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In vitro diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials

Dispositifs médicaux de diagnostic in vitro — Mesurage des grandeurs dans des échantillons d'origine biologique — Traçabilité métrologique des valeurs de concentration catalytique des enzymes attribuées aux agents d'étalonnage et aux matériaux de contrôle

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Foreword

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International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 18153 was prepared by the European Committee for Standardization (CEN) in collaboration with Technical Committee ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

Throughout the text of this document, read "...this European Standard..." to mean "...this International Standard...".

For the purposes of this International Standard, the CEN annex regarding fulfilment of European Council Directives has been removed.

Contents

Foreword

This document (EN ISO 18153:2003) has been prepared by Technical Committee CEN/TC 140 "In vitro diagnostic medical devices", the secretariat of which is held by DIN, in collaboration with Technical Committee ISO/TC 212 "Clinical laboratory testing and in vitro diagnostic test systems".

This European Standard EN ISO 18153:2003 including the Amendment shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by February 2004, and conflicting national standards shall be withdrawn at the latest by February 2004.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s).

For relationship with EU Directive(s), see informative annex ZA, which is an integral part of this document.

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the European Confederation of Laboratory Medicine (ECLM), and the European Diagnostic Manufacturers Association (EDMA) have contributed to its preparation.

This standard includes a Bibliography.

Annexes A and B are informative.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland and the United Kingdom.

Introduction

The Directive 98/79/EC on in vitro diagnostic medical devices requires that the metrologically traceability of values assigned to calibrators and control materials be assured through available reference measurement materials and reference measurement procedures of higher order. Following this concept, the European Standard prEN ISO 17511 on "traceability" has been elaborated which describes a hierarchical order of measurement procedures and calibration materials. The general rules expressed in that standard also apply to quantities involving catalytic activity. Whenever possible, metrological traceability should be demonstrated to the SI unit which forms the top of the calibration hierarchy.

For the measurement of the catalytic activity concentration of enzymes (hereafter called 'catalytic concentration'), a hierarchy of calibrators and measurement procedures is described in the present standard. For enzyme measurements, the definition of the derived coherent SI unit "mole per second cubic metre", given the special name "katal per cubic metre" by the General Conference on Weights and Measures, is the top of the hierarchy followed by a primary reference measurement procedure to which lower level measurement procedures, calibrators, and control materials should be traced whenever possible.

Enzymes in blood or other biological fluids can be measured for diagnostic purposes in terms of their catalytic concentrations. The analytical principle of the measurement of the catalytic rate of conversion of substrate has considerable advantages of speed, low limit of detection, analytical specificity, and low cost. Results of catalytic concentration measurements are only comparable if the enzyme activities are measured under the same conditions. Therefore, an enzyme measurand cannot be described only by kind-of-quantity (e.g. catalytic concentration), name of enzyme and of system, but requires also the specified measurement procedure and especially the indicator component of the measured reaction. At the top of the calibration hierarchy, the measurement procedure should be internationally agreed, e.g. 'creatine kinase measured by the conversion rate of NADH in the IFCC reference measurement procedure'.

Thus, the primary reference measurement procedure is an integral part of the definition of the measurand and has to be followed in all detail, e.g. as concerns:

— kind of substrate (where the specificity of the enzyme allows this to be varied) and its concentration,

— activators and their concentrations,

— direction of catalysed reaction,

— indicator component,

— buffer system and pH,

— temperature,

— pre-incubation time,

— material used for starting the reaction,

— lag time,

— reaction time.

The disadvantage of the procedure-dependence of the definition of the enzyme measurand and therefore of the results of the measurements are well known: problems are caused in external quality assessment (EQA) and in assessing the transferability of methods; a multiplicity of biological reference intervals exists with the consequent risk of clinical misinterpretation of enzyme results. The standardization of routine enzyme measurements is important to laboratory medicine, to improve the clinical utility and comparability of results through the elimination of existing differences in biological reference intervals.

Two approaches can be considered:

a) the exclusive routine use of a recommended or standardized procedure for each enzyme;

b) calibration of one or more routine procedures by commutable enzyme calibration materials with values assigned by a chosen reference measurement procedure.

