

EP34

Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking

It is often medically necessary to provide results for specimens with concentrations above the analytical measuring interval of an *in vitro* diagnostic measurement procedure. This guideline helps manufacturers and laboratory scientists with establishing, validating, or verifying a dilution scheme that will provide an extended measuring interval for such specimens.

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

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Abstract

Clinical and Laboratory Standards Institute guideline EP34—*Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking* provides recommendations for establishing a dilution scheme to be used for patient specimens that contain measurand concentrations in the extended measuring interval above a measurement procedure's upper limit of quantitation. Guidance is provided on determining, validating, and verifying the appropriate diluent and dilution ratio to be used for such specimens. This guideline also covers creating spiked samples for use during dilution recovery studies and using spiking to determine the suitability of a sample matrix for dilution recovery studies. The intended users of this guideline are manufacturers of *in vitro* diagnostic tests and medical laboratory scientists, directors, and pathologists.

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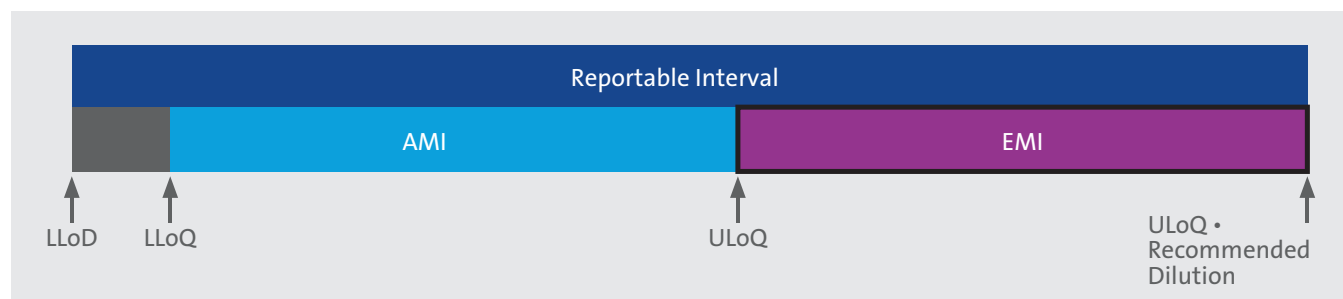
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Foreword

Measurement procedures provide measurand results within specified concentration intervals. These intervals are described in Figure 1.



Abbreviations: AMI, analytical measuring interval; EMI, extended measuring interval; LLoD, lower limit of detection; LLoQ, lower limit of quantitation; ULoQ, upper limit of quantitation.

Figure 1. Concentration Intervals

The **analytical measuring interval (AMI)** is the interval in which specimen concentrations are measured within the medical and laboratory needs for accuracy with no dilution, concentration, or other pretreatment not part of the standard or routine measurement process. The AMI includes the interval in which linearity, precision, and bias have been deemed acceptable and extends from the LLoQ to the ULoQ. The **extended measuring interval (EMI)** is the interval in which concentrations are measured with appropriate accuracy by diluting the specimen before taking a measurement with the developed measurement process. The upper limit of this interval is defined by the ULoQ multiplied by the dilution factor recommended in the established dilution scheme. The **reportable interval** includes the AMI and EMI but also extends to the LLoD. An example is included in Appendix A.

Guidance on determining the LLoD and LLoQ of the AMI is available in CLSI document EP17.¹ Guidance on determining the linearity interval is available in CLSI document EP06.² There is often great clinical need to provide results for specimens with measurand concentration values above the AMI. This guideline aims to assist manufacturers and laboratory scientists with establishing and verifying dilution schemes created to provide an EMI for such specimens.

Manufacturers typically provide recommendations on how to dilute a high-concentration specimen so its resultant concentration value is within the AMI. Thereafter, the measurand concentration value of the specimen before its dilution can be computed. The recommended dilution scheme should include the appropriate diluent and dilution ratio to ensure accurate dilution recovery. Manufacturers are encouraged to follow this guideline in developing measurement procedure—and measurand-specific dilution schemes. When manufacturers do not provide a dilution scheme that meets the laboratory's needs, the laboratory can use the techniques described in this guideline to determine an appropriate dilution scheme.

NOTE:

The AMI is the interval in which specimen concentrations are measured with appropriate accuracy with no dilution, concentration, or other pretreatment not part of the routine measurement process.

NOTE:

The EMI is the interval in which concentrations are measured with appropriate accuracy by diluting the specimen before taking a measurement.

