



**Subcommittee on Establishment of Manufacturer's QC Recommendations
Suite 400, McGraw Hill Building, 1200 G Street, N.W.
Washington D.C., USA
31 October – 1 November 2005**

Summary Minutes

A meeting of the Subcommittee on Establishment of Manufacturer's QC Recommendations was held on 31 October and 1 November 2005 in Washington, D.C. The purpose of the meeting was to review and revise the first preliminary draft of EP22-P, Principles for Validation of Manufacturer's Quality Control Recommendations; Proposed Guideline and to develop a path forward for completion of the document. The following were in attendance:

Members

Greg Cooper, CLS, MHA, Chairholder

Fred D. Lasky, PhD (via phone)
Dai J. Li, MD, PhD
James H. Nichols, PhD
Curtis A. Parvin, PhD
George M. Plummer,
Rhonda S. Whalen

Bio-Rad Laboratories

Genzyme Diagnostics
FDA/CDRH/OIVD
Baystate Medical Center
Washington University School of Medicine
Dade Behring, Inc.
Centers for Disease Control and Prevention

Members Absent

Gregory S. Makowski, PhD, DABCC, FACB University of Connecticut Health Center

Advisors

Adam Manasterski, PhD Centers for Disease Control and Prevention
John J. Murphy, MHS State of Connecticut Dept. of Public Health
Arleen Pinkos FDA Ctr. for Devices/Rad. Health

Observers

Sousan S. Altaie, PhD FDA Ctr. for Devices/Rad. Health
George P. Brotea, PhD Ortho-Clinical Diagnostics, Inc.
Paul D'Orazio, PhD Instrumentation Laboratory
Marilyn Fleming Rhodes Associates
Paul Glavina i-STAT Corporation
Steven I. Gutman, MD, MBA FDA Ctr. for Devices/Rad. Health
Louise Jackman COLA
Carolyn D. Jones, JD, MPH AdvaMed
Francisca L. Lehr, MS, MT(ASCP) Centers for Medicare & Medicaid Services
Elissa Passiment, EdM American Society for Clinical Laboratory Science
Judith A. Yost, MA, MT(ASCP) Centers for Medicare & Medicaid Services

Staff

Lois M. Schmidt, DA Clinical and Laboratory Standards Institute

Reference Materials Distributed Prior to the Meeting

- (1) Meeting Schedule/Agenda
- (2) Subcommittee Roster
- (3) Summary minutes for the meeting held on 31 August and 1 September 2005 in Washington, D.C.

Meeting background and reference materials provided by Mr. Cooper (listed below):

- (4) The “wish list” from the first writing assignment.
- (5) The survey approval/disapproval matrix
- (6) The Industry Working Group Assignment #2 on risk assessment from Fred Lasky et. al.
- (7) The Technical Working Group Assignment #2 from Paul Glavina et. al.
- (8) The User Needs Working Group Assignment #2 from Jim Nichols et. al.
- (9) The FDA's contribution to the second writing assignment
- (10) Mr. Cooper's work on the construct of the QC Recommendation
- (11) Comments from Carolyn Bergkuist on my section
- (12) Comments on my section from John Murphy
- (13) Jan Krouwer's comments on risk mitigation
- (14) EP22 Preliminary Draft

Opening Remarks

Mr. Greg Cooper opened the meeting at 9:00 a.m. by welcoming the participants and asking that each participant introduce themselves. Following the introductions, Mr. Cooper reviewed subcommittee activities that have been completed to date: 1) inaugural meeting held by conference call on 16 May 2005; 2) input on the title and content of the proposed document submitted by representatives of government, industry and professional sectors; 3) survey developed based on the input submitted; 4) survey results summarized and reviewed at the first face-to-face meeting held on 31 August – 1 September 2005; 5) during the last meeting three working groups reviewed subcommittee survey input to determine what should be incorporated into the document; 6) the working groups developed and submitted recommendations for content to be included to address: a) Risk management, b) Characteristics of control measures to instill confidence c) Characteristics of objective evidence and information provided by the manufacturer to instill confidence; and 7) based upon the survey results and the submitted subcommittee recommendations a preliminary working draft of EP22 was developed and circulated to the subcommittee for review prior to this meeting.