The "recommended procedure" approach (a)) has been pursued vigorously for more than twenty years. It has had considerable success in improving the quality and comparability of enzyme measurements and in discouraging the use of analytically unsatisfactory procedures. However, the recommended-procedure-approach to standardization appears to have reached the limits of its usefulness. Its disadvantages include: absence of a consensus of choice among a number of differing recommendations; intentional or unintentional modification of recommended procedures in routine use; unresponsiveness of recommended procedures to analytical and technical improvement; and partly non-adaptability of recommended procedures to preferred automation. As a change in routine enzyme procedures, whether recommended or not, inevitably entails a change of biological reference values, it is understandably unwelcome to clinicians.

Improvement of the design and analytical performance of enzyme measurements will, and should, continue. However, this should follow the normal practice of development and dissemination of scientific advances. Attempts to develop and promote further standardized procedures for universal use are neither practicable nor desirable.

The "reference measurement procedure and calibration material" approach (b)) has, in contrast, received relatively little attention. Among the objections that have been raised are:

1. lack of stable enzyme reference materials in appropriate matrices to serve as calibrators;

2. dissimilarity between candidate enzyme calibrators and the analyte enzymes in human samples, including differences in isoforms;

3. absence of a constant inter-procedure ratio between a calibrating (reference) procedure and calibrated (routine) procedure(s), for both the enzyme calibrator and patients' samples containing the analyte enzyme (also described as a lack of commutability).

The converse of these objections constitutes a list of specifications, both for higher order enzyme reference materials and for families of measurement procedures between which calibration is proposed. The calibrator should be stable and have an analyte enzyme that is close in its catalytic properties within its matrix to those of the analyte enzyme in the routine samples. The procedures themselves should have the same specificity for the catalytic activity of the target enzyme.

Harmonization of the results of routine enzyme measurements can thus be achieved by selecting a reference measurement procedure and identifying a family of related procedures for each clinically important enzyme. Results obtained by any procedure included within such a family will be metrologically traceable to the chosen reference measurement procedure.

1 Scope

This European Standard specifies how to assure the metrological traceability of values assigned to calibrators and control materials intended to establish or verify trueness of measurement of the catalytic concentration of enzymes. The calibrators and control materials are those provided by the manufacturers as part of, or to be used together with, in vitro diagnostic medical devices.

The following subjects are outside the scope of this standard:

a) requirements for the design or selection of a reference measurement procedure;

b) quantities involving mass of enzyme or immunoreactivity of enzymes;

c) control materials that do not have an assigned value and are used only for assessing the precision of a measurement procedure, either its repeatability or reproducibility (precision control materials);

d) control materials intended for intralaboratory quality control purposes and supplied with intervals of suggested acceptable values, each interval obtained by interlaboratory consensus with respect to one specified measurement procedure, and with limiting values that are not metrologically traceable;

e) metrological traceability of routine results to the product calibrator and their relations to any medical discrimination limit;

f) properties involving nominal and ordinal scales.

2 Normative references

This European Standard incorporates by dated or undated reference, provisions from other publications. These normative references are cited at the appropriate places in the text, and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this European Standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publication referred to applies (including amendments).

prEN ISO 17511, *In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials: (ISO/FDIS 17511:2002)*

International Vocabulary of Basic and General Terms in Metrology, 2nd edition, Geneva: ISO, 1993[1)]

Guide to the Expression of Uncertainty in Measurement, 1st edition, Geneva:ISO, 1993[2)3)]

3 Terms and definitions

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

3.1
analyte
component indicated in the name of a measurable quantity

1) The abbreviation VIM:1993 is used in this standard

2) This monograph has been prepared simultaneously in English and French by a joint working group consisting of experts appointed by: BIPM (International Bureau of Weights and Measures), IEC (International Electrotechnical Commission), IFCC (International Federation of Clinical Chemistry and Laboratory Medicine), ISO (International Organization for Standardization), IUPAC (International Union of Pure and Applied Chemistry), IUPAP (International Union of Pure and Applied Physics), OIML (International Organization of Legal Metrology)

3) The abbreviation GUM:1993 is used in this standard

EXAMPLE In the type of quantity "catalytic concentration of lactate dehydrogenase isoenzyme 1 in plasma", "lactate dehydrogenase isoenzyme 1" is the analyte. The long phrase designates the measurand (see 3.5).

