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Clinical Evaluation of Immunoassays; Approved Guideline

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

A guideline for global application developed through the NCCLS consensus process.

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Clinical Evaluation of Immunoassays; Approved Guideline

Abstract

This document addresses the need for the clinical evaluation of new immunoassays and new applications of existing assays. Existing NCCLS documents provide guidance for assessing analytical performance, methods comparison, and clinical accuracy of laboratory tests. However, none of the documents define the elements that are integral to generating clinical data. As a guide to designing, executing, and analyzing a clinical evaluation, this document will aid clinical and regulatory personnel responsible for commercializing products, developers of "in-house" assays for institutional use, and developers of assays used for monitoring pharmacologic effects of new drugs or biologics.

The elements of this guideline include (1) a brief review of the analytical performance measures that must be in place prior to testing clinical specimens; (2) a thorough 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 development plan for an effective analysis and evaluation.

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Contents

Foreword

Currently, no uniform guidelines exist that adequately describe the requirements for the clinical evaluation of immunoassays. Historically, assay developers—primarily *in vitro* diagnostic manufacturers—have based their approach to designing and conducting clinical evaluations on what may be required by government regulatory agencies, who review the demonstration of safety and effectiveness. Increasingly, assays developed by nongovernment-regulated entities are being used as clinical measures. These assays may include those developed for the purpose of measuring end points of drugs under development. While these end-point assays may provide appropriate analysis of analytical performance that is consistent with laboratory requirements and regulations, evaluation of clinical performance may be incomplete or lacking.

In preparing this guideline, the subcommittee considered three areas of need regarding the clinical use of immunoassays. First, 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. Second, 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. And third, for those scientists involved in evaluating new therapeutic agents, this guideline will provide direction in establishing immunoassays as reliable clinical end points.

For the purposes of this document, clinical performance refers to accuracy— correct classification, i.e., clinical 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 NCCLS documents (see Related NCCLS Publications) 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 subcommittee has used the term "clinical evaluation" in place of "clinical study" or "clinical trial." While considered interchangeable from the subcommittee's perspective, the reader should use the term that is appropriate for the reader's 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. A reference for comparative evaluations is NCCLS document EP9—*Method Comparison and Bias Estimation Using Patient Samples*. While it may involve a comparative approach, the clinical evaluation is required for the application of a new assay, a new analyte, or for a new, intended use of an existing analyte.

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 assay formats. It is the subcommittee's intent that this document will be expanded to ensure that the full range of *in vitro* diagnostic assays is addressed.

A Note on Terminology

NCCLS, as a global leader in standardization and harmonization, is firmly committed to achieving global harmonization wherever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. NCCLS recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in NCCLS, ISO, and CEN documents; and that

legally required use of terms, regional usage, and different consensus timelines are all obstacles to harmonization. In light of this, NCCLS recognizes that harmonization of terms facilitates the global application of standards and is an area of immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

In the context of this document, it is necessary to point out that several terms are used differently in the USA and other countries, notably those in Europe.

In Europe the term "performance evaluation" is used for the assessment of quality of *in vitro* diagnostic products both with their analytical and medical (diagnostic) characteristics. "Clinical evaluation" in European terms is applied mostly to the evaluation of medical products, which are used on or in patients or when it refers to clinical studies of drugs, under much more stringent conditions. Appropriately, the USA term "clinical evaluation" in the context of this document would translate into "diagnostic evaluation" in Europe. Consequently, the terms "diagnostic sensitivity" and "diagnostic specificity" are used in Europe, with the corresponding expressions "clinical sensitivity" and "clinical specificity" in the USA, as they are applied in this document.

Also, in order to align the usage of terms to ISO, the term "trueness" is used in this document when referring to the closeness of the agreement between the average value from a large series of measurements and to a true value of a measurand. The term "accuracy," in its metrological sense, refers to the closeness of the agreement between the result of a (single) measurement and a true value of a measurand, thus comprising both random and systematic effects.

All terms and definitions will be reviewed again for consistency with international use, and revised appropriately during the next scheduled revision of this document.

