# **C**linical

# **L**aboratory

# **I**mprovement

# **A**dvisory

# **C**ommittee

Summary Report

**January 8, 1997**

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

# Clinical Laboratory Improvement Advisory Committee

## January 8, 1997

## Summary

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## Record of Attendance

**Committee Members**

Dr. David Baines
Dr. Regina Benjamin
Dr. Thomas Bonfiglio
Dr. Lemuel Bowie
Dr. Mary Burritt
Dr. Ronald Cada
Dr. Patricia Charache
Dr. Susanne Gollin
Dr. Verlin Janzen
Dr. Aliza Lifshitz
Dr. Bereneice Madison
Ms. Diana Mass
Ms. Deborah McHugh
Dr. Glenda Price
Ms. Sharon Radford
Mr. Elliott Segal

**Ex Officio Members**

Dr. Kaiser Aziz, FDA
Dr. Carlyn Collins, CDC
Ms. Judith Yost, HCFA

**Liaison Representatives**

Dr. Fred Lasky (HIMA)

**Centers for Disease Control and Prevention**

Dr. Rex Astles
Ms. Rosemary Bakes-Martin
Ms. Carol Bigelow
Dr. Joe Boone
Ms. Gail Bosley
Ms. Diane Bosse
Ms. Cheryl Coble
Ms. Deborah Coker
Ms. Crystal Frazier
Ms. MariBeth Gagnon
Ms. Sharon Granade
Dr. Thomas Hearn
Dr. Ed Holmes
Dr. John Krolak
Dr. Harvey Lipman
Dr. James Lange
Dr. Adam Manasterski
Ms. Anne O'Connor
Dr. John Ridderhof
Dr. Eunice Rosner
Dr. Sharahan Shahangian
Ms. Marianne Simon
Mr. Darshan Singh
Mr. Gregory Smothers
Dr. Steve Steindel
Dr. Roger Taylor
Ms. Julie Wasil
Ms. Rhonda Whalen
Ms. Laurina Williams

## 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, Health Care Financing Administration; 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 will also include a non-voting liaison representative who is a member of the Health Industry Manufacturers Association 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 law, the reader should not infer that all of the advisory committee's recommendations will be automatically accepted and acted upon by the Secretary.**

## Welcome and Announcements

The meeting was called to order by CLIAC Chairman Dr. Morton Schwartz. The committee members made self-introductions and disclosure statements of their relevant financial interests as they relate to the topics to be discussed during the CLIAC meeting.

Note: An orientation for new CLIAC members was held prior to the meeting (See Addendum A).

## Presentations and Committee Discussion

### CLINICAL LABORATORY IMPROVEMENT AMENDMENTS (CLIA) UPDATE/CDC

Addenda B-C

Dr. Carlyn Collins, Director of the Division of Laboratory Systems, CDC, discussed CLIAC's potential involvement in updating the CLIA regulations applicable to genetics testing. Dr. Collins is an informal participant on the National Institutes of Health Task Force on Genetic Testing that is examining the ethical, legal and social implications of genetics testing. Dr. Collins anticipates that the task force will recommend the establishment of a CLIAC subcommittee to make recommendations to revise the CLIA regulations to ensure the quality of genetics testing. She indicated that CDC is working to establish a genetics subcommittee which will include CLIAC members and others with expertise in genetics testing.

Then, Dr. Collins briefly described the regulations development and publication process and provided an update on the status of various CLIA regulations. At this time, there are no projected publication dates for the regulation extending the date for the phase in provisions pertaining to quality control and personnel, the CLIA fee schedule revision notice, and the final waiver regulation (see addendum B). Dr. Collins noted that initial work has begun to develop the final, final regulation which will incorporate changes in proficiency testing (PT) and quality control (QC).

Rosemary Bakes-Martin briefly reviewed issues presented at the public QC meeting in Atlanta in September 1996. Many CLIAC members attended this meeting and heard presentations by representatives from manufacturers and other interested parties. Ms. Bakes-Martin reviewed CDC's approach for revising the CLIA QC requirements in the final, final regulation to address new technology (see addendum C). Ms. Bakes-Martin reminded the Committee that the QC phase in requirements expired in September 1996. She noted said that the main QC issue to be resolved prior to publication of the final, final regulation is alternative methods for performing QC.