3.2
catalytic activity
***z*$_E$**
property of a component corresponding to the catalysed substance rate of conversion of a specified chemical reaction, in a specified measurement system

NOTE 1 Adapted from IUPAC/IFCC 1995:9.101.3.

NOTE 2 In this standard the "component" is an enzyme.

NOTE 3 The quantity "catalytic activity" relates to an amount of active enzyme, not its concentration, see 3.3.

NOTE 4 The coherent derived SI unit is "katal" (kat), equal to "mole per second" (mol s^{-1}).

NOTE 5 The measurement procedure is an essential element of the definition of the measurand.

NOTE 6 In many instances, instead of the conversion rate of the substrate ascribed in the short name of the enzyme analyte, e.g. "creatine" in "creatine kinase", the conversion rate of an indicator substance as substrate of a combined reaction is measured. Then the measurand should be defined as 'catalytic activity of the enzyme as measured by the conversion rate of an indicator substance in a specified system according to a given measurement procedure', e.g. 'catalytic activity of creatine kinase as measured by the rate of conversion of $NADP^+$ in the IFCC reference procedure in human serum'.

3.3
catalytic-activity concentration
catalytic concentration
***b*$_E$**
catalytic activity of a component divided by volume of the original system

NOTE 1 Adapted from IUPAC/IFCC 1995:9.104.2.

NOTE 2 The coherent derived SI unit is "katal per cubic metre" or "mole per second cubic metre" (kat m^{-3} = mol s^{-1} m^{-3}). In laboratory medicine, the unit of volume can be chosen to be "litre" (l).

NOTE 3 In this standard the "component" is an enzyme and the "original system" can be, e.g., the plasma of a blood sample.

3.4
commutability of a material
closeness of agreement between the mathematical relationship of the measurement results obtained by two measurement procedures for a stated quantity in a given material, and the mathematical relationship obtained for the quantity in routine samples

3.5
measurand
particular quantity subject to measurement

[VIM:1993, 2.6]

NOTE See 3.1, Example.

3.6
metrological traceability
property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties

[VIM:1993, 6.10]

NOTE 1 Each comparison is achieved by a (reference) measurement procedure defined in a calibration transfer protocol.

NOTE 2 There are several types of traceability. Therefore the term 'metrological traceability' is used in the present text.

4 Metrological traceability chain and calibration hierarchy

4.1 Principles

4.1.1 The nomenclature and basic principles of calibration and of metrological traceability of values obtained by measurement of quantities in biological samples as given in prEN ISO 17511 shall also apply when the analyte is an enzyme and the measurand is the derived kind-of-quantity "catalytic activity" (or a further derived kind-of-quantity, e.g., "catalytic concentration" or "catalytic content"). A typical number of levels in a calibration hierarchy is shown in Figure 1. The primary reference measurement procedure shall assign a value to a primary calibrator which is used for calibration of the next lower measurement procedure and so on to the results obtained by the end-user for a routine sample.

NOTE The term 'primary reference measurement procedure' as used here refers to a fully detailed set of measurement instructions whereas the term 'primary method of measurement' as defined by the Consultative Committee for Amount of Substance (CCQM) is a generic description of a measurement principle or a measurement method covering various procedures.

