validation parameters shall include the detection limit, quantification limit, determination range, correctness and reproducibility of the method.

3.1.3 When the analysis method is sensitive to small changes in test conditions such as temperature, humidity, and lighting, the robustness of the method shall be examined, and the intermediate precision index shall be calculated.

3.1.4 When there are two or more methods with the same applicable scope for the same target analyte, the equivalence of the different methods needs to be validated.

3.1.5 When literature data on the stability of a reference material are lacking, its stability shall be validated.

3.1.6 Selection of intra-laboratory and inter-laboratory validation parameters is shown

use of the method.

- b) For a sample matrix, at least 3 concentration levels are required, including the lowest concentration, the middle concentration (generally the concentration of concern) and the highest concentration of the method's determination range. Their uniformity and stability are tested.

3.3.4 When selecting a standard addition sample for validation, the validation sample can be prepared as follows:

- a) The sample matrix shall be selected to be representative and meet the intended use of the method.
- b) For a sample matrix, at least 3 concentration addition levels are required, including the lowest concentration, the middle concentration (generally the concentration of concern) and the highest concentration of the method determination range.

3.4 Data processing requirements

All laboratory validation data need to be subjected to outlier testing and statistical analysis. The analysis method can use statistical methods such as Grubbs test. After eliminating outliers through technical analysis, the number of laboratories and the amount of validation data shall meet statistical requirements.

4 Validation of performance parameters of chemical analysis methods

4.1 Validation of method performance parameters

4.1.1 Specificity

4.1.1.1 Validation requirements

The ability of the analytical method to differentiate between the target analyte and other substances shall be validated. There shall be no interference factors (signals, interference peaks, etc.) that lead to errors in the identification of the target analyte and affect the accuracy of quantitation.

4.1.1.2 Validation method

Analyze representative samples that match the scope of the method. Check whether there are any interferences (signals, peaks, etc.) that lead to incorrect identification of

the target analytes and/or affect accurate quantitation. A certain concentration of substances that may interfere with the identification and/or quantification of the target analyte is added to a representative sample and then analyzed. Check whether these interfering substances can be effectively identified.

4.1.2 Detection limit

4.1.2.1 Validation requirements

The detection probability of the target analyte at the detection limit level shall be no less than 95% (at the 95% confidence level). The detection limit needs to be independently validated for each representative sample matrix.

4.1.2.2 Validation method

4.1.2.2.1 Estimation method

Methods for estimating detection limits include:

- a) Signal-to-noise ratio method (applicable to spectroscopy, chromatography, and mass spectrometry): Add target analytes to a blank sample matrix. Use the added concentration when the signal-to-noise ratio is 3 as the estimated detection limit.
- b) Blank standard deviation method (method suitable for non-zero response values of blank samples): The detection limit is determined by analyzing a large number of sample blanks. The number of independent tests shall be no less than 10 ($n \geq 10$). Calculate the standard deviation of the sample blank response. The concentration corresponding to the average of the sample blank response values plus 3 times the standard deviation shall be the estimated detection limit.
- c) Calibration equation estimation method (applicable to instrument method): If sample data at or near the detection limit cannot be obtained, use $3S/b$ (S is the standard deviation of the calibration curve, b is the slope of the calibration curve) as the estimated detection limit.
- d) Gradual dilution method (applicable to all methods): The target analyte is serially diluted at certain concentration intervals. Test according to the method to be validated. The concentration at which the target analyte can be detected shall be the estimated detection limit.

4.1.2.2.2 Determination method

Select at least 20 parallel samples of blank sample matrix. Target analytes at estimated detection limit concentrations are added separately. When the detection probability of the target analyte is not less than 95%, it is determined as the detection limit. When blank samples are unavailable, isotope-labeled compounds or structural analogs can be used for validation.

4.1.3 Limit of quantitation

4.1.3.1 Validation requirements

The quantitation limit shall be validated using certified reference materials/standard samples, quality control samples or standard spiked samples of the same concentration. Its accuracy and precision shall meet method and regulatory requirements. The limit of quantification plus 3 times the standard deviation of the sample at the concentration of interest shall be less than the concentration of interest. For target analytes with limited values, the limit of quantitation shall be 0.5 times the limit value or less.

4.1.3.2 Validation method

4.1.3.2.1 Estimation method

Methods for estimating quantitation limits include:

- a) Add target analytes to blank sample matrix. Use the added concentration when the signal-to-noise ratio is 10 as the estimated quantitation limit.
- b) Three times the detection limit is used as the estimated quantification limit.
- c) The concentration corresponding to the average of the sample blank response values plus 10 times the standard deviation is used as the estimated quantification limit.

4.1.3.2.2 Determination method

For each representative sample matrix, independent testing is performed using certified reference materials/standard samples, quality control samples or standard spiked samples at the quantitation limit concentration level. Test at least 6 replicate samples. Perform statistical analysis of data. If the accuracy and precision of the measurement results at this concentration meet the requirements of Table 2 to Table 4, this concentration can be used as the quantitative limit of the method.

4.1.4 Measuring range

The measurement range of the method shall cover the concentration of interest of the method. Its validation requirements are as follows:

- a) The correctness and precision of at least the lowest and highest concentrations of the method's measurement range need to be validated. For target analytes with limited limit values, the accuracy and precision of the limit value concentration shall also be validated.
- b) If the measurement range of the method is linear and the standard curve method

Depending on the properties of the standard solution or sample solution, choose different storage conditions and time intervals. Use the same analysis method and analysis conditions to measure the target analyte in the standard solution or sample solution.

4.1.7.3 Evaluation of stability validation results

4.1.7.3.1 For analytical target substances with only two time point detection results, the stability can be evaluated using formula (1).

$$|\rho_0 - \rho_i| \leq U_E \quad \dots\dots\dots (1)$$

Where,

ρ_i - the measured concentration of the target analyte at time point i ;

ρ_0 - the initial measured concentration of target analyte;

U_E - the expanded uncertainty of the instrument method (excluding sample pretreatment steps) at ρ_0 concentration, $U_E \leq 15\%$.

4.1.7.3.2 For analytical target substances with multiple time point test results, the stability can be evaluated using the t test or F test.

4.1.8 Robustness

Robustness testing is a testing procedure that examines the impact of environmental or other conditional variables on an analytical method. A robust analysis method shall not be subject to significant changes caused by small changes in environmental factors, that is, it shall be insensitive to changes in environmental factors such as temperature, humidity, and air pressure, as well as to other factors such as the amount of reagent added and reaction time. The robustness test of the method is shown in Annex B.

4.2 Validation of method equivalence

4.2.1 Validation requirements

In the analytical method standards, there shall be no significant difference in the test results of different analytical methods with the same measurement range.

4.2.2 Validation method

4.2.2.1 Select at least 3 representative samples. For each representative sample, at least 6 standard substances/standard samples or standard spiked samples with concentrations

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