**Committee Discussion**

**Dr. Schwartz asked if the Health Care Financing Administration (HCFA) inspectors are aware that the phase in requirements expired in September. Ms. Yost replied that the inspectors are aware but are not enforcing the requirement for high complexity laboratory directors with a doctoral degree to be board certified by September 1, 1996, and are continuing to allow laboratories using commercial, non-modified, moderate complexity tests to meet less stringent QC requirements. One committee member asked for clarification of QC changes planned for the final, final regulation. Ms. Bakes-Martin explained that the QC model (discussed at previous CLIAC meetings) would allow laboratories to use non-traditional controls to assess the potential for error in the test system with each run and use traditional controls to monitor all components of the testing process (test system, environment, and operator) over time. This flexibility would make the regulations more appropriate for "new technology" test systems that have internal controls which check for errors in the test system. Another committee member asked if the CDC would provide a summary of presentations and comments from the September QC meeting. Dr. Collins explained that there is no meeting summary, but copies of each presentation are available. QC information provided at the meeting will be used to develop the final, final regulations.**

**CLIA UPDATE/HCFA** **Addenda D-I**

**Ms. Judy Yost, of the HCFA, presented a brief status report on CLIA implementation and referred to a summary of the types of deficiencies cited during first and second cycle inspections of all laboratories vs. inspections of physician office laboratories (POLs) (see addendum D). Noting that the majority of laboratories surveyed by HCFA are POLs, Ms. Yost summarized the number of POLs by CLIA application type and the number of application type 1 POLs (laboratories that hold a regular certificate) by certificate fee schedule based on volume and scope of services (see addendum E).**

**Ms. Yost then reviewed the process for surveying cytology laboratories (see addendum F). Since the late 1980s, HCFA has contracted with the American Society of Cytotechnologists (ASCT) to inspect these laboratories using cytotechnologists and pathologists. The contractor uses the HCFA survey forms and guidelines to evaluate compliance with the CLIA regulations. An ASCT survey may be initiated at the request of a State agency or HCFA regional office or as a result of a complaint. Ms. Yost described the laboratory selection by HCFA, noting that HCFA follows up on all laboratory complaints. She reviewed the contractor survey process, emphasizing that the surveys are outcome-oriented with an educational focus. At a minimum, 0.1% of the laboratory's**

**volume or 100 slides are rescreened by cytotechnologists, with discrepancies reviewed by a pathologist. The rescreened slides include negative and positive GYN and non-GYN smears. If a problem is suggested by the rescreen results, the sample would be expanded to determine whether the laboratory is correctly reporting cytology results. HCFA reviews personnel qualifications, follows up on correction of deficiencies, and takes any necessary enforcement action.**

**Ms. Yost noted that there are about 3,000 cytology laboratories (most of these are accredited). Then, she summarized the results from 109 cytology laboratories surveyed onsite by the contractor in 1995/96 (see addendum G). Included in the 109 were 40 laboratories in which complaints had been filed. Survey findings substantiated complaints in 13 of the 40 laboratories, and HCFA initiated enforcement actions against 4 laboratories. The other laboratories either have corrected, or are in the process of correcting, identified deficiencies.**

**Ms. Yost discussed the most frequently cited standard and condition level deficiencies in cytology laboratories in FY 95-96 (see addendum H). Noting that condition level deficiencies impact patient outcomes more than standard level deficiencies, Ms. Yost reported that 41 of 109 laboratories (38%) surveyed in 1995/96 had condition level deficiencies, and cytology QC is the most frequently cited condition level deficiency. When compared to the three previous years, the actual number of laboratories with condition level deficiencies has increased, while the percent has decreased (see addendum I).**

**In conclusion, Ms. Yost noted that the contractor cytology survey process has become more streamlined and has been educational for the laboratories and for HCFA.**

