CLINICAL AND LABORATORY STANDARDS INSTITUTE®

2nd Edition

CLSI EP32™

Implementation of Metrological Traceability in Laboratory Medicine

CLSI EP32 provides guidance on establishing, validating, and documenting metrological traceability for end-user calibrators and results for human samples measured using *in vitro* diagnostic medical devices (IVD MDs) in medical laboratories based on the metrological traceability requirements for IVD MDs in ISO 17511.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

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Implementation of Metrological Traceability in Laboratory Medicine

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Abstract

Clinical and Laboratory Standards Institute EP32—*Implementation of Metrological Traceability in Laboratory Medicine* provides guidance on establishing, validating, and documenting metrological traceability for end-user calibrators and results for human samples measured using *in vitro* diagnostic medical devices (IVD MDs) in medical laboratories based on the metrological traceability requirements for IVD MDs in ISO 17511.[1] Though CLSI EP32 is intended for use primarily by manufacturers of IVD MDs, the concepts and approaches recommended may be extended to apply to measurements performed in the medical laboratory either with commercially available or laboratory-developed tests.[1]

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Foreword

CLSI EP32 provides guidance for *in vitro* diagnostic medical device (IVD MD) developers to implement metrological traceability in laboratory medicine and describes the benefits associated with its implementation.

CLSI EP32 aids in interpreting and implementing metrological traceability according to ISO 17511.[1] It also references the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommendations on assessing commutability of calibrators, when applicable, because their commutability is crucial for implementation of calibration hierarchies. CLSI EP32 covers the principles of all six model calibration hierarchies described in ISO 17511[1] and their implementation in situations representing substantial variations of the six model calibration hierarchies.

CLSI EP32 outlines what is required by IVD MD developers to establish metrological traceability. It provides guidance on explaining the results of studies to end users and describes what end-user laboratories must do to verify results based on traceability concepts. These concepts are explained in general terms in the main text and in detailed examples in the appendixes.

Establishing, validating, and documenting metrological traceability is part of a range of activities for improving and maintaining the usefulness of measurements performed in laboratory medicine and public health. Implementing metrological traceability is facilitated by different frameworks, such as those developed by formal national and international standardization programs or stakeholder organizations.

Examples of such frameworks are those from the Centers for Disease Control and Prevention's standardization programs for lipids, hormones, and vitamin D[2]; the NGSP for hemoglobin A_{1c} (HbA_{1c})[3]; and the IFCC (HbA_{1c}[4] and thyroxine).[5]

Reference measurement laboratories operating reference measurement procedures to assign values to human samples (HS) or calibration materials and trueness controls must provide information about the highest order of reference to which their measurement result is traceable and how this traceability was established, according to ISO 15195.[6]

Overview of Changes

CLSI EP32-Ed2 replaces the previous edition of the approved report, CLSI EP32-R, published in 2006. CLSI EP32 has been completely rewritten and focuses on reflecting the changes implemented in the current edition of ISO 17511,[1] specifically:

- Metrological traceability of measurement results for HS, not just values assigned to product calibrators
- Details on which calibrators in a calibration hierarchy must be commutable and how to handle noncommutability in these materials
- Discussion of validation of metrological traceability

Furthermore, seven worked examples have been developed to illustrate key aspects and considerations for different

calibration hierarchies. An introduction to the worked examples is found in Appendix A. The worked examples are included as Appendixes B through H:

- Appendix B: Worked Example of Glucose in Plasma
- Appendix C: Worked Example of pH in Whole Blood
- Appendix D: Worked Example of Alanine Aminotransferase Catalytic Concentration in Serum
- Appendix E: Worked Example of Free Thyroxine in Serum
- Appendix F: Worked Example of Hemoglobin A_{1c} in Whole Blood
- Appendix G: Worked Example of Human Chorionic Gonadotropin and Immunoglobulin G in Serum
- Appendix H: Worked Example of D-dimer in Serum

NOTE: The content of CLSI EP32 is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

KEY WORDS

calibration hierarchy
calibrator
certified reference material
commutability
measurement uncertainty
metrological traceability
reference measurement procedure
traceability chain
value assignment

Chapter 1

Introduction

Implementation of Metrological Traceability in Laboratory Medicine

1 Introduction

1.1 Scope

CLSI EP32 provides information for implementing metrological traceability according to ISO 17511.[1] It describes the necessary components and their use for *in vitro* diagnostic medical device (IVD MD) manufacturers to correctly establish, implement, and maintain metrological traceability. CLSI EP32 explains different calibration hierarchies for end-user medical laboratory measuring systems that are metrologically traceable to the highest available measurement procedures (MPs) and calibration materials.

CLSI EP32 describes related procedures (eg, commutability assessment, estimation of measurement uncertainty [MU], and analytical performance specifications [APS]) used in implementing metrological traceability. However, CLSI EP32 refers to other publications for detailed design and execution of these procedures.

1.2 Background

A primary goal of laboratory medicine is to provide test results to support clinical decision-making and foster optimal health care. The test results should be interpretable to end users regardless of the laboratory or IVD MD. The test results must be equivalent for the same measurand from various MPs and laboratories.

Metrological traceability is necessary for the establishment and maintenance of the equivalence of measurement results. Metrological traceability is a property of a measurement result that can be related to a higher-order reference material (RM) or reference measurement procedure (RMP) through a documented unbroken chain of calibrations, each contributing to the MU.