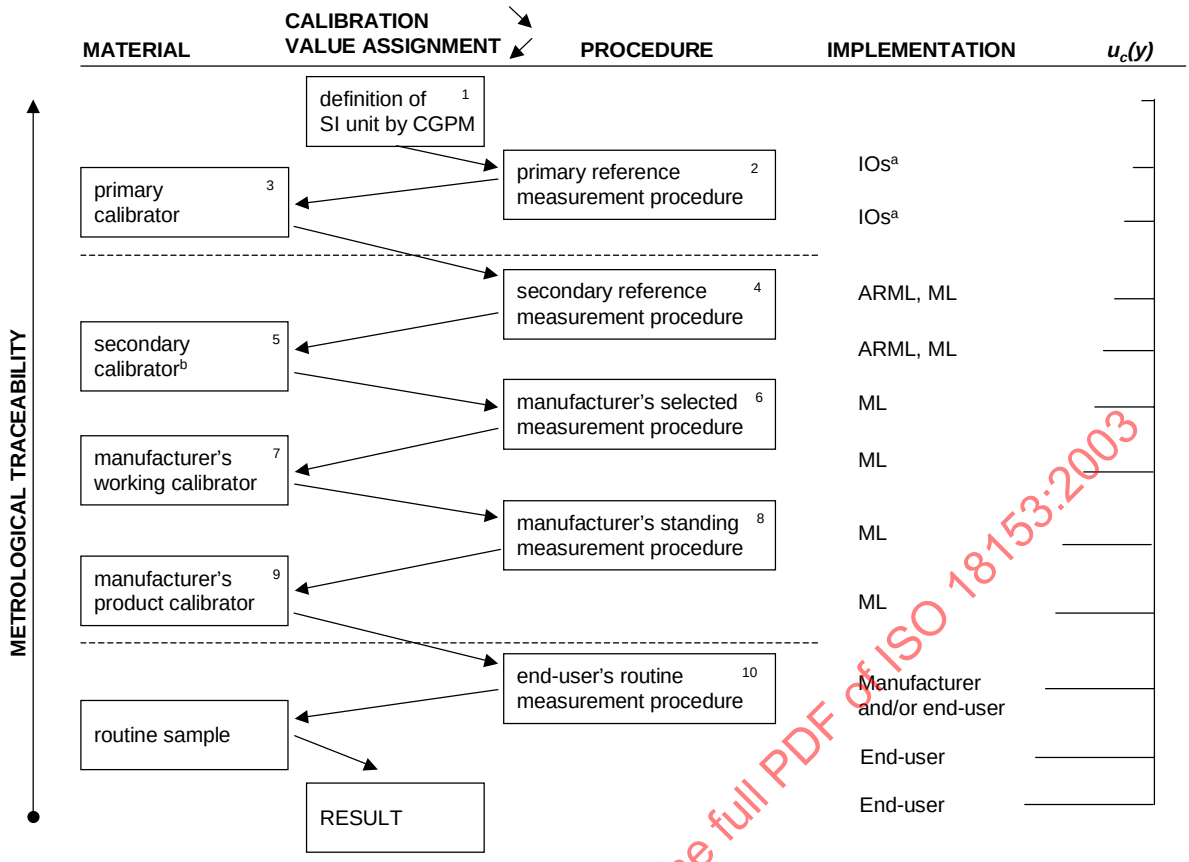
4.1.2 It is a prerequisite for the applicability of such a transfer protocol that the measurement procedures used in descending order in the hierarchical scheme measure the same quantity. Therefore, it shall be demonstrated that procedures subordinate to the primary reference measurement procedure in the calibration hierarchy measure the same measurands, e.g. the catalytic concentration of a particular isoenzyme or a group of isoforms to the same relative extent in a given system.

NOTE 1 Since the kind-of-quantity catalytic activity is defined by the rate of conversion of a specified substance in a specified reaction mixture (specified, e.g., as to substrate concentration, co-factors, volume fraction of analytical portion, temperature), the measurement conditions should be sufficiently similar throughout the descending order of measurement procedures. Deviations from those reaction conditions that will increase the uncertainty of the result assigned to a calibrator or control material should be avoided.

NOTE 2 The moderate catalytic specificity of some enzymes allows the nature of the substrate to be varied, but if the chosen substrate in a hierarchically lower measurement procedure varies from that in the reference measurement procedure, additional experimental evidence is needed to demonstrate that the same quantity is being measured in the modified procedure.

4.1.3 In principle, the primary reference measurement procedure and the manufacturer's product calibrator shall be required if metrological traceability to SI is to be claimed for the value assigned to a manufacturer's product calibrator.

NOTE To reduce uncertainty, it is desirable to omit as many pairs of consecutive levels (calibrator and procedure) of a calibration hierarchy as practicable.



The index numbers correspond to the third place decimal numbers in subclause 4.2. Further explanations are found in prEN ISO 17511.

Abbreviations: ARML Accredited reference measurement laboratory (such a laboratory may be an independent or a manufacturer's laboratory); BIPM International Bureau of Weights and Measures; CGPM General Conference on Weights and Measures; IOs International scientific organizations (e.g. IFCC); ML Manufacturer's laboratory; NMI National metrology institute.