**Committee Discussion**

**The Chairman expressed concern that determining that a slide had been misread may be subjective, depending on the surveyor. Another committee member commented that there is no standard cytology accuracy rate against which a laboratory may compare itself. The Chairman referred to Q-Probes 1993: Pap Smear Rescreening Data Analysis and Critique which reported a false negative rate of 5.6% for focused rescreens, "using a narrow definition, and 12.5%, using a broad definition." The report also concluded that "poorer performance was associated with higher Pap smear volume, higher number of cytotechnologist FTEs, and high ratios of Pap smears per cytotechnologist and per cytopathologist." One committee member asked for clarification on focused rescreening. Several committee members expressed concern about the cytology laboratory image problem and one member commented that the format HCFA uses to report survey results may magnify deficiencies and**

**contribute to the image problem. Another committee member was concerned that sample selection for rescreening might skew the statistics. Other committee members indicated that there is much public interest in the automated cytology systems and one member asked if HCFA's statistics included any laboratories that use automated systems. Ms. Yost noted that the incidence of cervical cancer had not declined, but pointed out that the laboratory detection of abnormal conditions has improved. She said that one reason for increased detection is that focused rescreens are performed in cytology, as required by the CLIA law. Ms. Yost said that determining that a slide had been misread is not based on the opinion of a single cytotechnologist on the survey team, but is determined by a cytotechnologist and a pathologist. She also explained that although HCFA previously cited a deficiency by referencing each applicable regulation, HCFA now cites the deficiency only once, by referencing the regulation most likely to affect patient care. Ms.Yost noted that HCFA would like input on this process. Ms. Yost acknowledged the concern about sample selection for rescreening during the survey. She also said that automated systems have only recently been in laboratory use and are not included in the statistics.**

**CYTOLOGY PT** **Addendum J-K**

**Ms. Rhonda Whalen of CDC reviewed the requirements in the CLIA law and regulations concerning cytology PT (see addendum J). She explained the basis for the lawsuit filed by Consumer Federation of America/Public Citizen against the Department of Health and Human Services (HHS) related to cytology PT and the decision of the district court that cytology PT slides should be examined at the maximum rate allowed for examining patient slides. HHS appealed the district court ruling and complied with the court order by publishing a proposed rate change for examining PT slides in November 1995. HHS solicited public comments to the proposed rate change and on computer-based PT programs (CLIAC previously recommended the development of computer technology to test locator and interpretive skills), since implementation of glass slide PT had not been achieved. CDC received more than 750 comment letters. Almost all the commenters disagreed with the proposed rate change and more than half the letters commented on computer-based PT. The appellate court upheld the CLIA PT rate, but directed HHS to publish the rationale supporting the time frame for examining PT slides. HHS will publish a notice withdrawing the proposal to revise the PT rate and plans to revise the regulations to allow approval of computer-based PT programs.**

**Ms. MariBeth Gagnon of CDC reviewed the background for the CDC development of a prototype computer-based PT program (see addendum K). After a 1993 Request for Proposal to develop a PT program using glass slides received no response, CDC awarded three cooperative agreements to**

develop and pilot test model computer-based cytology PT programs. Based on the input from the cooperative agreements, CDC developed a computer-based PT program. Ms. Gagnon then described the features of the CDC model program and gave a demonstration for the CLIAC.

### Committee Discussion

A committee member commented that some patients want their Pap smears examined by a laboratory that uses an instrument to assist in QC performance. Another member felt that some of the manufacturers' advertisements or claims are beyond the instruments' capabilities. He suggested that routine manual rescreens of all slides would detect more positives at a lower cost than automated methods. The Chairman asked about the relevance of developing a computer PT program which would more closely resemble microscopic examinations. Dr. Collins indicated that participant response to computer images in the pilot study was positive. Another CLIAC member commented that technology in histopathology and cytology is moving away from oculars and that, in the future, normal working conditions will involve computer screens. One CLIAC member asked about hardware requirements to administer the CDC prototype program. Dr. Collins indicated that nationally available computer training centers could be used to administer the cytology PT. Dr. Schwartz noted that cytology PT does not evaluate sample collection. Another CLIAC member commented that computer images would provide more uniform testing than glass slides. Dr. Schwartz recognized Ms. Theresa Somrak [co-investigator on the American Society of Clinical Pathologists (ASCP)/CDC cooperative agreement] who stated that ASCP believes that marginal practitioners may not be reliably identified by means of a 10-slide proficiency test. She emphasized the importance of criterion-based validity instead of face validity for the development of cytology competency tests.

