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# Evaluation of measurement uncertainty of calibrators for in vitro diagnostic kits

体外诊断试剂用校准物测量不确定度评定

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# Table of Contents

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# Evaluation of measurement uncertainty of calibrators for in vitro diagnostic kits

## 1 Scope

This Standard specifies evaluation methods of measurement uncertainty of calibrators for in vitro diagnostic kits.

This Standard is applicable to evaluation of measurement uncertainty of product calibrators for in vitro diagnostic quantitative kits.

## 2 Normative references

The following referenced documents are indispensable for the application 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.

GB/T 21415, *In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials*

## 3 Terms and definitions

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

### 3.1 product calibrator; calibrator

The calibrator intended for the manufacturer's final product.

**NOTE:** The product calibrator here includes the calibrator used by the manufacturer for final product calibration. The calibration information of the calibrator will be transmitted to the measurement of the clinical sample through ways such as electronic carrier.

### 3.2 working calibrator; master calibrator

Measurement standard used for calibration of manufacturer's permanent measurement procedures.

### 3.3 metrological traceability

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Absolute value of standard uncertainty divided by measured value.

[JJF 1001-2011, definition 5.23]

**3.9 combined standard measurement uncertainty; combined standard uncertainty**

The standard measurement uncertainty of the output obtained from the standard measurement uncertainty of each input in a measurement model.

[JJF 1001-2011, definition 5.22]

**3.10 expanded measurement uncertainty; expanded uncertainty**

The product of the combined standard uncertainty and a digital factor greater than 1.

**NOTE:** “Factor” refers to coverage factor.

[JJF 1001-2011, definition 5.27]

**3.11 coverage probability**

The probability that the measured set of values is contained within the specified containment interval.

[JJF 1001-2011, definition 5.29]

**3.12 coverage factor**

A number greater than 1 multiplied by the combined standard uncertainty, in order to obtain expanded uncertainty.

[JJF 1001-2011, definition 5.30]

# 4 Evaluation process

## 4.1 General

### 4.1.1 Basic flow

According to the flow shown in Figure 1, evaluate the measurement uncertainty of in vitro diagnostic calibrator.

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repeatability standard deviation $s_r$ of the test method can be used to estimate.

If there are more than 2 concentrations of the product calibrator, it needs to conduct uniformity inspection on the calibrator of each concentration (except for zero concentration calibrator).

If the product calibrator contains multiple test items, it needs to evaluate the uniformity between bottles of each test item separately, unless there is a clear distribution relationship between the two items.

#### 4.2.2 Test scheme

##### 4.2.2.1 Test method

The test method shall meet the following requirements:

a) It can use manufacturer's permanent measurement procedures or other measurement procedures that set values for product calibrators. Complete the test under repeatable conditions.

b) The reportable concentration range shall cover the expected concentration of the product calibrator. If the expected concentration of the product calibrator is higher than the concentration range of the test system, it can, under strictly specified test conditions, use weighing method to accurately dilute the product calibrator. And ensure that the dilution will not change the interchangeability of the calibrator and thus affect the uniformity test results.

c) The method precision shall reflect the difference between bottles and not be inferior to the precision of the valuation method. Under ideal conditions, $s_r \leqslant \frac{u_d}{3}$, where $s_r$ is the repeatability standard deviation of the test method, $u_d$ is the target standard uncertainty of the calibrator.

d) The minimum sampling amount that can guarantee uniformity shall be specified. It is recommended not to be higher than the sampling volume when calibrating the matching kits.

**NOTE:** If the calibrator is diluted and then used in the calibration kit, then the minimum sampling volume for uniformity testing is not higher than the minimum sampling volume for the dilution operation (for gradient dilution, take the minimum sampling volume for the first dilution operation).

##### 4.2.2.2 Sample extraction

According to random stratification method, extract the calibrator from the smallest packaging unit for uniformity inspection. Number the samples in

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If there are more than 2 concentrations of the product calibrator, it needs to inspect the stability of each concentration of calibrator (except zero concentration calibrator).

If the product calibrator contains multiple test items, it needs to evaluate the stability of each test item separately, unless there is a clear distribution relationship between the two items.

#### 4.3.2 Test scheme

Stability test can choose "classic" scheme or "synchronous" scheme design. The classic scheme is to put the samples prepared at the same time under the expected storage conditions. Take some samples for measurement over time. It is real-time tracking test of sample stability under reproducibility conditions. The synchronous scheme takes samples in time-sharing and place them under certain reference conditions. It is considered that the influence of instability is not considered under these conditions. Take them out together after the expected stabilization time. Conduct simultaneous measurement under the repeatability conditions. The specific choice depends on the precision of the method and the stability of the sample. Accelerated stability studies or experience gained from similar in vitro diagnostic kits can only be considered for estimating the initial expiration date. It cannot substitute the real-time stability test.

The expected stable timeliness of the calibrator can be preliminarily determined by referring to the experience of literature and other materials in combination with the use of requirements. According to the principle of dense first then sparse, within at least 5 time-intervals of expected stable aging, randomly select at least 2 calibrators of the smallest packaging unit for stability test. Perform 3 measurements for each packaging unit. The test system used for stability inspection can choose the same test system as the uniformity inspection. The precision is not lower than the fixed value system, with good sensitivity and stability. Pay attention to the consistency of each experiment operation and experiment conditions.