The symbol $u_C(y)$ stands for combined standard uncertainty of measurement.
The horizontal bars at the extreme right under $u_C(y)$ are not to scale.

[a] In collaboration with BIPM, NMIs, ARMLs, and manufacturers

[b] The calibrator can be an appropriate surrogate reference material or a human sample.

Figure 1 – Extensive calibration hierarchy and metrological traceability to SI

4.2 Structure

4.2.1 The coherent derived *SI unit of measurement* "katal per cubic metre" or "mole per second cubic metre", symbolized kat m^{-3} (= mol s^{-1} m^{-3}) shall be the top of any calibration hierarchy for catalytic concentration of an enzyme when a primary reference measurement procedure is available.

NOTE 1 The kind–of-quantity "catalytic concentration" is catalytic activity of component in katal (or mole per second) divided by volume of (original) system sampled in cubic metres.

NOTE 2 In laboratory medicine, the denominator can be chosen to be "litre", giving the non-coherent derived unit "katal per litre", symbolized = kat l^{-1} = kat/l = mol s^{-1} l^{-1} = (mol/s)/l.

NOTE 3 Another, non-coherent unit used is based on the unit for catalytic activity "enzyme unit" (or "international unit"), symbolized U, with the conversion equation, 1 U = 1 µmol min^{-1} ≈ 16,667 × 10^{-9} kat. Consequently, 1 U/l ≈ 16,667 × 10^{-9} kat/l.

The unit of measurement is independent of the measurement procedure.

4.2.2 A *primary reference measurement procedure*, which by a description of the measuring system, including the reaction conditions, defines the measurand, especially the enzymatic component, shall preferably be the next level of a given calibration hierarchy, and the first operational level.

The results of measurement shall be given directly as catalytic concentration, e.g. in the derived SI unit katal per litre or mole per second litre, or one of its mutiples or submultiples as appropriate.

Each step of the measurement shall be clearly defined so that a standard uncertainty can be estimated. The function for calculating the value of the output quantity, the measurand, from all input quantities shall be given explicitly so that the combined uncertainty can be calculated preferably according to GUM:1993.

NOTE 1 The estimation of uncertainty requires that each measurement step is clearly described and controllable by experiment, which is not always the case for automated measurement procedures.

NOTE 2 The primary reference measurement procedure preferably should be recommended by international consensus, e.g. by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). If there is no internationally approved primary reference measurement procedure, a national metrology institute or scientific society can be encouraged to develop such a procedure for subsequent international endorsement.

NOTE 3 The IFCC is currently updating its reference measurement procedures to allow a reaction Celsius temperature of 37 ^{o}C instead of 30 ^{o}C. New 37° C reference measurement procedures for ALT, AST, CK, *γ*-GT and LDH have already been published. A list of primary reference measurement procedures is given in annex A.

4.2.3 A *primary calibrator* shall have its value and uncertainty of measurement assigned by a primary reference measurement procedure (see 4.2.2), through a formal interlaboratory certification exercise including evaluation of commutability.

NOTE 1 The preparation and certification of primary calibration materials should be undertaken on behalf of international organizations.

NOTE 2 Examples of primary calibrators are the BCR ® [4)] certified reference materials, developed within the "Measurement and Testing, Infrastructure" of the European Commission or by cooperation between the "Institute of Reference Materials and Measurements" (IRMM) of the European Union and the "IFCC".. They are listed in annex B.

4.2.4 A *secondary reference measurement procedure* shall describe a measuring system calibrated by one or more primary calibrators (see 4.2.3). The reaction conditions shall be such that the measurand is the same as that of the primary reference measurement procedure. The principles of description as well as of calculation of values and uncertainties given in 4.2.2 shall apply.

NOTE 1 For ease of operation, a secondary reference measurement procedure can be more mechanized than a primary one, but 4.2.2, Note 1 still applies.

NOTE 2 A secondary reference measurement procedure can be described and implemented by a reference measurement laboratory or by the manufacturer.

4.2.5 A *secondary calibrator* shall have its value assigned according to a secondary reference measurement procedure (see 4.2.4).

NOTE 1 A secondary calibrator can be accompanied by a certificate.

