Clinical

Laboratory

Improvement

Advisory

Committee

Summary Report

September 10-11, 2008
Atlanta, Georgia

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Clinical Laboratory Improvement Advisory Committee
September 10-11, 2008, Summary Report
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Record of Attendance

Committee Members Present

Ms. Elissa Passiment, Chair
Dr. Ellen Jo Baron
Dr. Christine Bean
Ms. Susan Cohen
Dr. Nancy Elder
Ms. Julie Gayken
Dr. Carol Greene
Dr. Geraldine Hall
Dr. Lee Hilborne
Dr. James Nichols
Dr. Gary Overturf
Dr. Stephen Raab
Dr. David Smalley
Dr. Emily Winn-Deen
Dr. Rosemary Zuna
Ms. Luann Ochs, AdvaMed (Liaison Representative)

Committee Members Absent

Ms. Merilyn Francis
Dr. Norman Harbaugh, Jr.
Dr. Linda Sandhaus
Dr. Jared Schwartz

Executive Secretary

Dr. Thomas Hearn

Ex Officio Members

Dr. Steven Gutman, FDA
Dr. Devery Howerton, CDC
Ms. Judith Yost, CMS

Record of Attendance - cont'd.

Centers for Disease Control and Prevention

Ms. Nancy Anderson
Ms. Shannon Barker
Dr. Joe Boone
Ms. Diane Bosse
Dr. Sal Butera
Dr. Bin Chen
Ms. Joanne Eissler
Ms. MariBeth Gagnon
Dr. Genny Gallagher
Mr. James Handsfield
Dr. Lisa Kalman
Dr. Deborah Koontz
Dr. John Krolak
Ms. Debra Kuehl
Mr. Nattawan Lanier
Dr. Ira Lubin
Ms. Leslie McDonald
Ms. Connie Miller
Ms. Andrea Murphy
Ms. Abrienne Patta
Ms. Anne Pollock
Ms. Anne Rice
Dr. John Ridderhof
Dr. Shahram Shahangian
Ms. Colleen Shaw
Dr. Julie Taylor
Mr. Howard Thompson
Ms. Pam Thompson
Ms. Glennis Westbrook
Ms. Irene Williams
Dr. Laurina Williams
Dr. Hui Zhou

Department of Health and Human Services (Agencies other than CDC)

Ms. Carol Benson (FDA)
Dr. Elliot Cowan (FDA)
Ms. Daralyn Hassam (CMS)
Ms. Penny Kellar (CMS)
Ms. Penny Meyers (CMS)
Ms. Cindy Munger (CMS)
Ms. Kathy Todd (CMS)
Ms. Harriet Walsh (CMS)

In accordance with the provisions of Public Law 92-463, the meeting was open to the public. Approximately 30 public citizens attended one or both days of the meeting.

Clinical Laboratory Improvement Advisory Committee

The Secretary of Health and Human Services is authorized under Section 353 of the Public Health Service Act, as amended, to establish standards to assure consistent, accurate, and reliable test results by all clinical laboratories in the United States. The Secretary is authorized under Section 222 to establish advisory Committees.

The Clinical Laboratory Improvement Advisory Committee (CLIAC) was chartered in February 1992 to provide scientific and technical advice and guidance to the Secretary and the Assistant Secretary for Health regarding the need for, and the nature of, revisions to the standards under which clinical laboratories are regulated; the impact on medical and laboratory practice of proposed revisions to the standards; and the modification of the standards to accommodate technological advances.

The Committee consists of 20 members, including the Chair. Members are selected by the Secretary from authorities knowledgeable in the fields of microbiology, immunology, chemistry, hematology, pathology, and representatives of medical technology, public health, clinical practice, and consumers. In addition, CLIAC includes three ex officio members, or designees: the Director, Centers for Disease Control and Prevention; the Commissioner, Food and Drug Administration; the Administrator, Centers for Medicare & Medicaid Services; and such additional officers of the U.S. Government that the Secretary deems are necessary for the Committee to effectively carry out its functions. CLIAC also includes a non-voting liaison representative who is a member of AdvaMed and such other non-voting liaison representatives that the Secretary deems are necessary for the Committee to effectively carry out its functions.
Due to the diversity of its membership, CLIAC is at times divided in the guidance and advice it offers to the Secretary. Even when all CLIAC members agree on a specific recommendation, the Secretary may not follow their advice due to other overriding concerns. Thus, while some of the actions recommended by CLIAC may eventually result in changes to the regulations, the reader should not infer that all of the Committee's recommendations will be automatically accepted and acted upon by the Secretary.

CALL TO ORDER – INTRODUCTIONS/FINANCIAL DISCLOSURES

Dr. Thomas Hearn, Executive Secretary, Clinical Laboratory Improvement Advisory Committee (CLIAC), and Deputy Director, National Center for Preparedness, Detection, and Control of Infectious Diseases (NCPDCID), CDC, welcomed the Committee and the members of the public, acknowledging the importance of public participation in the advisory process. He explained that the primary focus of the meeting would be consideration of the Genetic Testing Workgroup report in order to provide CLIAC recommendations for good laboratory practices for genetic testing. The recommendations would be included in a *Morbidity and Mortality Weekly Report: Recommendations and Reports (MMWR R&R).* Other presentations on the agenda for Committee discussion were laboratory quality control through risk management; a CMS update on the status of waived testing; and a report on the FDA Waiver Panel meeting.

Dr. Hearn paid tribute to Rosemary Bakes-Martin who passed away earlier this year, highlighting her career at CDC, the influence she had on CLIA activities, and her contributions to CDC, the Division of Laboratory Systems, and public health. In closing, Dr. Hearn introduced the new CLIAC Chair, Ms. Elissa Passiment.

