CLSI: Overview

2018 OIR Submissions Workshop

Marina V. Kondratovich, Ph.D.
Associate Director for Clinical Studies
OIR, CDRH, FDA

April 16, 2018

FDA

- Commitment to good science – valid scientific evidence

- Commitment to standards –

  original force in CLSI,

  outspoken participant,

  one of the primary users

- Involves OIR staff in drafting and recognition

FDA and Standards

- Mechanisms for plugging into review process
- Most of standards used in OIR are CLSI documents
- Most of OIR submissions have some citation to a CLSI document

What is CLSI? www.clsi.org

- An accredited consensus standards organization
- A not-for-profit organization
- An educational organization
- A global organization
- A volunteer organization

Balanced - by representatives from industry, government, and professionals (if the document is relevant for the OIR reviews – FDA participates);

Practical – addressed to non-statisticians, technically – good enough;

Timely - to keep pace with technological change and better development of concepts in laboratory medicine science (revision after 5 years or earlier)

WHY use CLSI guidance

- Provides framework for types of studies along with study designs and data analysis
- Scientifically sound methods not described in the CLSI documents
- CLSI documents have usually state-of-the-art concepts
- Speed review time at FDA

Guidelines

- Nonbinding
- Flexible

CLSI Evaluation Protocols

- Good news – broad use, general;
  good science;
  an engine for developing concepts in laboratory medicine science

- Bad news – horizontal standards sometimes lack clarity for some particular type of IVD devices (e.g., EP05 for fingerstick?);
  are used in part, not total;
  underlying assumptions in the CLSI guidance for analysis may be not met (e.g., assumption in EP06 about constant SD))

Understand the intent of CLSI document

- Read Forward, Scope and Introduction

Understand the intended users of CLSI document

- Developer (manufacturer, laboratory developing the test), laboratorian
- Sections that have “Validation”, “Establishing” in titles is usually for manufacturers
- Sections that have “Verification” in titles is usually for laboratorians

Appendices with Examples in the end of CLSI document

Recognition by FDA

- After CLSI document is published, this document is considered for recognition.
- If the CLSI document is irrelevant for OIR reviews, the document is not considered for recognition (for example, document can be used only by laboratorians)
- CLSI document can be recognized as “complete” or “partial”

Link to database with FDA recognized documents
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

Recognition by FDA

Link to database with FDA recognized documents
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

- In search, use “CLSI”

- Then click on the title of the CLSI document, see whether recognition is “complete” or “partial”

- Technical contacts – questions ONLY about CLSI document

Harmonized Terminology Database

http://htd.clsi.org/

Definition in blue – internationally preferred
Definition in black – acceptable
Definition in red – not acceptable in the international standard community

Example:

accuracy
(of measurement) closeness of agreement between a measured quantity value and a true quantity value of a measurand (JCGM 200:2012)

accuracy
1) how close a test result for a specific analyte is to how much of the analyte is there; 2) the closeness of agreement between a test result and the accepted reference value (ISO 5725-1)
Project: POCT08

EP19-Ed2 “A Framework for Using CLSI Documents to Evaluate Clinical Laboratory Measurement Procedures, 2nd Edition”.

- Published in June, 2015
- Free
- FDA recognized

- Quantitative test – most of CLSI EP documents
- Qualitative (Binary) test – EP12
- Semi-quantitative test - ???

Next slides:
List of CLSI EP documents – green (new ones, last 4 years),
red (under revision)

Status of CLSI EP documents, April 2018

	Code	Title	Comments
1	**EP05-A3**	**Evaluation of Precision Of Quantitative Measurement Procedures**	**Published in Sept., 2014; Recognized by FDA**
2	**EP06-A**	**Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach**	**Published in Apr., 2003; Recognized by FDA; Under revision**
3	**EP07-A2**	**Interference Testing in Clinical Chemistry**	**Published in Nov., 2005; Recognized by FDA; EP07-A3 ready for publication**
4	**EP09-A3**	**Measurement Procedure Comparison and Bias Estimation Using Patient Samples**	**Published in Aug., 2013; Recognized by FDA => Revision will be published**
5	**EP10-A3**	Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures	Not used by OIR; Not recognized by FDA

Status of CLSI EP documents, April 2018 (cont.)

	Code	Title	Comments
6	EP12-A2	User Protocol for Evaluation of Qualitative Test Performance	Published in Jan., 2008; Recognized by FDA; Under revision
7	EP14-A3	Evaluation of Commutability of Processed Samples	Published in Aug., 2014; Recognized by FDA
8	EP15-A3	User Verification of Precision and Estimation of Bias	Published in Sept., 2014; Recognized by FDA
9	EP17-A2	Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures	Published in June, 2012; Recognized by FDA
10	EP18-A2	Risk Management Techniques to Identify and Control Laboratory Error Sources	Published in Nov., 2009; Recognized by FDA

Status of CLSI EP documents, April 2018 (cont.)

	Code	Title	Comments
11	**EP19-Ed2**	**Framework for CLSI EP Protocols**	**Published in June, 2015; Recognized by FDA**
12	**EP21-2nd Ed.**	**Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures**	**Published in July, 2016; Recognized by FDA**
13	**EP23-A**	**Laboratory Quality Control Based on Risk Management**	**Not used by OIR; Not recognized by FDA**
14	**EP24-A2**	**Assessment of the Diagnostic Accuracy of Laboratory Tests Using Receiver Operating Characteristic Curves**	**Published in July, 2011; Partially recognized by FDA (Issues with selecting a cutoff)**
15	**EP25-A**	**Evaluation of Stability of in Vitro Diagnostic Reagents**	**Published in Sept., 2009; Recognized by FDA; Under revision.**
16	**EP26-A**	**User Evaluation of Between-Reagent Lot Variation**	**Not used by OIR; Not recognized by FDA**

Status of CLSI EP documents, April 2018 (cont.)

	Code	Title	Comments
17	**EP27-A**	**How to Construct and Interpret an Error Grid for Quantitative Diagnostic Assays**	**Published in Sept., 2012; Not recognized by FDA =>revision**
18	**EP28-A3c (old C28-A3c)**	**Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory**	**Published in Oct., 2010; Recognized by FDA**
19	**EP29-A (old C51-A)**	**Expression of Measurement Uncertainty in Laboratory Medicine**	**Not used by OIR; Not recognized by FDA**
20	**EP30-A (old C53-A)**	**Characterization and Qualification of Commutable Reference Materials for Laboratory Medicine**	**Not used by OIR; Not recognized by FDA**
21	**EP31-A-IR (old C54-A-IR)**	**Verification of Comparability of Patient Results Within One Health Care System**	**Not used by OIR; Not recognized by FDA**
22	**EP32-R (old X05-R)**	**Metrological Traceability**	**Published in Feb., 2006; Recognized by FDA; Under revision**

Status of CLSI EP documents, April 2018 (cont.)

	Code	Title	Comments
23	EP33	Delta Checks to Detect Patient Sample Misidentifications	Not used by OIR Not recognized by FDA
24	EP34	Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking	EP34 is ready for publication
25	EP35	Assessment of Equivalency of Specimen Types for Clinical Laboratory Methods	Under development
26	EP36	Harmonization of Symbology and Equations	Not used by OIR Not recognized by FDA
27	EP39	Surrogate Sample Framework	Under development

Thank you!

Marina.Kondratovich@fda.hhs.gov
(301) 796-6036