**NOTE:** For calibrators with poor stability, increase the frequency of monitoring appropriately. For calibrators with poor uniformity between bottles, increase the amount of extraction at each time point. And for test systems with poor precision, the number of measurements per package can be increased.

#### 4.3.3 Result statistics

Check test data. Test data shall not be excluded for non-technical operation reasons.

Use t test to analyze the significance of the trend. Suppose there are stability

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When the user needs it, the manufacturer shall provide the user with the uncertainty of the calibrator assignment and be able to provide the uncertainty component results and uncertainty evaluation process.

It is recommended that the uncertainty of the product calibrator be reported in the form of standard uncertainty "(digital value assigned $\pm u_c$) unit". If it is reported in the form of expanded uncertainty "(assignment ± U numerical value) unit", it needs to specify the value of coverage factor k.

If the measurement uncertainty of the calibrator is less than the preset target uncertainty, the traceability of the calibrator's set value is confirmed. Otherwise, analyze and find the reasons, improve the preparation process or test system. Change the traceability chain if necessary and re-assign the calibrator assignment and uncertainty evaluation.

## 5 Uncertainty of changing batch of calibrator

Usually the calibrator needs to re-evaluate the uncertainty.

If the historical batch data of uncertainty component or combined uncertainty is used, the following conditions must be met:

a) The characteristic value of the calibrator varies within ±10%;

b) The source of key raw materials and article numbers have not changed, and the preparation process has not changed;

c) The calibrator assignment system (including traceability chain, working calibrator, equipment and operating procedures) has not changed;

d) There are 3 consecutive batches and above calibrator uncertainty evaluation data, showing that the variation of the combined standard uncertainty is within the allowable range specified by the manufacturer.

If both a) and b) are satisfied, the stability uncertainty component of historical batches can be quoted. But the stability shall still be monitored in real time. The manufacturer can accumulate multiple batches of stability data as the basis for evaluating stability and introducing uncertainty components.

If a)~d) are satisfied, the maximum uncertainty of the historical batch can be selected as the uncertainty of the future batch of calibrators. The manufacturer shall still periodically verify the validity of the uncertainty. Ensure to meet the requirements of target uncertainty and reflect changes in technical capabilities in a timely manner.

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# Annex B

(informative)

**Examples of uncertainty introduced by stability**

The uncertainty evaluation introduced by stability takes the calibrator of the Follicle Stimulating Hormone (FSH) project product of XX company as an example.

## B.1 Scheme

The calibrator is a lyophilized powder matrix. Store at 2°C~8°C. Expect good storage stability. Use the magnetic particle chemiluminescence method of the XX company's test system to test the long-term stability and short-term stability (including transportation stability and reconstitution stability) of the calibrator.

### B.1.1 Long-term stability

The calibrator shall be stored in accordance with the stipulated 2°C~8°C. Take out 2 bottles at 0, 3, 6, 9, 12, 15 and 18 months respectively. Each bottle is tested 3 times.

### B.1.2 Transport stability

Although cold chain transportation is adopted, changes in the transportation environment and time are considered to investigate transport stability at room temperature and 37°C. At 0d, 1d, 2d, 3d, 4d, 5d, 6d and 7d respectively, take out 2 bottles each at the simulated temperature. At the 7d, uniformly test under repeatable conditions. Each bottle is tested 3 times.

### B.1.3 Reconstitution stability

Use weighing method to reconstitute 2 bottles of calibrators. Store at 2°C~8°C. At 0d, 1d, 2d, 3d, 4d, 5d, 6d and 7d respectively, take out to test. Each bottle is tested 3 times.

## B.2 Inspection results

See Table B.1~Table B.4 for the results.

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# Annex C

(informative)

**Example of uncertainty evaluation introduced in process of valuing**

The uncertainty evaluation introduced in the valuing process takes the valuing process of the calibrator of XX company's total bilirubin (TBiL) project as an example.

## C.1 Valuing process

Perform product calibrator valuing with permanent measurement procedures. The permanent measurement program consists of a testing system composed of Beckman AU5800 automatic biochemical analyzer and supporting kits. It has been verified that the batch difference between the kits used can be ignored. Assignment experiment uses the same batch of kits. Use the company's working calibrator to calibrate the permanent measurement program. Take 2 product calibrators of the smallest packaging unit. Each unit is tested 5 times on 1 instrument each. Complete 5d experiments continuously. Daily test needs to be re-calibrated. Get a total of 50 test data. Obtain the product calibrator assignment after analysis.

Use new product calibrators and routine measurement procedures to form a measurement system. Directly test the national frozen human serum total bilirubin standard substance GBW09184. Compare with target value for assignment confirmation.

## C.2 Results

The specific assignment data is shown in Table C.1. Conduct statistics on suspicious value of 5d data. No need to exclude data for outlier review. Calculate its total mean value $\overline{\overline{X}}$ as the initial assignment of the calibrator.

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