Ms. Elissa Passiment, Chair, CLIAC, welcomed the Committee and called the meeting to order. She introduced the four new members of the Committee: Dr. Christine Bean, Ms. Julie Gayken, Dr. Linda Sandhouse, and Dr. Rosemary Zuna. All members then made self-introductions and financial disclosure statements relevant to the meeting topics.

The CLIAC observed a minute of silence in remembrance of those who died on September 11, 2001.

AGENCY UPDATES AND COMMITTEE DISCUSSION

Food and Drug Administration (FDA) Update ***Addendum A***

Steven Gutman, M.D.
Director, Office of In-Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health
Food and Drug Administration

Dr. Gutman listed new FDA staff, noting the hire of Dr. Robert Becker as Chief Medical Officer. Dr. Gutman reported the In Vitro Diagnostic Multivariate Index Assays (IVDMIA) guidance is under review, and that Analyte Specific Reagent (ASR) manufacturers have been reminded to comply with the FDA rules. There are several notable new clearances, he said, including IVDMIA products from Pathworks and Allomap. He mentioned that some of the FDA's post-market activities included providing contaminated heparin alerts and safety tips for certain glucose meters. Dr. Gutman updated the Committee on developments in Critical Path Programs, the evolution of electronics, and user fee mandates. He commented positively on the Secretary's Advisory

Committee on Genetics, Health, and Society (SACGHS) Report recommendations, the DLS-commissioned Lewin Report on the status of laboratory medicine, and the Clinical and Laboratory Standards Institute's (CLSI) EP 22 and EP 23 documents. He said the FDA has been monitoring "The Genomics and Personalized Medicine Act of 2008" (H.R. 6498) in Congress, a bill aimed to advance personalized medicine and pharmacogenomics. Dr. Gutman concluded by referring to the recent FDA Complete Blood Count (CBC)/Differential Cell Count Waiver Panel meeting, saying he looked forward to CLIAC's discussion of this topic.

Centers for Medicare and Medicaid Services (CMS) Update ***Addenda B& C***

Judith Yost, M.A., M.T.
Director, Division of Laboratory Services
Center for Medicaid and State Operations
Centers for Medicare & Medicaid Services

Ms. Yost began her presentation with an overview of the current CLIA statistics noting that 82% of the laboratories have no direct regulatory oversight. She then turned her attention to cytology proficiency testing (PT). She reported that the cytology PT Notice of Proposed Rule Making (NPRM) was in clearance at the Department of Health and Human Services (HHS). In addition, legislation that would eliminate cytology PT and replace it with required continuing medical education has passed the House and is being debated in the Senate (S.2510). Ms. Yost next discussed the oversight of genetic testing and CMS' actions in lieu of creating a genetic testing specialty. Commenting on CMS' plan for the revision of the CLIA PT regulation, she said the revision would first require the publication of an NPRM and, although a plan with milestones and an estimated timeline have been developed, there is no firm target date for publication. She added that CMS is soliciting a CLIAC recommendation to proceed with the plan. Continuing on the topic of PT, Ms. Yost reviewed CMS' warnings about proper conduct during PT events. She emphasized laboratories should not communicate with each other regarding PT results and warned that PT referral, whether intentional or not, results in the most serious CLIA penalties. Ms. Yost deferred portions of her presentation for later in the Committee meeting and closed with a review of the Certificate of Waiver (CW) Project, reviewing the background of the project and the results compiled as of 2006.

Committee Discussion

- One member referred to a recent CMS notification that said CMS regional offices, rather than state surveyors, should perform inspections of public health laboratories. Ms. Yost clarified this was done to avoid conflict of interest of state inspection teams inspecting their own state health laboratories—thus all inspections of state health laboratories will be conducted by the CMS regional office inspectors. She added the General Accounting Office (GAO) recommended funding has allowed CMS to increase the staffing in regional offices in order to conduct these inspections.

The Chair opened for discussion the question of recommending formation of a workgroup for updating the CLIA regulations pertaining to PT.

- One member asked whether the workgroup's charge would be to provide technical information and thoughts that would drive the PT regulatory update. The Chair responded yes.
- Ms. Yost added that representation by PT program providers, including states with PT programs, and subject matter experts would be desirable for the workgroup. She said genetic testing will probably need a totally different approach for PT, therefore representation will be needed from individuals with genetic testing expertise. Ms. Yost added that CMS is looking at every aspect of PT including mechanisms to update the analytes or tests for which PT should be required.
- A member commented that the workgroup should also address alternative PT, methodology PT, and unstable samples.
- Another member agreed that genetic testing would require a different approach from current PT.
- One member emphasized it would be desirable to write the regulations in a way that would be flexible enough to address changes in technology without a need for regulatory revision on an ongoing basis. Ms. Yost agreed that another mechanism for specifying required PT should be explored.
- Another member queried if the workgroup would consider expanding PT to cover waived testing. Ms. Yost replied it was not under consideration at this time, as that would call for a statutory change.
- Several members voiced support for forming a PT workgroup to examine and provide suggestions concerning the need for revisions to the CLIA PT requirements. The Committee voted to recommend the formation of the workgroup.

Centers for Disease Control and Prevention (CDC) Update ***Addendum D***

D. Joe Boone, Ph.D.
Acting Director, Division of Laboratory Systems
National Center for Preparedness, Detection, and Control of Infectious Diseases
Coordinating Center for Infectious Diseases
Centers for Disease Control and Prevention

Dr. Boone introduced and reported progress on the Laboratory Medicine Best Practices (LMBP) project to develop methods for evaluating evidence-based best practice effectiveness. Using a diagram, he explained a method of rating and integrating various quality indicators that determine relative strengths of recommendations for implementing best practices. He described three funded projects underway to identify and develop new pre- and post-analytic evidence-based laboratory medicine performance measures. Dr. Boone also updated the Committee on post-2007 Quality Institute: Managing for Better Health activities. He outlined efforts to establish an Institute of Laboratory Medicine, with the charge to develop a national strategy for U.S. laboratories, and listed the members of the "Roadmap" and "Integration" Work Groups. He highlighted the issue of quality by mentioning an article from *The Dark Report* that described training as inadequate to cover the complexities of laboratory medicine and referred to the publication of the 2007 National Status Report on Laboratory Medicine available on line at http://wwwn.cdc.gov/dls/bestpractices/.

