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In vitro diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values 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 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 17511 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 17511:2003) 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 17511:2003 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of an identical text or by endorsement, at the latest by February 2004, and conflicting national standards shall be withdrawn at the latest by February 2004.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).

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.

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

For measurements of quantities in laboratory medicine, it is essential that the quantity is adequately defined and that the results reported to the physicians or other health care personel and patients are adequately accurate (true and precise) to allow correct medical interpretation and comparability over time and space.

NOTE In this European Standard the concept "accuracy of measurement" (see 3.1) is related to both "trueness of measurement" (see 3.33) and "precision of measurement" (see 3.23) whereas the Directive 98/79/EC on in vitro diagnostic medical devices uses the term ‘‘accuracy’’ instead of ‘‘trueness’’.

To allow 'correct medical interpretation' involves more than the metrological (analytical) aspects of the traceability chain. As the measurement results are eventually used by the physician for the benefit of the patients, the physician should gather information on a number of other aspects, such as knowledge about the pre- and post-analytical phase, the diagnostic sensitivity and specificity, and relevant reference interval(s). The present European Standard deals only with the analytical aspects of measurements in Laboratory Medicine (see also 1 e)).

The measurement of quantities in biological samples requires reference measurement systems including:

- the definition of the analyte in the biological sample with regard to the intended clinical use of the measurement results;

- a reference measurement procedure for the selected quantity in human samples;

- suitable reference materials for the selected quantity, e.g. primary calibrators and secondary matrix-based calibrators that are commutable.

The trueness of measurement of a value assigned to a defined quantity of a calibrator or trueness control material, depends on the metrological traceability of the value through an unbroken chain of alternating measurement procedures and measurement standards (calibrators), usually having successively decreasing uncertainties of measurement (see Figure 1). The uncertainty of the value assigned to a given calibrator or trueness control material depends on the stated metrological traceability chain and the combined uncertainties of its links.

The ideal end-point of a metrological traceability chain is the definition of the relevant unit of the International System of Units (SI), but the selection of steps and the level at which metrological traceability for a given value stops, depend on the availability of higher order measurement procedures and calibrators. In many cases, at present, there is no metrological traceability above the manufacturer's selected measurement procedure or the manufacturer's working calibrator. In such cases, trueness is referred to that level of the calibration hierarchy until an internationally agreed reference measurement procedure and/or calibrator becomes available.

The objective of a chosen metrologically traceable calibration is to transfer the degree of trueness of a reference material, and/or reference measurement procedure, to a procedure that is of a lower metrological order, e.g. a routine procedure. Metrological traceability of calibration requires that the reference and routine measurement procedures measure the same measurable quantity with an analyte of the same pertinent characteristics.

In this context, it is important to recognize that different procedures purporting to measure the same quantity may in fact give different results when applied to a particular sample or reference material. This may arise, for example, when two or more immunoprocedures purporting to measure the concentration of a hormone such as thyrotropin (thyroid stimulating hormone, TSH) are applied to a reference material of the hormone, because the respective reagents recognize and react to different extents with various epitopes in the material, thus leading to results for different although related quantities.

Laboratory medicine routinely provides results for 400 to 700 types of quantity. For most of these, the metrological traceability of the assigned value for a product calibrator stops after only one metrologically higher step consisting of a (reference) measurement procedure, or after two steps consisting of a measurement procedure and a (reference) calibrator. The reason is that many of such quantities are related to mixtures of molecular species with clinically relevant properties in common, but with different structures and molecular masses in varying proportions, e.g. glycoproteins.

Depending on the possibility of metrological traceability to SI and on the availability of various metrological levels of measurement procedures and calibrators, the following five typical upper ends of the metrological traceability chain can be identified.

a) Quantities for which results of measurements are metrologically traceable to SI.

   A primary reference measurement procedure and one or more (certified) primary reference materials (used as calibrators) are available. These levels exist for approximately 25 to 30 types of quantity having well defined components, e.g. some electrolytes, metabolites, steroid hormones, and some thyroid hormones. These types of quantity cover a large proportion of the routine results provided by medical laboratories (see 4.2.2, 5.2, Figures 1 and 2).

b) Quantities for which results of measurements are not metrologically traceable to SI.

   1) An international conventional reference measurement procedure (see 3.12) (which cannot be called a primary reference measurement procedure) and one or more international conventional calibration materials (see 3.11) with values assigned by that procedure are available. These conditions apply for quantities with components such as HbA_{1c} (see 5.3 and Figure 3).

   2) An international conventional reference measurement procedure is available but no international conventional calibration materials. These conditions apply for about 30 types of quantity with components such as haemostatic factors (see 5.4 and Figure 4).

   3) One or more international conventional calibration materials (used as calibrators) with a protocol for value assignment are available, but no international conventional reference measurement procedure. These conditions apply for over 300 types of quantity, e.g., for quantities referred to World Health Organization's International Standards, such as protein hormones, some antibodies, and tumour markers (see 5.5 and Figure 5).

   4) Neither reference measurement procedure nor reference materials for calibration are available. The manufacturer can establish 'in-house' measurement procedure(s) and calibrator(s) to support value assignment to his product calibrator. These conditions apply for about 300 types of quantity with components such as tumour markers and antibodies (see 5.6 and Figure 6).

The principles of the respective transfer protocols (calibration hierarchies) are presented, given the provisions of the European Standards EN 12286 on presentation of reference measurement procedures and EN 12287 on the description of reference materials.

It is the aim of metrology in laboratory medicine to improve metrological traceability for results of a type of quantity from the conditions described under b2), b3), and b4) to those of b1) by providing the missing reference measurement procedures and reference materials, based on international consensus.

The special problems of metrological traceability for values of catalytic concentration of enzymes are considered in prEN ISO 18153.