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February 2006

EP32-R

Metrological Traceability and Its Implementation; A Report

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This document provides guidance to manufacturers for establishing and reporting metrological traceability.

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Metrological Traceability and Its Implementation; A Report

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Abstract

Clinical and Laboratory Standards Institute document EP32-R—*Metrological Traceability and Its Implementation; A Report* provides guidance on establishing traceability of the chemical calibration step in clinical laboratory measurements, based on the traceability requirements for *in vitro* diagnostic (IVD) medical devices as given in ISO 17511[1] and ISO 15183,[2] and in accordance with the requirements for traceability as stated in the IVD Directive [i.e., Directive of the European Parliament on *In Vitro* Diagnostic Medical Devices (Directive 98/79/EC)[3]]. Though this report is aimed principally at manufacturers of IVD medical devices, the concepts and approaches recommended may be extended to apply to routine analysis conducted in the clinical laboratory either with commercially available or "home-brew" IVDs.

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Foreword

Clinical and Laboratory Standards Institute document EP32-R—*Metrological Traceability and Its Implementation; A Report* is intended to explain traceability, how it is established, and how it benefits the *in vitro* diagnostics (IVD) industry and the practice of clinical laboratory medicine.

Metrological traceability is one way to ensure comparability in laboratory test results between laboratories, regions, and countries. Much confusion exists on how to implement the traceability scheme on a practical level. For some measurands, there is a clearly established traceability pathway; for others, demonstrating traceability is more complex.

EP32-R explains the basics of traceability and defines a reference measurement system that includes reference materials, reference measurement procedures, and reference laboratories and laboratory networks.

EP32-R outlines what is required by manufacturers to demonstrate traceability, provides guidance on explaining the results of studies to the customers, and describes what laboratories must do to validate results based on traceability concepts. EP32-R has been developed as a companion to ISO 17511[1] and ISO 18153[2] standards on metrological traceability, and draws on discussions and outcomes of the Joint Committee on Traceability in Laboratory Medicine (JCTLM), which has developed criteria for acceptable reference materials and procedures and a provisional list of acceptable reference materials and procedures.

This report is intended for industry and clinical laboratorians.

The development of EP32-R—*Metrological Traceability and Its Implementation; A Report* is a joint responsibility of IFCC and CLSI. EP32-R has been developed by a working group composed of representatives from National Institute of Standards and Technology (NIST), International Bureau of Weights and Measures (BIPM), IFCC, and CLSI.

Key Words

Calibrator, certified reference material, commutability, metrological traceability, reference measurement procedure, uncertainty of measurement, validation, value assignment

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Metrological Traceability and Its Implementation; A Report

1 Scope

EP32-R provides guidance on establishing traceability of the chemical calibration step in clinical laboratory measurements, based on the traceability requirements for *in vitro* diagnostic (IVD) medical devices as given in ISO 17511[1] and ISO 18153,[2] and in accordance with the requirements for traceability as stated in the IVD Directive (i.e., Directive of the European Parliament on *In Vitro* Diagnostic Medical Devices Directive 98/79/EC[3]). Though this report is aimed principally at manufacturers of IVD medical devices, the concepts and approaches recommended may be extended to apply to routine analysis conducted in the clinical laboratory either with commercially available or "home-brew" IVDs.

This report specifically addresses traceability of the chemical calibration of a routine measurement procedure to the highest order reference that is available for a measurand. A traceable result requires that traceability be established for all quantities that have significant influence on the magnitude of the results. Traceability is discussed in more complete scope in other references, most notably, the Eurachem/CITAC[a] Guide: Traceability in Chemical Measurements[4] (available at http://www.measurementuncertainty.org/), the principles of which are applied for laboratory medicine in this report.

The primary area of activity to which this report can be applied is the determination of "assigned" values for calibrators and trueness controls for IVD measurement devices that are intended for use in the quantitative measurement of defined substances in human body fluids. While the focus of this report is on establishing traceability of manufacturers' product calibrators, this is likely to be the key element in the traceability of results at the patient bedside performed on bodily fluids from patients.

This report discusses measurement uncertainty and method validation in relation to their respective roles in achieving traceability. Detailed descriptions of these processes are not provided, and may be found elsewhere (see the References section).

Throughout this report, it is assumed that laboratories or manufacturing facilities following the present guidance have in place effective quality assurance and control measures to ensure that all applicable measurement processes are stable and in control. These measures include, but are not limited to, appropriately qualified staff, continuous documented training of the technical staff, proper maintenance of equipment, correctly prepared reagents, and use of documented measurement procedures and control charts. ISO 17025[5] provides a detailed description of the expectations of a competent laboratory responsible for chemical calibration and testing in general. ISO 15189[6] builds on ISO 17025[5] and provides recommendations specific to medical laboratories. Also of interest is ISO 15195[7] which identifies specific aspects of calibration laboratories in the field of laboratory medicine.

