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CLINICAL AND LABORATORY STANDARDS INSTITUTE®

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I/LA21-A2

Clinical Evaluation of Immunoassays; Approved Guideline—Second Edition

This document addresses the need for clinical evaluation of new immunoassays and new applications of existing assays, as well as multiple assay formats and their uses. As a guide to designing and executing a clinical evaluation, this document will aid developers of "in-house" assays for institutional use, developers of assays used for monitoring pharmacologic effects of new drugs or biologics, and clinical and regulatory personnel responsible for commercializing products.

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

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Clinical Evaluation of Immunoassays; Approved Guideline—Second Edition

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Abstract

Clinical and Laboratory Standards Institute document I/LA21-A2—*Clinical Evaluation of Immunoassays; Approved Guideline—Second Edition* addresses all aspects of the clinical evaluation of immunoassays developed for commercial or in-house use.

Existing CLSI documents provide guidance for assessing analytical performance, methods comparison, and clinical accuracy of laboratory tests. This document focuses on unique characteristics of immunoassays, and provides a guide to designing, executing, and analyzing a clinical evaluation. In addition, this document will aid developers of "in-house" assays for institutional use, developers of assays used for monitoring pharmacologic effects of new drugs or biologics, and clinical and regulatory personnel responsible for commercializing products.

The elements of this guideline include: 1) a development plan for an effective analysis and evaluation; 2) a discussion of the planning and design considerations that are necessary for a successful evaluation; 3) a description of requirements for conducting the evaluation through monitoring and database management; and 4) a brief review of the analytical performance measures that must be in place before testing clinical specimens.

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Foreword

This document updates previous guidelines describing the requirements for the clinical evaluation of immunoassays. In preparing this guideline, the working group considered three areas of need regarding the clinical use of immunoassays: 1) for laboratories engaged in the development of immunoassays for use within their institutions, this guideline will provide direction in designing an evaluation of the assay's clinical performance; 2) for those scientists involved in evaluating new therapeutic agents, this guideline will provide direction in establishing immunoassays as reliable clinical end points; and 3) for manufacturers of *in vitro* diagnostic assays, this guideline will provide a checklist to review against their approach to addressing regulatory requirements for commercialization of products.

For the purposes of this document, clinical performance refers to correct classification (ie, clinical [diagnostic] sensitivity and specificity) and does not refer to clinical utility, which may include the effects of environment, economy, and patient outcomes. While there is mention of an assay's analytical performance, users should refer to existing CLSI documents (see the Related CLSI Reference Materials section) and to other sources for more detailed information.

Because the scope of this document does not limit its application to industry or to the clinical or research laboratory, the working group has used the term *clinical evaluation* in place of "clinical study" or "clinical trial." While considered interchangeable from the working group's perspective, the reader should use the term that is appropriate for his or her institution.

It should also be acknowledged that there are different types of evaluations for new assays, including comparative and clinical. Comparative evaluations are typically performed when the laboratorian is considering substituting an assay from one manufacturer with another from a different manufacturer. While having its own unique forms of execution and analyses, this evaluation is simply comparing one assay to another without the postulation of any clinical questions. See the related reference for comparative evaluations (see CLSI/NCCLS document EP09).[1] While it may involve a comparative approach, the clinical evaluation is required for the application of a new assay, a new analyte (measurand), or for a new, intended use of an existing analyte (measurand).

In the assay development to implementation/commercialization continuum, this guideline addresses the activities associated with preclinical testing and clinical evaluation requirements, evaluation design, and analysis. While written for immunoassay developers, the information has broad application to other clinical and research assay formats.

This Revision

During the revision process, the working group updated the content and expanded the current document for assessment of immunoassays to include specific details on selection and use of test specimen panels; specimen library collections; reference panels including specimen commutability issues; and sample size considerations for evaluation studies. An appendix was also added to guide the user in sample size selections. Numerous revisions were made to enhance and ensure global applications.

Key Words

clinical evaluation, clinical evaluation investigator, clinical performance characteristics, database management, diagnostic evaluation, diagnostic performance characteristics, evaluation population, informed consent, institutional review board, pilot evaluation, sponsor, statistical tests

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1 Scope

This document provides specific recommendations for the clinical evaluation of new immunoassays and new applications of existing assays, as well as multiple assay formats and their uses. It focuses on unique characteristics of immunoassays, and provides a guide to designing, executing, and analyzing a clinical evaluation.

The intended users of this guideline are developers of "in-house" assays for institutional use, developers of assays used for monitoring pharmacologic effects of new drugs or biologics, and clinical and regulatory personnel responsible for commercializing products.

2 Introduction

In vitro diagnostic (IVD) assay development occurs in multiple environments, each with different requirements for the actual use of the assay. Developers that manufacture and market their assays are required to obtain approval in accordance with regulations in countries where the product is being registered or used. (Consult appropriate local regulations and institutional policies for specific applications.) Others may develop assays that do not require the same extent of testing and review. For example, clinical and research laboratories may develop assays for use within their institutions, thereby limiting the assay's use to a select patient population. Another example is the development of research assays for use in monitoring pharmacologic effects or unfavorable reactions. A third example is the development of assays for point-of-care (POC) testing, which require evaluation under conditions in which the assay is performed. This document addresses the need for clinical evaluation of new immunoassays and new applications of existing assays, as well as multiple assay formats and their uses. Whatever the intended use, the assay can only provide medical benefit when it has undergone adequate clinical evaluation.

Separated into four basic sections, this guidance is intended to provide all assay developers with a consistent approach to establishing clinical performance characteristics. First, the immunoassay (preclinical) evaluation is described, including recommendations for establishing analytical performance. Second, the planning and design of the clinical evaluation is discussed. Third, a description of conducting the clinical evaluation is given; and fourth, analysis and summary documentation is reviewed.

3 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to "standard precautions." Standard precautions are guidelines that combine the major features of "universal precautions and body substance isolation" practices. Standard precautions cover the transmission of all infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the US Centers for Disease Control and Prevention.[2] For specific precautions for preventing the laboratory transmission of all infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious disease, refer to CLSI document M29.[3]

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