A reference selected for metrological traceability should have a characteristic(s) among the following:

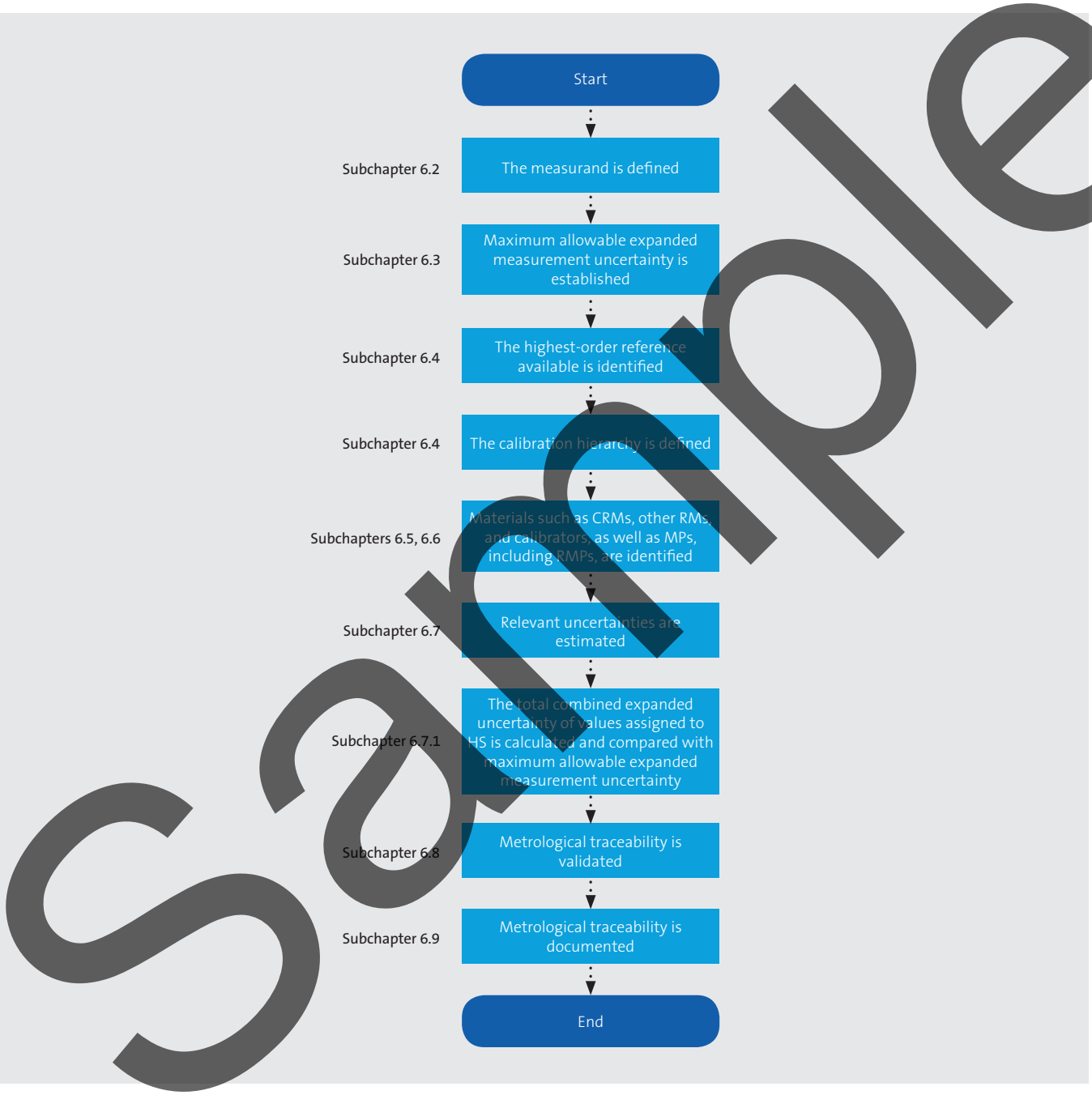
- Link of measured quantities to the definition of the International System of Units (SI)
- A certified value of an RM
- The value assigned using an RMP
- The value assigned to an international conventional calibrator (ICC)
- The values assigned through an international harmonization protocol

If none of the above characteristics is available, an IVD MD developer is responsible for defining its internal reference.

Measurements of distances, masses, and time are used routinely in many aspects of daily life and industry. Therefore, such measurements are often intuitively understood. In contrast, measurements in laboratory medicine are usually concerned with the concentration of molecules frequently present in very low concentrations among a multitude of other molecules that comprise the human sample (HS) matrix. Furthermore, the molecules are rarely measured directly. Instead, measurement signals related to the analyte concentrations in HS are created through selective chemical reactions to target the molecules of interest. These reactions can be detected using physical methods, commonly the absorbance or emission of light at specific wavelengths, voltages, or an electric current as illustrated in Figure 1.

2 Path of Workflow

Chapters 3 and 4 introduce and explain the concepts of metrological traceability and calibration hierarchies. Chapter 5 explains the concept and purpose of commutability. Chapter 6 follows the structure of ISO 17511[1] and is intended to help interpret how to meet the requirements stated in ISO 17511.[1] Chapter 6 also details the steps for establishing and validating metrological traceability (see Figure 2).



Abbreviations: CRM, certified reference material; HS, human sample(s); MP, measurement procedure; RM, reference material; RMP, reference measurement procedure.
[a] Three basic symbols are used in this process flow chart: oval (signifies the beginning or end of a process), arrow (connects process activities), box (designates process activities).

Figure 2. Process Flow Chart[a]

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