NOTE 2 The value assignment can occur in a reference measurement labotory or a manufacturer's laboratory.

[4)] BCR ® certified reference materials are an example of suitable products available commercially. This information is given for the convenience of users of this European Standard and does not constitute and endorsement by CEN of these products

NOTE 3 A secondary calibrator can be, e.g., a material with a matrix resembling those of the samples of human origin to be measured by the end-users' routine measurement procedures.

4.2.6 A *manufacturer's selected measurement procedure* shall define a measuring system which is calibrated by one or more primary or secondary calibrators when available.

NOTE A manufacturer's selected measurement procedure can be a secondary reference measurement procedure (see 4.2.4).

4.2.7 A *manufacturer's working calibrator* shall have its value and uncertainty of measurement assigned by a secondary reference measurement procedure (see 4.2.4) or directly by a primary reference measurement procedure (see 4.2.2) as appropriate. The calibration material shall have demonstrated adequate commutability as regards the reference measurement procedure and the procedure to be calibrated (see 5.3).

NOTE A manufacturer's working calibrator can be, e.g., a material with a matrix resembling those of the samples of human origin to be measured by the end-users' routine measurement procedures.

4.2.8 The *manufacturer's standing measurement procedure* shall be calibrated by one or more of the manufacturer's working calibrators (see 4.2.7) or by metrologically higher types of calibrator.

NOTE A manufacturer's standing measurement procedure is based on a system close to that of the routine measurement procedure, but can have a lower uncertainty of measurement obtained by smaller tolerance intervals of input quantities and influence quantities and by performing replicate measurements.

4.2.9 The *manufacturer's product calibrator* shall have its value and uncertainty assigned by the manufacturer's standing measurement procedure (see 4.2.8) or by any procedure of metrologically higher order. The calibration material shall be adequately commutable for the measurement procedure assigning its value and the routine measurement procedure.

4.2.10 The *end-user's routine measurement procedure* shall be calibrated by one or more of the manufacturer's product calibrators (see 4.2.9). It shall be the manufacturer's responsibility to demonstrate that the routine measurement procedure measures the same quantity in routine samples for which the procedure is intended as the primary reference measurement procedure.

5 Validation of metrologically traceable calibration

5.1 Principles

Trueness transfer shall be ensured by having essentially the same analytical specificities of the measurement procedures involved and by adequate commutability of the calibrators.

NOTE 1 The object of the use of metrologically traceable calibrators in routine measurement procedures, such as those of in-vitro diagnostic medical devices, is to produce a result of measurement of the measurand that is as close as required to that which would have been obtained if the reference measurement procedure to which the calibrators are metrologically traceable had been applied to the same samples. Thus, the trueness of results given by a calibrated routine measurement procedure derives from that of the reference measurement procedure when such is available.

NOTE 2 Depending on the nature of the enzyme analyte and the matrix of the samples, even minor differences in measuring systems and measurement steps between two measurement procedures can cause differences in specificity.

5.2 Analytical specificity of measurement procedures

5.2.1 Firstly, the properties of the candidate measurement procedures shall be properly described according to available information to render probable that they measure the same quantity.

EXAMPLE 1 Alanine aminotransferase (EC 2.6.1.2[4]) is influenced by pyridoxal phosphate, and measurement procedures may *a priori* be separated in two non-compatible families measuring different types of quantity according to whether or not this co-factor is a part of the reagent mixture or not.

EXAMPLE 2 α-Amylase (EC 3.2.1.1) has isoforms so that their respective relative catalytic activities should be compared for each pair of measurement procedures before making them part of a calibration hierarchy.

5.2.2 Secondly, it shall be demonstrated that all the measurement procedures in the vertical calibration hierarchy have essentially the same analytical specificity. A set of human samples shall be used, typical of the end-users' types of sample, and having values spanning the measuring interval to the extent practical.

To show essentially the same analytical specificity of two measurement procedures, the ratio between the results given by the two procedures on each sample shall be constant within the common measuring interval with a defined experimental uncertainty.

NOTE All measurement procedures exhibiting the same analytical specificity can be said to constitute a family of measurement procedures for that quantity.