Addressing the Continuing Threat of Laboratory-Acquired Infections ***Addendum E***

Thomas L, Hearn, Ph.D.
Deputy Director,
National Center for Preparedness, Detection, and Control of Infectious Disease
Centers for Disease Control and Prevention

As a part of the CDC update, Dr. Hearn reported to CLIAC on biosafety activities initiated by CDC following the potential exposure of 916 people in 254 laboratories to an attenuated strain of *Brucella abortus* RB51 during a recent PT event. He summarized the laboratory safety issues raised by this incident and discussed on-going activities, including those of professional organizations, as well as the formation of a trans-federal task force charged with optimizing oversight of all high containment/clinical testing laboratories. He then turned his attention to the Blue Ribbon Panel (BRP), formed by CDC following the *B. abortus* incident to assess practices in clinical testing and make recommendations for assuring the safety of laboratory workers. He described the May 2008 inaugural BRP meeting as a focused discussion on several topics: standards, guidelines, and regulations; education and training; safety management programs; and reporting of laboratory-acquired infections. He concluded with a review of the BRP's recommendations to CDC, including proposed topics for new guidelines and next steps.

Committee Discussion

- One member commented that it would be useful to acquire data on laboratory personnel exposure to infectious agents not resulting in infections and asked if the panel had discussed this. Dr. Hearn acknowledged the BRP had addressed this and went on to emphasize the BRP discussed at length the importance of identifying how exposures happen and recognized that if the laboratory community is to reduce those at-risk behaviors leading to work-associated exposures, they must first identify the root cause for the exposure.
- A member asked with a reduced work force, increased turnover, and added demands of cross-training, how can laboratory training keep pace with job-specific exposure risks? Dr. Hearn replied the BRP also saw this as a challenge to laboratories, especially training and educating an increasing number of laboratory workers lacking fundamental laboratory science credentials. He added the BRP recognized the vast amount of detailed training materials in existence and recommended these be distilled into "What is really important for me to know to perform this job safely?" The BRP also recommended the development and use of wall posters and user-friendly documents in the work area. Dr. Hearn emphasized they did not see this challenge as limited to the clinical laboratory but extending to research laboratories in university settings and beyond. The conclusion was that any individual working with at-risk samples must be identified and provided with specific information on how to perform the job safely.
- A member commented that many hospitals use contract occupational health programs and that these programs frequently have an inadequate understanding of how to handle laboratory exposures. The member asked if the BRP's recommendations would also apply to these programs. Dr. Hearn responded the BRP had not talked about contracted programs.
- One member said that the common denominator for many laboratory exposures is failure to follow standard operating procedures (SOPs). The member suggested the BRP focus on why SOPs are not followed and what barriers exist preventing "good people from doing the right thing." In response, a BRP member stated the primary question became "What are the right behaviors for a given job?" With little evidence available to support existing "right behavior,"

the BRP concluded that studies are urgently needed to quantify the risks of different behaviors and establish evidence to support the "right behaviors" associated with a given job description.

- CLIAC members stated some safe work practice behaviors were intuitive but concurred with the BRP recommendation that studies are needed to establish evidence-based safe laboratory work practice behaviors.
- Several members had questions and recommendations on oversight and safe work practices in biosafety level 3 (BSL3) and biosafety level 4 (BSL4) laboratories to which Dr. Hearn replied that a separate federal task force was focused on these laboratories and charged with developing a document that would focus on the threat of laboratory-acquired infections in BSL3 and BSL4 laboratories. CLIAC asked that their BSL3 and BSL4 input and suggestions be presented to the federal task force as well as back to the Blue Ribbon Panel.
- Members recognized the efforts of the BRP and unanimously agreed to provide support to the BRP's recommendations and efforts to address the threat of laboratory-acquired infections.

PRESENTATIONS AND COMMITTEE DISCUSSIONS

Introduction: CLIAC Genetics Workgroup ***Addendum F***

Dr. Joe Boone presented the "Introduction of the CLIAC Genetics Workgroup on Good Laboratory Practices (GLP) for Molecular Genetic Testing (MGT)." He reviewed CLIA activities related to genetic testing quality, including genetic testing recommendations made by CLIAC over a 10-year period. Dr. Boone then introduced the CLIAC Genetic Testing Workgroup, which met in the spring and summer of 2008, and outlined its focus and tasks. Their primary charge had been to provide a framework to assist CLIAC develop recommendations for molecular genetic testing (MGT) good laboratory practices (GLP) for CDC to publish in the *MMWR R&R*. Dr. Boone added that the practices in this publication would be voluntary and may go beyond regulatory requirements.

CLIAC Genetics Workgroup ***Addenda G & H***

Dr. Carol Greene, Chair, CLIAC GLP for MGT Workgroup, presented the workgroup report. The workgroup reviewed current regulatory and voluntary standards in order to evaluate good laboratory practices for the total genetic testing process and provide input for CLIAC to consider. The report provided suggestions and clarifications on the total testing process (i.e., preanalytic, analytic, postanalytic phases), PT and alternative assessments, confidentiality, personnel, competency assessment, considerations before introducing genetic testing or offering new genetic tests, and quality management systems.