## STATUS OF CLIA RESEARCH STUDIES

### CLIA Research Update — Addendum L

Dr. Thomas L. Hearn, Chief of the Laboratory Practice Assessment Branch in the Division of Laboratory Systems at CDC, provided background information for three presentations on the CLIA research studies, which are part of CDC's broader laboratory practice research agenda referred to as EQLPS (Evaluation of Quality in Laboratory Practices and Standards). The CLIA research studies focus on aspects of PT, quality assurance (QA) and QC, personnel, extent to which errors in testing affect diagnosis and treatment of patients, and the identification of where errors occur in the testing process. These and other EQLPS studies are being carried out not as a single linked study but as individual discrete studies each within a fairly narrow circumspect perspective. CDC is

doing the studies through competitive government procurement processes (contracts and cooperative agreements), through professional collaborations, and by collaboration among CDC and HCFA staff. Within the EQLPS program there are more than 30 studies, some of which are now almost completed. Three of these studies are being presented today. They were chosen because they are at stages where there are important findings to share and because they represent the diversity in the approaches used for carrying out EQLPS research in terms of the questions asked and strategies used for doing the work. As individual studies are completed, they will be published in peer-reviewed journals.

**Calculation of Bias and Precision Tolerance Limits Using the Variation of Test Distributions** — **Addendum M**

Dr. George Klee reported on work being carried out at Mayo Clinic Laboratories which demonstrated the critical need for defining analytical precision and accuracy goals. Laboratory research has often focused on the analytical precision goals for testing and Dr. Klee has investigated the utility of defining analytical accuracy or bias goals. Small shifts in the accuracy of calcium, thyroid stimulating hormone, and prostate specific antigen tests were shown to have potentially adverse effects on the diagnosis and treatment of large groups of patients. Improved detection and prevention of these small, but significant shifts, will require better QC and QA approaches and may also be dependent upon having more accurate and robust test systems.

**Association Between HIV Testing Accuracy and the Use of External QC Samples** — **Addendum N**

Drs. Rex Astles and Harvey Lipman of the CDC, using results from a qualitative test, HIV antibody testing data from CDC's Model Performance Evaluation Program (MPEP), investigated the association between HIV testing accuracy and the use of either in-house or commercially obtained QC material. After considering potentially confounding independent variables [such as the kit used for testing, the type of laboratory (e.g., hospital, public health), the number of specimens routinely tested, requiring a minimum degree for testing personnel, and requiring retro viral specific training], the only variable (other than the use of QC materials) found to be independently associated with the error rate was the type of test kit used for analysis. After controlling for all significant confounders, the use of QC materials was associated with a strongly significant (p=0.0002) 31% reduction in the error rate on MPEP samples. Further statistical analyses of the data revealed that systematic errors occurred in both laboratories that did and did not use QC. However, laboratories that did not use QC had a systematic error rate that was more than twice as great as laboratories that used QC, meaning that laboratories that did not use QC were much more likely to have

made two or more errors in each panel of six MPEP samples than laboratories that used QC.

## Laboratory Medicine Sentinel Monitoring Network Addendum O

Ms. Kathy LaBeau, Project Director for a cooperative agreement between the Washington State Department of Health and CDC, reported on laboratory practices in a group of 266 laboratories which voluntarily participate in a sentinel network organized in the Pacific Northwest. Information about laboratory practices was collected through five mailed surveys and additional issues of general interest were discussed in two regional focus group meetings. Information about QA practices, access to testing, reasons for recent increases or decreases in testing workload, analysis of common problems that result in laboratories issuing corrected reports, and personnel issues were addressed in the surveys. The sentinel network, although not a statistically representative sample of the laboratory population, serves as a useful monitoring mechanism for identifying general problems in laboratory medicine and serves as a resource for laboratories to obtain additional information about testing practices.

## Committee Discussion on CLIA Research Studies

The presenters responded to several requests for clarification on study design and findings from CLIAC members.

