First edition
2003-08-15

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

Reference number
ISO 18153:2003(E)

PDF disclaimer

This PDF file may contain embedded typefaces. In accordance with Adobe's licensing policy, this file may be printed or viewed but shall not be edited unless the typefaces which are embedded are licensed to and installed on the computer performing the editing. In downloading this file, parties accept therein the responsibility of not infringing Adobe's licensing policy. The ISO Central Secretariat accepts no liability in this area.

Adobe is a trademark of Adobe Systems Incorporated.

Details of the software products used to create this PDF file can be found in the General Info relative to the file; the PDF-creation parameters were optimized for printing. Every care has been taken to ensure that the file is suitable for use by ISO member bodies. In the unlikely event that a problem relating to it is found, please inform the Central Secretariat at the address given below.

ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

Published in Switzerland

Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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.