Committee Discussion ***Addenda I & J***

Ms. Passiment and the Committee commended Dr. Greene and the workgroup members for their efforts in providing a comprehensive list of suggestions for good laboratory practices for molecular genetic testing. Committee members discussed each aspect of the workgroup report and recommended adopting the document with the following additions or modifications to form the CLIAC-recommended GLPs for inclusion in the *MMWR R&R*. A complete set of the CLIAC recommendations can be found in Addendum K.

CLIAC Additions or Modifications to MGT Workgroup Suggestions ***Addendum K***

Scope of Genetic Testing GLP that CLIAC Should Consider; Applicability of the MMWR Document

- The title of the MMWR document should clearly identify the document as applicable to molecular genetic testing for heritable diseases and conditions.
- Biochemical genetic testing should be the next focus for an additional good laboratory practices MMWR publication. Future documents should also address cytogenetic and somatic genetic testing.

Role of Laboratories in Providing Information to Users of Their Services

- Present the information on test methodology in user-friendly language that will help users understand the test's intended use and limitations so they can determine appropriate testing for their patients.
- Include a statement indicating that preauthorization may be needed for the test request.

Role of Laboratories in Informed Decision-making and Informed Consent

- Informed decision-making regarding a genetic test is based on the healthcare provider's and the patient's understanding of the test, whereas informed consent may be a signed document attesting to the information provided to the patient for decision-making and the patient's decision. The laboratory should be responsible for providing its users with information necessary for making informed decisions whether or not informed consent is required for the test. In circumstances when informed consent for a genetic test is required by law or other applicable requirements, the laboratory should be responsible for including appropriate means for documenting the informed consent on the test requisition form and for reviewing whether the consent information is provided with the test requisition.
- Include references that provide templates for informed consent documents.

Test Request

- Clarify that the minimum information required to identify a specimen for MGT should include the patient's name, date of birth, and any other necessary unique identifier.
- Include International Classification of Disease (ICD) codes and other codes indicating the disease or condition for which testing is requested, such as codes associated with an advance beneficiary notice (ABN), when appropriate.
- Strategies to address documentation of informed consent could include a bold statement on the test requisition that it is the responsibility of the clinician to engage the patient in decision-making and secure any consent required by regulations. A check off box may be included to indicate that consent has been obtained for the requested testing.

Specimen Submission, Handling, and Referral

- Specimens for patient testing must be referred to a CLIA-certified laboratory or laboratory meeting equivalent requirements as determined by CMS.

Individuals Authorized to Order Genetic Tests

- No additions or clarifications

Preanalytic Systems Assessment

- Emphasize that laboratories should have procedures to assess whether the appropriate test was ordered for the history provided and to recognize if the requested test is not consistent with clinical expectations.

Performance Establishment and Verification

- CLIAC members could not agree on a definition of "robustness, as included in the workgroup report." Therefore, they felt the term should not be used and recommended using reproducibility or reagent stability as an example of additional performance characteristics that should be included in performance establishment and verification.
- Clarify that, if some of the characteristics of clinical validity to be documented (clinical sensitivity, clinical specificity, positive predictive value, and negative predictive value) are not available, the laboratory may report the clinical validity information that is available for the test population.

Control Procedures

- No additions or clarifications

Unidirectional Workflow and Monitoring of Molecular Amplification Procedures

- No additions or clarifications

Proficiency Testing and Alternatives

- No additions or clarifications

Test Report

- To be consistent with the information elements recommended for the test request, specimen identification should include the patient's name, date of birth, and any other necessary unique identifier.

Retention of Records and Reports

- Genetic test reports should be retained for at least 25 years after the test is complete.

Retention of Specimens

- Emphasize that specimen stability should be considered along with technology, space, and cost when the timeframe for specimen retention is determined.
- Provide clarification that if testing is performed on an unstable sample (e.g., RNA) there is still value in retaining the cDNA samples.
- Acknowledge that specimen retention issues will be different for somatic molecular genetic

testing and biochemical testing for which samples are often less stable and of larger size.

Confidentiality

- No additions or clarifications

Qualifications and Responsibilities of the Laboratory Director

- No additions or clarifications

Qualifications and Responsibilities of the Technical Supervisor

CLIAC considered the options suggested by the workgroup for technical supervisor qualifications and recommended the following:

- Technical supervisors for molecular genetic testing for heritable diseases and conditions should have the following qualifications:
    - Be equivalent to the CLIA qualification requirements for clinical cytogenetics technical supervisors with four years of training or experience in genetics, two of which have been in the area of molecular genetic testing for heritable conditions; or
    - Have current certification in molecular genetic testing by an HHS-approved board such as the American Board of Medical Genetics (ABMG) or the Molecular Genetic Pathology Board jointly administered by ABMG and the Molecular Genetic Pathology Board.

Qualifications and Responsibilities of the Clinical Consultant

- No additions or clarifications

Qualifications and Responsibilities of the General Supervisor

- No additions or clarifications

Qualifications and Responsibilities of the Testing Personnel

- No additions or clarifications

Personnel Competency Assessment

- No additions or clarifications

Considerations before Introducing Genetic Testing or Offering New Genetic Tests

- No additions or clarifications

Quality Management Systems

- No additions or clarifications

The discussion of good laboratory practices for molecular genetic testing ended with two motions made and carried.

1. A recommendation to publish the CLIAC recommendations for good laboratory practices for molecular genetic testing document in the *MMWR R&R* and
2. A recommendation to form a workgroup on biochemical genetic testing to consider similar good laboratory practices for these tests.