Standard Precautions

Because it is often impossible to know what might be infectious, all human blood specimens are to be treated as infectious and handled according to “standard precautions.” Standard precautions are new guidelines that combine the major features of “universal precautions and body substance isolation” practices. Standard precautions cover the transmission of any pathogen and thus are more comprehensive than universal precautions which are intended to apply only to transmission of blood-borne pathogens. Standard precaution and universal precaution guidelines are available from the U.S. Centers for Disease Control and Prevention (*Guideline for Isolation Precautions in Hospitals*. Infection Control and Hospital Epidemiology. CDC. 1996;Vol 17;1:53-80), (MMWR 1987;36[suppl 2S]2S-18S), and (MMWR 1988;37:377-382, 387-388). For specific precautions for preventing the laboratory transmission of blood-borne infection from laboratory instruments and materials and for recommendations for the management of blood-borne exposure, refer to NCCLS document M29—*Protection of Laboratory Workers from Occupationally Acquired Infections*.

Key Words

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

The Quality System Approach

NCCLS subscribes to a quality system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents through a gap analysis. The approach is based on the model presented in the most current edition of NCCLS HS1— *A Quality System Model for Health Care.* The quality system approach applies a core set of "quality system essentials (QSEs)," basic to any organization, to all operations in any healthcare service's path of workflow. The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The quality system essentials (QSEs) are:

QSEs

Documents & Records	Information Management
Organization	Occurrence Management
Personnel	Assessment
Equipment	Process Improvement
Purchasing & Inventory	Service & Satisfaction
Process Control	Facilities & Safety

NCCLS document I/LA21-A—*Clinical Evaluation of Immunoassays* addresses the following Quality System Essentials (QSEs)

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessment	Process Improvement	Service & Satisfaction	Facilities & Safety
X			X		X	X					

Adapted from NCCLS document HS1—*A Quality System Model for Health Care.*

Clinical Evaluation of Immunoassays; Approved Guideline

1 Introduction

In vitro diagnostic 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 governmental approval or clearance in some countries, such as in the U.S., prior to commercial sales. Others may develop assays that do not require the same extent of testing and review. For example, clinical 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. Whatever the intended use, the assay can only provide medical benefit when it has undergone adequate clinical evaluation.

This document provides uniform guidelines for clinical evaluation of *in vitro* diagnostic immunoassays. 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 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 evaluation is given, and fourth, analysis and summary documentation is reviewed.

1.1 Scope

The scope of this document is to provide guidance for evaluating the clinical performance characteristics of an immunoassay, with no regard to the status or environment of the assay developer. The information provided will have broad applications to multiple assay formats and their uses.

1.2 Definitions[a]

Accuracy// Measurement accuracy// Accuracy of measurement, *n* - Closeness of the agreement between the result of a measurement and a true value of the measurand {/analyte}; See **Trueness**.

Analytical specificity, *n* - The ability of a measurement procedure to determine solely the measurable quantity it purports to measure.

Clinical evaluation, *n* - An investigation of the clinical performance characteristics of a new (or new indication for use) *in vitro* diagnostic assay in controlled clinical settings; NOTE**:** The term "clinical evaluation" is equivalent to the term "diagnostic evaluation."

Clinical feasibility/Pilot evaluation, *n* – An evaluation performed using patient specimens to assess the potential application of a new assay to some clinical use; **NOTE:** Typically conducted by the sponsor, the evaluation may take place in a clinical setting or in the sponsor's laboratory.

Clinical investigator, *n* – A person under whose direction a clinical evaluation is conducted.

Clinical sensitivity, *n* - The proportion of patients with a well-defined clinical disorder whose test values are positive or exceed a defined decision limit (i.e., a positive result and identification of the patients who have a disease); **NOTES:** a) It is the fraction of clinically true positive classifications divided by the sum

[a] Some of these definitions are found in NCCLS document NRSCL8—*Terminology and Definitions for Use in NCCLS Documents.* For complete definitions and detailed source information, please refer to the most current edition of that document.