5.3 Commutability of calibrators

5.3.1 The commutability of the manufacturer's working calibrator(s) shall be assessed by applying both reference measurement procedure and the routine measurement procedure to the manufacturer's working calibrator and to a set of relevant human (routine) samples.

If the mathematical relationship between the results of the reference measurement procedure, x, and the results of the routine measurement procedure, y, for the human samples is not statistically significantly different from that found for the manufacturer's working calibrator(s), then commutability of that calibrator material(s) shall have been demonstrated.

NOTE 1 If the spread of the points, (x, y), around the regression line and/or its offset are unacceptable, the reason for this outcome can be a difference in analytical specificity between the two measurement procedures.

NOTE 2 In cases where the mathematical relationship for human samples and the working calibrator is not the same, the difference can be accounted for by the correction factor or correction function applied to assign value(s) to the working calibrator(s). The correction factor or correction function should be available to users on request.

5.3.2 The validity of the manufacturer's product calibrator, shall be demonstrated by comparing the results of measurements, made by both the reference procedure and the calibrated routine procedure on a set of actual samples of a type to which the routine measurement procedure is intended to be applied.

The samples shall be preferably single-donation and unspiked human samples and shall have values as evenly distributed as practicable over the whole of the specified measuring interval for the type of quantity.

Spiking shall only be allowed if the resulting sample mimics natural samples.

5.4 Commutability of control materials

If a control material has a value assigned by a measurement procedure different from the routine measurement procedure, the commutability of the material shall be investigated in the same manner as for a calibration material.

4) Codenumber from Enzyme Commission of the the International Union of Biochemistry and Molecular Biology

Annex A
(informative)

List of IFCC primary reference measurement procedures

Here is a list of International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) primary reference measurement procedures:

1. Bergmeyer HU, Hørder M, Rej R. Approved recommendation (1985) on IFCC methods for the measurement of catalytic concentration of enzymes. Part 2. IFCC method for aspartate aminotransferase (L-aspartate:2-oxoglutarate aminotransferase, EC 2.6.1.1). J Clin Chem Clin Biochem 1986;24: 497-510.

2. Bergmeyer HU, Hørder M, Rej R. Approved recommendation (1985) on IFCC methods for the measurement of catalytic concentration of enzymes. Part 3. IFCC method for alanine aminotransferase (L-alanine:2-oxoglutarate aminotransferase, EC 2.6.1.2). J Clin Chem Clin Biochem 1986;24:481-95.

3. Shaw LM, Strømme JH, London JL, Theodorsen L. IFCC methods for the measurement of catalytic concentration of enzymes. Part 4. IFCC method for γ-glutamyltransferase [(γ-glutamyl)-peptide:amino acid γ-glutamyltransferase, EC 2.3.2.2). J Clin Chem Clin Biochem 1983;21:633-46.

4. Tietz NW, Rinker AD, Shaw LM. IFCC methods for the measurement of catalytic concentration of enzymes. Part 5. IFCC method (proposed) for alkaline phosphatase (orthophosphoric-monoester phosphohydrolase, alkaline optimum, EC 3.1.3.1). Clin Chim Acta 1983;135:339F-67F. J Clin Chem Clin Biochem 1983;21:731-48.

5. Hørder M, Elser RC, Gerhardt W, Mathieu M, Sampson EJ. Approved recommendation on IFCC methods for the measurement of catalytic concentration of enzymes. Part 7. IFCC method for creatine kinase (ATP:creatine *N*-phosphotransferase, EC 2.7.3.2). J Clin Chem Clin Biochem 1991; 29:435-56. JIFCC 1989;1(3):130-9; JIFCC 1990;2(1):26-35; JIFCC 1990;2(2):80-3.

6. Bais R, Philcox M. Approved recommendation on IFCC methods for the measurement of catalytic concentration of enzymes. Part 8. IFCC method for lactate dehydrogenase (L-lactate:NAD^+ oxidoreductase, EC 1.1.1.27). Eur J Clin Chem Clin Biochem 1994,32:639-55

7. Lorentz K. Approved recommendation on IFCC methods for the measurement of catalytic concentration of enzymes. Part 9. IFCC method for α-amylase (1,4-α-*D*-glucan 4-glucanohydrolase, EC 3.2.1.1). Clin Chem Lab Med 1998,36:185-203.