Alternative Quality Control (CLSI Update) ***Addendum L***

Judy Yost, MA, MT(ASCP)
Director, Division of Laboratory Services
Centers for Medicare & Medicaid Services

Ms. Yost began her presentation with a reminder of the quality control (QC) changes for analytic systems stipulated by the 2003 final CLIA regulations. Initially, changes to the analytic systems requirements were considered educational and laboratories were not penalized if they did not meet the revised requirements. Effective December 31, 2007, all laboratories are required to comply with the test method verification, maintenance and function checks, and calibration and calibration verification sections of the regulations. Until new QC policies are in place, laboratories will continue to receive "educational" surveys for control procedure requirements. In addressing alternative QC development, Ms. Yost discussed the 2005 CLSI meeting, "QC for the Future," sponsored by laboratory professionals, government, industry, and accrediting organizations. The meeting resulted in CLSI's decision to develop two evaluation protocol documents, EP 22, which focuses on protocols for risk mitigation for manufacturers, and EP 23, which focuses on alternative QC for laboratories. The documents are slated for CLSI subcommittee vote in the fall of 2008. Once EP 22 and EP 23 have been approved, CMS' interpretive guidelines will be updated with a phase-in period to allow for use of the CLSI documents as a means of meeting the CLIA QC requirements.

Committee Discussion

- A Committee member asked if the CLSI documents will apply to only moderate complexity testing. Ms. Yost responded they apply to all nonwaived testing. Another member commented moderate complexity laboratories may struggle more with risk mitigation than high complexity laboratories.
- Ms. Yost agreed that smaller laboratories, especially those that perform only moderate complexity testing, may need additional guidance that provides more specific implementation directions. Adoption of the new policy would include a phase-in period.

EP 22 – Presentation of Manufacturer's Risk Information ***Addendum M***

Greg Cooper, CLS, MHA (presented by Dr. Jim Nichols)
Chairman, Bio-Rad Laboratories

In Mr. Cooper's absence, Dr. Nichols presented a summary of CLSI's proposed document EP 22, *Risk Mitigation for Manufacturers*. Rather than a required frequency for performing QC testing, EP 22 focuses on manufacturers identifying device failures that could occur and the scope and effectiveness of design features intended to mitigate the failures. Suggested means for manufacturers to communicate this information to laboratory users are included in the document. EP 22 suggests a table format for manufacturers to convey the information to consumers with

headers that include the targeted failure mode, device feature or recommended action, known limitations of the feature or action, suggested recommendations for addressing the known limitations, and a summary of the studies that prove the design feature or action actually does mitigate the risk. Dr. Nichols stated that EP 22 should reduce or eliminate unsubstantiated QC recommendations made by manufacturers.

EP 23 Laboratory QC Based on Risk Management Update ***Addendum N***

James H. Nichols, Ph.D., DABCC, FACB
Associate Professor of Pathology
Tufts University School of Medicine
Director, Clinical Chemistry
Baystate Health System

Dr. Nichols began his presentation by describing the advantages and disadvantages of historically accepted external, surrogate QC material based on stabilized samples of similar matrix that are analyzed like patient specimens. He noted this type of QC monitors only the end result at one point in time without addressing other risks, and when a QC failure occurs it often results in the need to reanalyze patient samples since the last "good" QC. He said surrogate QC is often no longer adequate. There is a need to have fully automated analyzers that eliminate errors up front and provide assured quality with every sample. These features are particularly important in single use devices. However, Dr. Nichols noted that every instrument is different and total quality management (TQM) should encompass both hazard analysis and risk mitigation for each device.

CLSI's EP 23 is intended for users of laboratory and point-of-care systems with alternative control processes, but all laboratories should find the manufacturer's test limitations and risk mitigation useful. The scope of EP 23 provides laboratories with guidance to develop effective, cost-efficient QC protocols based on manufacturer provided risk mitigation information, as described in EP 22. Dr. Nichols cited examples of how carryover might be detected and mitigated on glucose instruments by both manufacturer and laboratory risk assessments. A key component of EP 23 is follow-up and occurrence management.

Dr. Nichols concluded with a description of the content of sections of EP 23. He noted the document incorporates surrogate QC to address the potential for certain risks and utilizes a risk management approach to developing a customized QC plan. It provides a scientific basis for justifying QC strategies and proactively addresses the potential risk before a wrong result is released as opposed to current QC strategies that react to QC failure. EP 22 and EP 23 are targeted for CLSI subcommittee vote in fall 2008.

Committee Discussion

- A Committee member asked if there are any patient safety laws that require instrument malfunctions to be reported. Dr. Gutman responded there are extensive requirements for reporting malfunctions, injuries, and deaths. Some of the occurrences are reported to the FDA through their post market surveillance program. The FDA works with manufacturers to encourage action on identified problems. Another Committee member commented patient safety organizations, resulting from the Patient Safety and Quality Improvement Act, would be a way

of collectively identifying and reporting issues that occur which may not come to the FDA's attention.