Discussion Highlights

Mr. Cooper had developed the preliminary working draft of EP22-P for review and discussion during this subcommittee meeting. The preliminary draft included the drafts completed and submitted by each of the working groups from the last subcommittee meeting, and content material in the survey that had received 75% or higher approval for inclusion in the document.

The meeting participants reviewed of the preliminary draft and discussed document title, purpose, scope, organization and content document from the global perspectives of manufactures of *in vitro* diagnostic devices; clinical laboratory professionals performing *in vitro* diagnostic assays; and regulatory and accreditation agencies/organizations

Title

It was agreed that the title of the document will be changed (Original proposed title: EP22-P, *Principles of Manufacturer's Validation of Risk Mitigation Using Quality Controls; Proposed Guideline*) to: EP22-P, *Establishment of Manufacturer's Recommendations for User Quality Control for in vitro Diagnostic Devices; Proposed Guideline.*

Guideline

In writing CLSI documents, it is especially important to differentiate between those elements for which it is imperative that the user follow and those that can be left to the user's discretion. Generally, the terms "will," "must," and "shall," indicate imperatives, and the terms "should," "could," "may," and "might" allow for user discretion. Mandatory terms, such as "shall" and "must," are most appropriately used in standards, rather than in guidelines. However, the definition of guideline allows for the occasional use of such mandatory terms, for example, in cases where the subcommittee feels strongly that a particular action is either required or prohibited. In such cases, the requirement should be clearly identified as a belief of the subcommittee (e.g., "the subcommittee believes that the user is required to..."). It is also appropriate to include mandatory terms in a guideline when addressing provisions based on regulations or which are otherwise externally imposed. In such cases, the basis for stating these provisions as requirements should be clearly stated (e.g., "OSHA requires..." or "According to OSHA, the user must...").

Definitions

The Definitions Section in the document will include definitions for terms that were identified as essential in the document. Mr. Cooper searched for each of the identified terms in the CLSI Harmonized Terminology Database to ensure harmonization of terminology; however, none of the identified terms are currently defined in the database. Definitions for the terms were submitted by subcommittee participants. If more than one definition was submitted for a term, one definition was shown in bold.

- Action item: Add the following terms and definitions
 - Objective evidence [Definition - A. Pinkos, C. Jones]
 - Internal monitoring system
 - QC recommendation

Risk Assessment and Quality Control (QC)

- Should apply to traditional QC and alternative quality control (AQC).
- Need to provide an example to tie risk assessment with AQC recommendation.
- Manufacturers must provide information obtained through risk assessment to establish a strong foundation for laboratory professionals to base their QC scheme.

Manufacturer's QC Recommendation

- Include all those recommendations to be done to assure quality.
- Not specifically focused on running external QC. This document should apply to all activities.
- How to conduct risk assessments and validation will not be included in this document.
- Information needed from perspective of laboratory director:
 - What instrument does – internal QC statement of claims. Build confidence of users in manufacturer's internal controls (risk mitigated)
 - For those things not covered (controlled) in design of the instrument, the manufacturer should describe what the laboratory director needs to do and why (normal practice to mitigate risk)
- "Validation" is not a correct term for this document; rather it is intended to provide information to support recommendations for QC.

Disclosure Guidelines for Manufacturers

- FDA holds all companies to the same standard in applying "truth in labeling." Manufacturer's claims must have supporting data.

- Must decide what information is to be provided by manufacturers to regulatory agencies or end users; how the information is to be provided (e.g., product insert, available upon request, etc.); and how it is to be updated.
- Adequate information and instructions for QC must be provided for use in small laboratories and physician office laboratories.

