QC for the Future: CLSI Standard Development and Option 4 Proposal

Luann Ochs, MS
(Roche Diagnostics Corporation, Indianapolis, IN)

Along with the laboratory community, the diagnostics industry in general, and AdvaMed’s CLIA working group in particular (which the author chairs), eagerly awaited the publication of CMS’S Surveys and Certification Inspector Guidelines. We were all aware that they were going to allow equivalent quality control in some form. Upon review of the published guidelines, AdvaMed’s participants were concerned at the contents. We were unable to understand the scientific reasoning behind the laboratories’ procedures for establishing EQC. For example, Option 1 allows the laboratory to perform 10 days of testing, and if all of the quality control functions properly, then they may switch to testing only once every 30 days. Traditional verification methods would require the laboratory to verify quality control functionality for longer than 30 days before switching to the 30 day interval. Because of this discrepancy, the procedures outlined in the Surveyor’s Guidelines seemed arbitrary in nature. The AdvaMed CLIA working group wanted a scientifically valid process for establishing appropriate EQC for diagnostic products, not an arbitrary process. Consequently, in response, the working group requested a meeting with CMS and CDC. At that meeting, in May of 2004, we proposed Option 4: a scientifically valid process for establishing EQC, with government oversight.

CMS and CDC, after hearing AdvaMed’s arguments and proposal, agreed that Option 4 might offer an appropriate pathway for establishing EQC, providing that the process could be agreed upon by all interested parties, including the laboratory professionals, the government, and industry. Because the Clinical and Laboratory Standards Institute (CLSI) already has a process for document development that includes all of these constituencies, it seemed a perfect fit to utilize that process to refine the proposal.

After identifying the potential risks, the manufacturer determines if the risks are controlled by internal failsafe mechanisms or internal quality control. Remaining risks may need to be controlled by an external QC protocol. The objective is to mitigate all risks through a combination of failsafe mechanisms and quality control, reducing risks to minimal or negligible levels, or at least detecting the risk as well as current traditional QC practices. The proposed alternative should be equivalent or better than traditional QC. Therefore, taking the example of damaged reagents, the alternative QC must be able to identify the damaged reagents as well as traditional QC.

Once the risks have been identified and the failsafes and quality checks needed to mitigate the risks have been identified, the next step is to prove that those failsafes and quality checks actually work. Looking again at the damaged reagents example, the manufacturer would need to simulate damaged reagent conditions, and prove that the failsafe or alternative QC did indeed detect the error condition and prevent the reporting of a false result. That proof data would then be submitted to FDA for review and approval.

As stated above, the CLSI consensus process for document development will be utilized in order to ensure that the views of laboratory professionals, government officials, and industry are all included. The definition of “scientifically rigorous validation” will be decided by a CLSI subcommittee that includes representation from all 3 of these constituencies. Once developed, the document will then proceed through CLSI’s process that provides an opportunity for all of CLSI’s members to provide comments and vote to accept or reject the document.

What Is AdvaMed’s Option 4 Proposal?

In a nutshell, AdvaMed’s Option 4 proposal consists of 3 steps:

First, the manufacturer performs a risk assessment of their product using risk assessment standards (eg, ISO 14197, CLSI/NCCLS EP 18-A) and tools (eg, failure modes and effects analysis, fault tree analysis). This risk assessment would focus primarily on conditions that would lead to erroneous test results, for example, operator error or damaged reagents.

The manufacturer validates their quality control proposal, it is reviewed and approved by the FDA, and then it can be implemented by laboratories in place of 1 of the current CLIA options.

The question of what constitutes “scientifically rigorous” validation of quality control will be answered by the development of a CLSI consensus document. This paper provides details of the Option 4 proposal, the CLSI process, and the proposed CLSI document.

CLSI Document Process

This CLSI consensus process ensures that all concerned parties have an opportunity to participate in the development of documents. Documents move through the process only after the participants reach consensus regarding the content and wording of the document. Once accepted, these documents then provide instruction and guidance to the various users of the document.

CLSI documents focus on various topics, including best practices, testing methods, data requirements, and labeling requirements.
The CLSI document process starts from authorization of the project by CLSI’s Board of Directors. A subcommittee authors a first draft of the document, after which votes and comments are taken at both the subcommittee and Area Committee levels. Once approved by the Area Committee, the document is available to the public as a proposed document. The proposed document is sent to all CLSI member delegates, with a request for vote and comments. The subcommittee reconvenes and edits the document, addressing all comments received. Finally, the document reaches the stage for vote and release as a final document. The process is set up to release a proposed document or “P-level” after 11 months, and a final approved document, or “A-level” after 22 months. The CLSI staff works very hard to keep the various subcommittees in adherence with the timelines.

Tying it all together, AdvaMed’s Option 4 proposal includes a provision for a consensus document describing data requirements for alternative QC validation. The proposed title for the document is “Principles of manufacturer’s validation of risk mitigation using quality controls.” The document will touch on each of the steps: risk assessment and mitigation, principles and concepts of QC validation, and examples. The inclusion of both concepts and examples will instruct the reader on what data is needed in order to validate an alternative quality control procedure.

The CLSI subcommittee will operate within the Evaluation Protocols Area Committee. As chair of the Area Committee, I will oversee the document development process, and provide both technical and process input, but I will not be participating in the actual authoring of the document. The chairperson of the subcommittee is Mr. Greg Cooper, manager of Clinical Standards and Practices at Bio-Rad Laboratories. The other members of the subcommittee represent professionals from government, laboratory, and industry. A number of advisors and observers also will be participating. The advisors and observers have essentially unlimited input into the document as well, but they do not have voting rights.

The scope statement in the document proposal reads as follows: "External, liquid quality control materials have long been used with IVDs. Traditionally, these quality controls are treated the same as, and run along side, patient samples. Obtaining quality control results within expected allowed ranges ensures the user that the patient results are acceptable. More recently, manufacturers have found ways to integrate quality controls into the test itself, so that the quality controls are run concurrently with the patient’s test. These integrated quality controls come in numerous forms, with differing degrees of effectiveness.

Using risk management principles, manufacturers can determine the various risks associated with the use of their product. They can then determine which of these risks can be mitigated by the use of internal or external quality controls. Once the risks are known and understood, the effectiveness of the quality controls for risk mitigation can be validated.

This document describes the principles, and gives procedural examples, for validation of the capability of the quality controls to mitigate the identified risks.

This document will be used by manufacturers and others who are interested in understanding the effectiveness of an IVD’s quality controls.

The CLSI document will clearly state that any alternative QC protocol provided by a manufacturer and cleared by FDA, serves at the foundation for quality control by the laboratory. The laboratory directors will need to consider whether the alternative QC, as presented, is appropriate for their laboratory, or if they feel they need additional QC measures. Once Option 4 appears in CMS’ Survey Guidelines, this should be clearly stated.

Summary

In conclusion, Option 4 will provide for a scientifically validated quality control protocol that may be selected by laboratories to ensure the quality of their tests. The definition of the appropriate scientific rigor will be determined by a CLSI consensus subcommittee, ensuring that the concerns and desires of all interested parties are considered.