- One member questioned if, based on disclosure of problems, manufacturers will be willing to work with laboratories to solve the problems. Dr. Nichols stated manufacturers want to advertise the risks they have mitigated. By putting risks on the table and showing how they have been mitigated, a learning process occurs. Ms. Ochs added most manufacturers want to show off their technological tools for risk mitigation.
- A member commented that Failure Mode Effects Analysis (FMEA) is required under International Organization for Standardization; therefore, manufacturers who sell internationally already comply. In the United States, EP 22 and EP 23 would create a demand to publish useful information for laboratorians. Dr. Gutman added the FDA requires risk management information exist but only reviews it in some settings and would not normally review this as part of the pre-market program.
- Another member noted hospitals already use FMEA, root cause analysis, and other techniques for addressing risk; these documents are another good means of proactive risk mitigation.
- A member expressed concern that EP 22 and EP 23 are too vague and leave too much in the QC plan up to the laboratory director. Another member wanted more specific information, such as number of high and low concentrations to run and how often, included in the documents. Dr. Nichols noted EP 22 and EP 23 would provide a scientific basis for such things as instrument maintenance and training but could only address the specifics of the device or environment. Currently, no evidence exists for confirming what QC is sufficient. Ms. Ochs added by using EP 22 and EP 23, laboratory directors would know what risk mitigations are built into the instrument so they can decide what other concerns need to be addressed in their QC plan. They have no way of knowing this now.
- A member mentioned for complicated tests involving many steps and answers that tie together, the manufacturer still does not state what kind of QC should be done. Ms. Yost responded using EP 22, the manufacturer would tell you not only the kind of QC to run but a list of many checks and balances. Dr. Nichols commented future revisions of the document may move away from only QC towards more TQM.
- One Committee member asked if a column could be added to the Manufacturer Risk Assessment table describing risks and what steps to take to mitigate that risk. This would aid laboratory directors in justifying their decision to the surveyors. Dr. Nichols replied the next to the last column in the table addresses that question. He stated another table in the document, not shown in the presentation, gives multiple suggestions for mitigating risks and will be helpful to laboratory directors when building their QC plans. The QC plan would incorporate "residual risk, acceptable or not."
- The same member then inquired what would happen if the inspector disagrees with the laboratory director's decision that the residual risk is acceptable. Dr. Nichols responded that if the director had data to support his decision and reasoning behind the decision-making in the QC plan, very few inspectors would second-guess the director. Stating surveyors are out-come oriented, Ms. Yost agreed if results have shown whatever the laboratory director is doing is working, surveyors should not question any particular item in the checklist.
- The Chair asked Ms. Yost how EP 22 and EP 23 would be integrated into current procedures for CMS and then how integrated into laboratory accreditation organizations whose surveyors CMS does not train. Ms. Yost replied CMS would need to incorporate the documents into their guidelines, develop educational materials, and train surveyors on compliance. There would be a

phase-in implementation time for laboratories to gain understanding and ask questions; nobody would be held accountable during this time. Accrediting organizations would be encouraged to follow suit.

- Dr. Howerton noted EP 22 and EP 23 are intentionally written for an international audience and CLIA is not mentioned. Some effort may be necessary to demonstrate how to use them specifically for CLIA.
- The Chair asked what CLIAC's role might be in the area of educational guidance as the two documents are finalized and integrated into the CLIA regulations or guidance documents. Dr. Hearn responded the Committee provided the impetus for EP 22 and EP 23 to be written and the next step is to roll them out and get feedback. He suggested a follow-up report from CMS and CLSI on the status of the documents.

Quality Control for Commercial Microbial Identification Systems ***Addendum O***

Nancy Anderson, MMSc, MT(ASCP)
Chief, Laboratory Practice Standards Branch
Division of Laboratory Systems
Centers for Disease Control and Prevention

Ms. Anderson presented a summary of the recently published CLSI guideline, *M50-A: Quality Control Requirements for Microbial Identification Systems (MISs)*. As background, she explained that laboratories had expressed concerns to CLIAC that the CLIA QC requirements for commercial MISs are excessive. Also, an American Society of Microbiology (ASM) survey report to CLIAC in 2006 indicated that the most common reason for QC failures was the QC organism rather than failure of the MISs. Therefore, the Committee supported the ASM recommendation that CLSI develop appropriate guidelines to streamline QC requirements for commercial MISs. Ms. Anderson discussed the laboratory user, manufacturer, and distributor responsibilities in the CLSI guideline and said the document does not change the required frequency of QC testing, only the number of organisms that are needed. The basic premise of the guideline is that if a laboratory uses an MIS produced by a manufacturer that meets quality standards, and the laboratory verifies that the MIS performs acceptably in their environment, then the laboratory may qualify to perform streamlined QC using key indicator strains of organisms specified by the manufacturer. Next steps for the M50-A document to be implemented include manufacturers' revisions of MIS instructions to include key indicator strains to be tested under streamlined QC. CMS intends to allow for streamlined QC as an exception to the CLIA requirements and the exception will be incorporated in the CMS surveyor and laboratory guidelines. CMS-approved accreditation organizations may then choose whether they will incorporate the streamlined approach into their standards.

Committee Discussion

- A Committee member requested clarification of the M50 guideline that seems to state that in order to go to the new "streamlined approach," laboratories first need to document a 95% success rate when they test every single reagent as required by CLIA. Ms. Anderson replied if the laboratory has data verifying performance for accuracy, precision, sensitivity, and specificity when the system was implemented, that is all that would be necessary to go to the streamlined QC approach. Some laboratories may not have performed the verification study when they

implemented a system, or may not have documentation of their verification. If that is the case, they may instead perform the historical QC review.

- Another member asked when the streamlined QC approach may become effective under CLIA, and if laboratories are required to continue positive and negative testing for every reagent and substrate until that time. Ms. Yost responded, reiterating information stated by Ms. Anderson, that there are a couple of actions that need to be taken before streamlined QC can be performed in lieu of comprehensive CLIA QC. First, CMS needs to get permission from CLSI to incorporate the relevant portion of the M50-A document into the CMS surveyor and laboratory guidelines and second, surveyors need guidance on how to assess compliance. She suggested that laboratories may choose to implement the document now if they already have data on test system verification; at most CMS would send a letter (which does not go on the laboratory's record) and would not cite a deficiency. However, she reminded CLIAC that states and accrediting organizations may have different requirements. Ms. Yost could not give an estimated timeframe for incorporation of the document into CLIA regulations.