Construct of the QC Recommendation

- Include definition of “QC recommendation” in this document.
- Intent – Acceptance testing.
- Character of QC – liquid, solid, electronic.
- Frequency of the QC process for detecting errors including non-persistent and persistent (event-driven onset errors, gradual onset errors, and sudden onset errors).
- Include description of systematic and random errors and cite reference. (Dr. Parvin)
- Include definition of acceptance criteria.
- Objective evidence or justification is required to support manufacturer’s frequency recommendation.
- From FDA perspective:
 - If manufacturer’s recommendation for QC frequency is to be reviewed for clearance by the FDA , scientific evidence must be provided to the FDA for evaluation.
 - The FDA requires data and criteria for interpretation.
 - Must clearly connect the translation of risk mitigation to QC recommendation with examples of simple, moderate and complex systems.
- Non-event related errors are too complex to get sufficient data to mathematically generate criteria for QC frequency recommendation. Such a mathematical model does not currently exist in the literature (per Dr. Parvin).
- Could provide QC frequency recommendations for event-driven and gradual onset errors, but not for sudden onset errors.
- Perhaps objective evidence to support QC frequency recommendations could be collected in the field, i.e., laboratories ranging in size, complexity of testing and expertise of staff.

Suggested changes in the scope and intent of the document to address constituencies’ issues of concern regarding a recommendation for QC frequency:

- (1) If this document does not recommend QC frequency, the document could identify what considerations must be addressed for appropriate QC in given populations and specific methods, and then the user could determine what frequency they should be running QC.
 - Document could provide a list of requirements for manufacturers to provide to end users.
 - It would be helpful for the user to know what the manufacturer has tested regarding performance and what risks have been mitigated with internal controls.
 - Based upon the information provided in the newly proposed guideline “Laboratory EQC Protocols Based on Manufacturer’s Risk Mitigation Information and the Laboratory’s Environment,” the end user would know how to build a QC scheme for their laboratory.
 - The scope/intent of this document could be to enable end users to customize QC based on test performance in their laboratories. Manufacturers could set the minimum requirements for QC in EP22 and the user could then use the newly proposed document on “Laboratory EQC Protocols” to customize QC for their laboratory.
 - Accreditation laboratory inspectors need information about how manufacturers mitigated risks so they can assess QC schemes (particularly in small laboratories and physician office laboratories).
 - Laboratory inspectors would need a process for evaluating appropriate QC, because QC frequency may be different in every laboratory.

- A source of performance data might be obtained from laboratories reporting how specific devices operated in their laboratory. This information could be used by laboratory directors to support developing a QC frequency for their laboratory.
- What is needed for determining QC frequency for three categories of persistent errors (i.e., errors that, when initiated, persist with subsequent tests)?:
 - a. *Event-driven onset errors* are those that are likely to occur after a given event, such as calibration, maintenance, and component or reagent lot changes. QC for such errors is most effective and efficient immediately after such events, before patient samples are tested.
 - b. *Gradual onset errors* are those that increase in magnitude over time from a tolerable to significant level. The optimal frequency of detecting such errors is typically based on the predicted rates of onset and the analytic error tolerance.
 - c. *Sudden onset errors* are those that can appear, unpredictably, at any time. The optimal QC frequency depends on the probability of onset, the probability of detecting the onset with each successive QC event, the magnitude of the analytic errors and the clinical consequences and risk tolerance of such errors. Because clinical factors may vary significantly, manufacturers should state the clinical assumptions on which their QC frequency recommendations for this type of error are based.

- Manufacturers could make QC frequency claims for “a” errors.

- For “b” and “c” errors, this document could identify the information required from manufacturers that could be used by end users and combined with the laboratory’s performance history the laboratory director could then decide on their QC scheme and frequency.

- For “c” errors, when a system is out of the control of the manufacturer and in the user’s laboratory, the manufacturer cannot be responsible for QC performance because there are so many factors that can affect performance.

(2) Perhaps the document should focus on very simple assays (unit use) to study and determine frequency recommendations.