For some measurement procedures, when a neat specimen is presented, the measuring system uses a process of treatment and conditional dilutions designed to expand the AMI without the need for preexamination dilution commonly used to create an EMI (see Appendix A). For such a measurement procedure, its performance within its AMI should be measured like any standard quantitative procedure. The performance of its internal dilution steps can be tested using some of the procedures provided in this guideline, but the specific testing of an EMI is not necessary unless an examination dilution is also provided as an option.

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

KEY WORDS

Analytical measuring interval

Extended measuring interval

Upper limit of quantitation

Diluent

Recovery

Dilution

Spiking

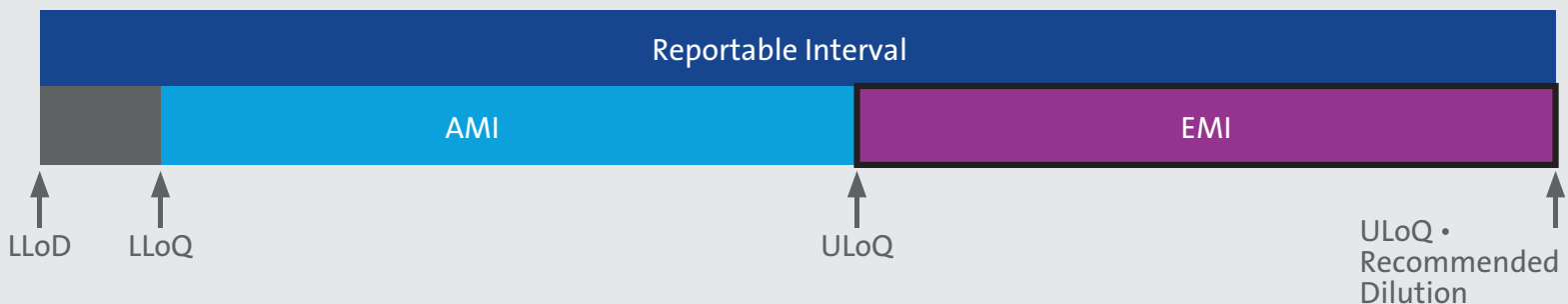
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Chapter 1

Introduction

This chapter includes:

- Guideline's scope and applicable exclusions
- Background information pertinent to the guideline's content
- Standard precautions information
- "Note on Terminology" that highlights particular use and/or variation in use of terms and/or definitions
- Terms and definitions used in the guideline
- Abbreviations and acronyms used in the guideline



Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking

1 Introduction

In vitro diagnostic (IVD) device manufacturers often find that to meet clinical needs, a dilution scheme is necessary to measure accurate results beyond the analytical measuring interval (AMI). Establishing and characterizing the dilution scheme using dilution and spiking studies occurs during manufacturers' internal measurement procedure development. This step is followed by validation of the selected dilution scheme and the extended measuring interval (EMI). Finally, the dilution scheme is verified in the laboratory before being used with patient specimens. This wider interval of reportable results provides physicians with important information for screening, diagnosing, monitoring, and treating patients.

1.1 Scope

This guideline provides procedures for establishing, validating, and verifying a dilution scheme to use for obtaining results for patient specimens with measurand concentrations or activity values above a measurement procedure's upper limit of quantitation (ULoQ). This guideline is intended to be used for measurement procedures that have an established AMI within which linearity, precision, and bias have been deemed acceptable. Guidance is provided on determining the appropriate diluent and dilution ratio for these specimens. This guideline also covers creating spiked samples for dilution recovery studies and using spiking studies to determine the suitability of a specimen type for dilution recovery studies. This guideline covers the measurement procedure after it meets design inputs and the resultant AMI has been established. The intended users of this guideline are IVD measuring system manufacturers and medical laboratory scientists, directors, and pathologists.

This guideline does not cover the process of developing a measurement procedure or determining the AMI or interval in which incremental results linearly correspond to increments in a measurand. Thus, it does not cover instituting a set of autonomous dilution steps or reflex examinations as part of the measurement procedure to create accurate results within the AMI. However, it is possible to test the performance of a measuring system's autonomous dilution steps using the protocols described in this guideline.

NOTE:

This guideline covers an already established measurement procedure with an AMI within which acceptable linearity, precision, and bias have been demonstrated.

NOTE:

A measurement procedure may include numerous steps, including dilutions and reflex examinations. However, this guideline does not cover the development of such processes.