CMS Certificate of Waiver Project Data Review ***Addendum P***

Judy Yost, M.A., M.T. (ASCP)
Director, Division of Laboratory Services
Center for Medicaid and State Operations
Centers for Medicare and Medicaid Services

Prior to her presentation, Ms. Yost gave a recap of significant points related to the CMS surveys of waived testing sites from the previous day's CMS update, indicating that CMS intervention does result in improvement in laboratory performance. She reviewed the basic regulatory requirements for laboratories issued a certificate of waiver (CW), then presented categorical findings from CW laboratory surveys noting laboratories in states with licensure programs performed better. She stated the overall study observation was that most deficiencies were a result of high staff turnover, insufficient training, poor understanding of good laboratory practice (GLP), and a lack of clinical personnel performing the tests; however, the numbers of deficiencies decreased after guidance was provided to the CW sites. Ms. Yost concluded her presentation by indicating that CMS is exploring the possibility of expanding the CW study sample each year to identify additional laboratories that may be testing beyond the scope of their waived certificate, raise awareness of the importance of following the manufacturer's recommendations, and educate more personnel about CLIA and GLP.

Committee Discussion

- During the presentation, a member asked Ms. Yost if there were comparable data for nonwaived laboratories. She replied that CMS does have the most frequently cited deficiencies available for the nonwaived laboratories; their problems are similar to the CW laboratories. Another member asked if CMS had an estimate of the percentage of physician offices, nursing homes, and pharmacies in the CW category and if CMS includes those facilities in their surveys in direct proportion to that percentage. Ms. Yost answered that CMS includes a representative sample of CW sites in their surveys.
- After the presentation, a member noted CMS' intent to expand the survey and wanted to know if there was an actual plan to do that. Ms. Yost explained that because of cost and personnel

restrictions at this time, CMS was just exploring the possibility.

- One member stressed that many physician offices do not have laboratories; the accessibility of point-of-care testing is a plus for patients but only one aspect of the services provided. She suggested that it may be better to ask "How do we improve point-of-care testing and PT" and look at the culture of where the waived tests are performed, because a great proportion do not consider themselves laboratories.
- Another member said that in New Hampshire, during a pandemic flu drill, they realized the first line of testing in the case of an actual pandemic could be waived laboratories. They identified the waived laboratories in their state and began offering training on good laboratory practices to these sites, assuming a role they thought a state public health laboratory should take.
- A member suggested it might be useful if laboratories would volunteer their guidance to assist CW sites that need help or have questions.

CLIA Waiver ***Addendum Q***

Carol C. Benson, M.A.
Associate Director, Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Federal Drug Administration

Ms. Benson opened her presentation with a general definition of CLIA waiver and elaborated on the three ways a test system may qualify for CLIA waived categorization. She summarized the impact of CLIA waived test systems on laboratory testing, then highlighted the principles of the waiver guidance document, "Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices," issued by the FDA in January 2008. In conclusion, Ms. Benson described how a manufacturer can demonstrate that a test system meets the CLIA waiver criteria of being "simple" and having an "insignificant risk of erroneous result" and provided guidance on studies that show how these criteria are met. The guidance document can be accessed at http://www.fda.gov/cdrh/oivd/guidance/1171.pdf.

Potential Waiver of Complete Blood Count/Differential Testing ***Addendum R***

Valerie Ng, M.D., Ph.D.
Professor Emeritus
Department of Laboratory Medicine
School of Medicine, UCSF, and
Chair, Laboratory Medicine & Pathology Department
Alameda County Medical Center

As a panelist on the FDA Hematology and Pathology Devices Panel, Dr. Ng presented a summary of the panel's recommendations about the suitability for waiver of automated devices intended to identify and count cells in peripheral blood. She discussed seven main questions on pre-analytic, analytic, and post-analytic issues posed to the panel by the FDA and summarized the corresponding answers to those questions. Question and answer topics included the potential for erroneous results,

identifying analytical issues, unreasonable risk to the patient from erroneous results, provisions for results follow-up, untrained personnel identifying post-analytical problems, allowable total error, and frequency of quality control.

Committee Discussion

Prior to the Committee discussion of the potential waiver of complete blood count/differential testing, a member noted that although no specific test system was being considered for waiver, the only such device on the market in the United States was owned by the same company that owned the laboratory where he served as Medical Director. The member was informed that due to the potential for an actual or perceived conflict of interest, he should recuse himself from the discussion and move to the public audience for that part of the meeting. Nevertheless, and after the fact, it was noted he had remained at the table and provided several comments during the course of the Committee's discussion. At the end of the discussion, the only CLIAC recommendation that was made was not specific to any particular testing device nor did it refer to whether or not complete blood count/differential testing should be considered for waiver. The Committee discussion and resulting recommendation follows. (Updated 05/18/2010)

- A member asked if convening a panel was the mechanism the FDA will use for future waiver decisions when test systems might not have published performance limits that can be used to evaluate them. Dr. Gutman responded that the process is evolving. He stated that one of the changes in the approach specified in the FDA waiver guidance is that the decision to waive a test may be based on a tradeoff between access and performance, which might differ depending on the particular analytes involved, and would potentially allow for more flexibility. Therefore, convening a panel for advice will be an option.
- A member asked what parameters would be included in a waived complete blood count (CBC) and white blood cell (WBC) differential. Another member agreed this was an important question since a CBC and WBC differential may include different parameters depending on the instrumentation being used and the laboratory that is doing the testing. When making a waiver decision the parameters to be included in a test need to be identified before a test system can be evaluated to determine whether it meets the waiver criteria.
- Dr. Ng explained the individuals on the panel would be uncomfortable with the concept of making clinical decisions based on a total WBC count without the additional information they are accustomed to receiving as part of a differential. A Committee member agreed that from a clinical standpoint any single component of the CBC, such as a WBC count or hematocrit, is only a single part of a screening test and should not be confused with the CBC.
- Dr. Gutman stated the issue being considered is what part or combination of the CBC might be appropriate for waiver and what type of performance data or other information would be needed to evaluate a test system. He confirmed that currently there are no devices that perform either a WBC count or a complete CBC on the list of waived tests.
- Dr. Ng further explained there was no specific device presented to the FDA, so the panel was considering a hypothetical test system. She mentioned that the panel felt a WBC count was fairly reliable based on the current technology but had concerns about releasing a WBC result as a single measurement without the context of other test parameters used in conjunction with that count to steer medical decision making. She mentioned there were also concerns about potentially providing a WBC count in a waived laboratory setting, where there may be the absence of a person with knowledge of what to do with the result.