In response to questions about the expense of establishing bias goals and the number of observations needed, Dr. Klee reported that the cost and effort involved in maintaining bias goals are dependent on several factors including access to sufficient patient values and the distribution of the population of test results around clinical decision points. One committee member reported PT failures when his laboratory requested lot numbers of QC materials with specific values. Dr. Klee noted that a potential downside to minimizing bias shifts is that a few laboratories may actually be penalized in some PT events if the majority of laboratories in their "peer" grading group are not as diligent and use reagents which are less reliable.

Commenting on the MPEP data on HIV antibody testing, one committee member felt strongly that the choice of test kit could be the most important variable associated with the error rate. He suggested that the kits used by the study participants may not be representative of kits used by other laboratories. The Chairman asked how the study controlled for the quality of the participating laboratories. Dr. Lipman responded that the study controlled for testing volume, personnel degree and training requirements, and the results were unaffected by these variables.

With respect to the sentinel network, one committee member asked if laboratories which perform only waived testing or have stopped testing are included. Ms LaBeau responded that only laboratories performing moderate or high complexity testing are included in the network. Therefore, data from the Pacific Northwest network do not reflect the experiences of laboratories that formerly may have performed such testing but either are currently performing only waived tests or may have stopped testing completely. Ms. Yost commented that many tests performed by POLs are now waived. Commenting on access to testing, another committee member suggested that any studies to estimate the cost to patients of not having testing available at their health care site should include transportation, babysitting costs, etc.

**PUBLIC COMMENTS** **Addenda P-Q**

1. William G. Cooper, QC Manager of Bio-Rad Laboratories, summarized the results from a December 1996 survey of QC practices and preferences in U.S. clinical laboratories selected from the Medical Laboratory Observer mailing list. This survey was designed and conducted without any involvement or input from CDC. Based on the survey results, Mr. Cooper submitted written recommendations to CDC and CLIAC concerning possible revisions of the CLIA regulations (see addendum P).

2. Theresa Somrak, Director of Cytopathology Education Consortium Activities, recommended that a cytology PT program consist of either mailed challenges in a variety of formats, including glass slides and photomicrographs, or computer-based images and should evaluate the performance of the laboratory. She suggested that laboratory directors could use education-based exercises provided by professional organizations, such as ASCP and the College of American Pathologists, to evaluate cytology personnel (see addendum Q).

3. Toni Casey, I-Stat Corporation, asked about the status of Accurate and Precise Technology (APT) testing and if there would be another open meeting for manufacturers to discuss QC. Chairman Schwartz considered the questions out of order, but indicated Ms. Casey's remarks could be presented to CLIAC as a public comment at a later date.

4. Don Parker, Director of Clinical Trials at Bayer Corporation, suggested that the waiver review process be presented to CLIAC, to clarify the steps that could be taken if a waiver application is not approved.

**Committee Discussion**

One CLIAC member asked about the status of waiver applications and how to obtain comments submitted in response to CDC's request for data and

**information on QC practices following the September 1996 QC meeting. Ms. Bakes-Martin replied that CDC has denied no waiver requests thus far and said that several applications are under review. She also pointed out that CDC is evaluating waiver applications using guidelines which were published in the waiver proposed rule and that publishing a final regulation on the waiver process is a high priority. Ms. Bakes-Martin explained that significant QC comments might be presented to CLIAC in the future and noted that copies of comments submitted following the QC meeting could be obtained through a Freedom of Information Act request.**

**Another committee member asked about the time line for the results of the CDC contract to evaluate cytology PT which includes: (1) an assessment of the CDC computer-based PT program by cytotechnologists and pathologists; and (2) comparison of glass slide PT and computer-based PT to rescreening results. Ms. Gagnon said that the contractor performing these studies should have data available this summer.**

**A CLIAC member inquired about the mechanism for getting items on the CLIAC agenda. Dr. Schwartz replied that agenda items may be submitted by committee members or the public to any CLIAC member, but are usually submitted to Dr. Ed Baker, CLIAC Executive Secretary.**

**CONCLUDING REMARKS**

**Dr. Schwartz announced that the dates for the next CLIAC meeting will be September 11-12, 1997, and then adjourned the meeting.**

**I certify that this summary report of the January 8, 1997, meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.**

/S/ Morton K. Schwartz, Ph.D.
Chairman