- FDA perspective: If the scope of document includes all devices (i.e., simple to complex), it is doubtful that all systematic errors can be identified for complex instruments. If the scope were to be limited to simple devices (defined as “no dependence” on user), a QC frequency recommendation could be achievable.
- A burden of proof required by FDA: No predictable gradual onset errors and no sudden onset errors.
- The subcommittee is hesitant to limit the scope because option 3 of EQC allows reduction of QC on complex systems.

Requirements and Disclosures

- Include (note: could be in table format) information to be supplied by manufacturers:
 - Information required in labeling (e.g., product inserts, instruction manuals)
 - Information to be available to users upon request
 - Information for regulatory agencies but not for users.

- Complete table and provide information in labeling so user can review what the manufacturer has done and can determine what the user needs to do and to determine what their QC scheme will be.

Conclusions and Recommended Actions

- EP22 will cover simple, moderate and complex systems.
- If a manufacturer wants to make QC recommendations other than regulated requirements (e.g., 2 levels of control/day) then this document applies.
- If following local regulations, identify what information the manufacturer should provide.
- If recommending different QC frequency, identify what information is required.
- Option 4: list of mitigated risks to support option 4 (temporal QC not required)
- Information supporting risk mitigation for non-persistent errors and persistent errors including event-driven onset errors and gradual onset errors. (Excluding sudden onset errors)
- Reorganize the document to remove redundancy and clearly articulate what information manufacturers should provide for use of regulators and what information is for end-users.
- Include example(s) demonstrating connection of risk mitigation to QC recommendation for simple, moderate and/or complex systems.
- Revise the scope and introduction to better articulate the intended use of this document by the manufacturer, regulators and end users.

Path forward

- Mr. Cooper will revise the Scope, Introduction and Outline and will circulate to the subcommittee for comment.
- The content of the document will be reorganized according to the revised Outline.
- The revised preliminary draft will be distributed to the subcommittee for review, comment and discussion during the next subcommittee meeting to be held by conference call.
- The revised timeline for EP22 document development is attached.

Next Meeting

The next subcommittee meeting will be held by teleconference for which a poll will be issued in the future. The purpose of this meeting will be to review and revise the preliminary draft of EP22-P.

Adjournment:

Mr. Cooper thanked the meeting participants for their attendance and contributions and adjourned the meeting at 3:50 p.m. EST on Thursday, 1 November 2005.

Respectfully submitted,

Lois M. Schmidt, DA
Director, Standards and Development

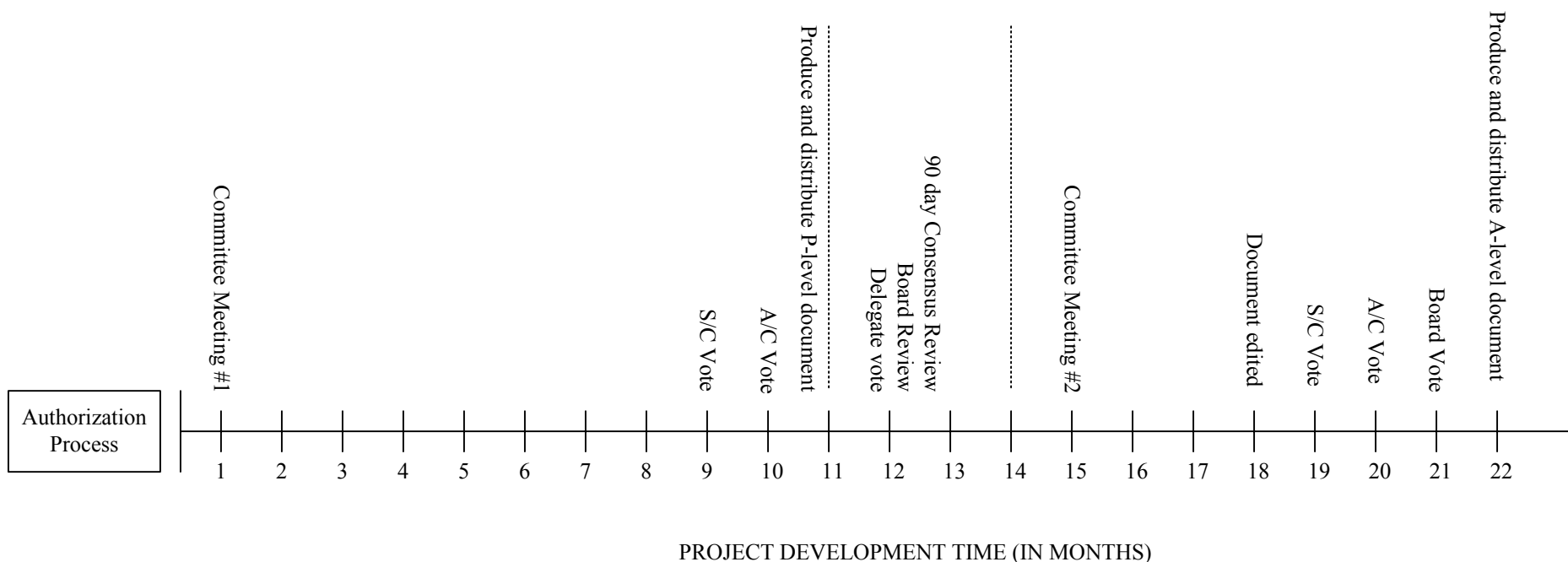
Timeline for finalizing and voting on the EP22-P and EP22-A guideline:

See attached the CLSI Project Development 22-Month Timeline

EP22-P, *Establishment of Manufacturer’s Recommendations for User Quality Control for in vitro Diagnostic Devices; Proposed Guideline.*

Action	Target Date	Target Dates (revised 1 Nov 05)
Development and advancement of EP22-P:		
S/C Inaugural Conference Call	16 May 05	
S/C submits writing assignments – description of the information to be included in the document from the respective perspectives of the three constituencies.	30 Jun 05	
Template document incorporating S/C input to be distributed to S/C	29 Jul 2005	
SC Meeting to be scheduled – Meeting poll in process	31Aug – 1Sep 05	
All writing assignments to be submitted	10 Oct 05	
Draft distributed to SC for review	21 Oct 05	
Second Subcommittee face-to-face meeting:	31 Oct - 1Nov 05	
S/C draft completed	Nov 2005	Jan 2006
S/C final review and revisions	Nov 2006	Jan 2006
S/C vote (20-days)	Nov 2006	Feb 2006
S/C addresses S/C voting comments / revises draft	Dec 2006	Mar 2006
A/C vote (20 days)	Jan 2006	Apr 2006
S/C addresses A/C voting comments / revises draft	Feb 2006	May 2006
Published as P-level document - Delegate vote/ Board Review	Mar – Jun 2006	June - Sept 2006
Development and advancement of EP22-A		
Summary of Delegate comments sent to S/C Chairholder to be addressed	June 2006	Sept 2006
Tentative conference call	July 2006	Oct 2006
Draft revisions, if applicable		
Subcommittee final review and revisions, if applicable (2 weeks)	Aug 2006	Nov 2006
Completion of “final” subcommittee draft	Sept 2006	Dec 2006
Subcommittee voting period: EP22-A (20 days)	Oct 2006	Jan 2007
Area Committee Voting period: EP22-A (20 days)	Nov 2006	Feb 2007
Board Voting Period: EP22-A (20 days)	Jan 2007	Apr 2007
EP22-A Published	Feb 2007	May 2007

CLSI Project Development Timeline



NOTES:

1. Delayed projects are flagged for management intervention at month 12 (proposed-level) and month 19 (approved-level) if committee voting has not started.
2. For scheduled 3-year review of approved-level document:
 - Extensive revision: Start at month 3
 - Moderate revision: Functional (different equipment or reagents, alternate sampling or other procedure) or definition changes / no significant change in scope of, purpose of or methodology used in the consensus document