2 Introduction

The primary goal of laboratory medicine is to provide information that is useful to assist medical decision-making and foster optimal health care. This information should be interpretable regardless of the laboratory or particular device employed to measure it. To achieve this, one must be able to obtain equivalent measurement results for the same measurand from a variety of measurement procedures and laboratories.

The ability to achieve equivalent results depends on *traceability* to common standards and is facilitated by expressing results in common units. A traceability network and common units lead to a harmonized

[a] CITAC is the Cooperation of International Traceability in Analytical Chemistry.

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measurement system, enabling comparability over space and time, and also enable quality systems to be put in place to enhance the reliability of laboratory results.

Results from a harmonized measurement system support the establishment of common reference intervals and decision limits, which allows for global application of clinical study findings.

To meet the goal of uniformly interpretable clinical information, results from test kits deployed in the field must be traceable to references of higher order as described in Table 1. While several comparisons may be required to establish traceability between field results and higher order standards, there is no requirement that these comparisons be based on identical, or even similar, protocols. The acceptability of more than one protocol permits the creation of a chain of traceable results with minimal disruption of systems already in place. As established in ISO 17511[1] and ISO 18153[2], a reference of higher order (hereafter often termed merely "reference") can be a certified reference material, a reference measurement procedure, or a network of reference laboratories.

Table 1. Certified Reference Materials and Reference Measurement Procedures of Higher Order

ISO 17511	Category A	Category B
	"SI-traceable"	"NON-SI traceable;" arbitrary units e.g., WHO IUs

JCTLM	List 1	List 2
Characteristics	Trueness	NO trueness
	Precision	Precision
		Consistency of performance only
	Results independent of method/procedure	Results dependent on method/procedure

2.1 Quality in Laboratory Medicine

Over time, measurement science has developed a robust set of concepts for the systematic establishment of measurement quality. That system is based on establishing traceability of the measurement result to recognized references, on establishing an uncertainty budget for the measurement result, and on establishing the validity of the measurement approach being applied to determine the result.

ISO 17511[1] and ISO 18153[2] are intended to establish a framework of "metrological traceability" for delivery of clinical measurement results of known and appropriate quality. These documents are intended to provide guidance to realize that framework. ISO 17511 begins its introduction with the following statement:

> "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 personnel and patients are adequately accurate (true and precise) to allow correct medical interpretation and comparability over time and space." [1]

This statement refers to all three concepts that establish measurement quality: "*adequately defined and … adequately accurate (true and precise)…*" calls for a valid method with known uncertainty, and "*comparability over time and space*."

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Related CLSI/NCCLS Publications*

C24-A2 **Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline—Second Edition (1999).** This guideline provides definitions of analytical intervals, plans for quality control procedures, and guidance for quality control applications.

C37-A **Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for Cholesterol Measurement Procedures; Approved Guideline (1999).** This guideline details procedures for the manufacture and evaluation of human serum pools for cholesterol measurement.

EP5-A2 **Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline—Second Edition (2004).** This document provides guidance for designing an experiment to evaluate the precision performance of quantitative measurement methods; recommendations on comparing the resulting precision estimates with manufacturer's precision performance claims and determining when such comparisons are valid; as well as manufacturer's guidelines for establishing claims.

EP6-A **Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (2003).** This document provides guidance for characterizing the linearity of a method during a method evaluation; for checking linearity as part of routine quality assurance; and for determining and stating a manufacturer's claim for linear range.

EP9-A2 **Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (2002).** This document addresses procedures for determining the bias between two clinical methods or devices, and for the design of a method comparison experiment using split patient samples and data analysis.

EP10-A2 **Preliminary Evaluation of Quantitative Clinical Laboratory Methods; Approved Guideline—Second Edition (2002).** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of an analytical method or device.

EP12-A **User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline (2002).** This document contains a protocol that optimizes the experimental design for the evaluation of qualitative tests, to better measure performance and provide a structured data analysis.

EP14-A2 **Evaluation of Matrix Effects; Approved Guideline—Second Edition (2005).** This document provides guidance for evaluating the bias in analyte measurements that is due to the sample matrix (physiological or artificial) when two measurement procedures are compared.

EP15-A2 **User Demonstration of Performance for Precision and Accuracy; Approved Guideline—Second Edition (2005).** This document describes the demonstration of method precision and trueness for laboratory quantitative methods utilizing a protocol designed to be completed within five working days or less.

EP21-A **Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline (2003).** This document provides manufacturers and end users with a means to estimate total analytical error for an assay. A data collection protocol and an analysis method which can be used to judge the clinical acceptability of new methods using patient specimens are included. These tools can also monitor an assay's total analytical error by using quality control samples.

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