- The Chair clarified that regardless of what is ordered, her system generates all CBC parameters. A Committee member commented that is not comparable to a device that would report only WBC counts.
- Dr. Ng stated that in a study of 13,000 CBC samples, about twenty percent of them had instrument flags and would require some higher level thinking about what to do before reporting results. She commented again that single analytes are difficult to interpret in isolation and that, if they are approved for waiver, they must be repackaged with a different name so as not to be confused with a CBC.
- One member commented there might be some instances in which a single analyte result would be useful, such as hemoglobin in an operating room setting. Dr. Ng rebutted that point, stating it is important to know the methodology by which that hemoglobin is being determined in order to accurately interpret the result, citing possible interferences in certain point-of-care devices that could affect the results. Stating the CBC has many intended uses, she asked how one would consider a device could meet all of those if only certain test parameters were being reported.
- A CLIAC member noted the cost consciousness of laboratories and inquired if laboratories would adopt a kit for performing a WBC count or a hemoglobin accurately and with less cost if it were offered. Another member said that it would be hard to make a point-of-care device for only one analyte that would cost less than a routine CBC analyzer but noted there are limited situations where a WBC count for a particular clinical question may be sufficient. The member commented better data are needed about the safety of waived testing so the Committee can make better decisions in the future.
- Considering the questions posed to the FDA panel, the Chair commented on the difficulty in determining the limits of error based on the patient's situation. Dr. Ng warned the Committee to be aware of the false negatives. She noted the total WBC count can have huge physiologic fluctuation based on the stage of a person's illness, and if the count is measured at the wrong point in the course of a disease, the patient may receive inappropriate treatment. A member added that the issue is appropriate selection of when to use the test. Another member cited a study in which 10-15 percent of septic children had WBC counts that fell within the normal range; they would have been missed entirely, including those that went on to develop septic shock.
- The Chair reminded the members that waived testing is a statutory requirement and suggested the Committee might discuss how far beyond expectations waived testing has advanced.
- A member suggested a triage for determining whether a test or analyte is appropriate for the waived category. (e.g., Is the test appropriate for the waived category? Does it meet defined ranges for accuracy? Should it be sent for panel review?)
- The member also noted the need to reach a balance in terms of improving the practice of medicine, when and where appropriate, by bringing testing closer to the patient. The Chair posed the question of why it is assumed that every time a test is brought closer to a patient it has to be waived. Dr. Gutman noted a document where experts examined whether point-of-care testing is worthwhile and determined where it might be of value. He said the FDA panel deemed it would be daunting to cover all of the analytical, pre-analytical, and post-analytical variables that play into getting the correct result, but they did not close the door on the technology.
- Referring to the previous suggestion of a triage for determining whether a test is appropriate for the waived category, a member stated a test such as the CBC, with its many potential clinical outcomes, should not be the first test considered for waiver. Ms. Ochs commented the statute did not seem to specifically address appropriateness for waiver; although that might be imbedded

within the concept of simple. She asked if a test is waived, how can the use be controlled and kept from expanding into areas where it absolutely should not be waived. A member said experience shows that once a test is waived, it is often used in areas it should not be used in. Another member voiced concern about the safety of waived testing and the pressure being applied by industry for waiver of tests.

- A member questioned the need for point-of-care testing for hematology. Consideration for its use should include clinical need and what is best for patients, consumers, and the cost of healthcare.
- Noting a lack of data on whether or not waived testing actually improves the outcome of patients, one member suggested CLIAC recommend that CDC conduct a study to look at the benefits and risks of waived testing. Another member agreed it would be useful to know the benefits and risks of waived testing, however, in the end this information will not assist in determining whether a test should be waived. One member commented that a lot of waived testing is performed because of desire to know, not need to know. There are many aspects to waived testing and how it is used and these should be examined carefully.
- The Chair queried the Committee's interest in making a recommendation that CDC or the agencies conduct a study to gather data about the impact of waived testing on patient outcome, clinician behavior, and similar issues. The Committee voted to recommend the study.

PUBLIC COMMENTS

- **George Birdsong, M.D., FCAP, on behalf of the American Society of Cytopathology (ASC)** ***Addendum S***
- **Paul Rust, Vice President, Point-of-Care Testing, Quest Diagnostics and President, HemoCue, Inc**. ***Addendum T***
- **Mr. Ray Ozmon** ***Addendum U***

ADJOURN

Ms. Passiment acknowledged the CDC staff that assembled the meeting program and thanked the CLIAC members and partner agencies for their support and participation.
The following reflects the Committee recommendations from this meeting:

- Publish the CLIAC recommendations on "Good laboratory Practices for the Molecular Genetic Testing" in the *Morbidity and Mortality Weekly Report*: *Recommendations and Reports*.
- Form a workgroup to consider good laboratory practices for biochemical genetic testing.
- Establish a workgroup to examine and provide suggestions regarding the need for revisions to the CLIA requirements for proficiency testing.
- Conduct a study to gather data about the impact of waived testing on patient outcomes, clinician behavior, and other similar issues.

Ms. Passiment announced CLIAC meeting dates for the next two years:

- 2009 – February 4-5 and September 2-3
- 2010 – February 10-11 and September 9-10

In closing, Ms. Passiment adjourned the Committee meeting.

I certify this summary report of the September 10-11, 2008 meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.

_____ Dated: 12/3/2008

Elissa Passiment, EdM, CLS(NCA), CLIAC Chair