Clinical Laboratory Improvement Advisory Committee (CLIAC)
February 7-8, 2001

Summary Report

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Committee Members
Dr. Toby L. Merlin, Chair
Dr. George G. Birdsong
Dr. Joseph M. Campos
Dr. Patricia Charache
Dr. Brenta G.C. Davis
Dr. Andrea Ferreira-Gonzalez
Dr. Jaime L. Frias
Dr. Ronald J. Gagne
Dr. Barbara M. Goldsmith
Ms. Cynthia S. Johns
Dr. Valerie L. Ng
Dr. Timothy J. O'Leary
Dr. Stewart Lee Richardson
Dr. Lawrence Mark Silverman
Dr. Lawrence S. Sturman
Dr. Roland Valdes, Jr.
Dr. Alice Schauer- Weissfeld

Ex Officio Members
Dr. Robert Martin
Dr. Steven I. Gutman
Ms. Judith Yost

Liaison Representative
Ms. Kay A. Setzer, AdvaMed

Centers for Disease Control and Prevention:
Ms. Nancy Anderson
Dr. Rex Astles
Ms. Carol Bigelow
Dr. Joe Boone
Ms. Diane Bosse
Ms. Sandra Browning
Dr. Bin Chen
Ms. Deborah Coker
Ms. Sharon Granade
Dr. Tom Hearn
Ms. Theresa Lawrence
Dr. Ira Lubin
Mr. Kevin Malone
Dr. Adam Manasterski
Ms. Priscilla Patin
Ms. Anne Pollock
Mr. Darshan Singh
Ms. Marianne Simon
Dr. Barbara Slade
Dr. Ana Stankovic
Dr. Steve Steindel
Mr. Howard Eric Thompson
Ms. Pam Thompson
Ms. Rhonda Whalen

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 (CDC); the Commissioner, Food and Drug Administration (FDA); the Administrator, Health Care Financing Administration (HCFA); 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 AdvaMed (formerly 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 regulations, the reader should not infer that all of the advisory committee's recommendations will be automatically accepted and acted upon by the Secretary.

Call to Order

Dr. Toby Merlin, Chair
Chief Medical Officer and
Senior Vice President
Lovelace Health Systems

Dr. Toby Merlin, CLIAC Chair, called the meeting to order and reviewed the agenda. He pointed out that Dr. Edward Baker, Director, Public Health Practice Program Office (PHPPO), CDC, and Dr. Robert Martin, Director, Division of Laboratory Systems (DLS), PHPPO, CDC, were not present, although Dr. Martin would participate in the second day of the meeting. He noted CLIAC is a public meeting, and pointed out the times during which public comments would be heard. Upon reviewing the role of CLIAC (to advise the Department of Health and Human Services - HHS), Dr. Merlin requested the members introduce themselves, and disclose statements of their relevant financial interests and affiliations as related to the topics to be discussed during the CLIAC meeting. He indicated any members with conflicts of interest pertaining to votes taken during the meeting would be required to recuse themselves from the voting procedure. Dr. Merlin extended a special welcome to Dr. Bernard Statland, Director of the Office of Device Evaluation (ODE) at the FDA.

Addendum A:
American Society for Clinical Laboratory Science (ASCLS) Summit on the Shortage of Clinical Laboratory Personnel

Dr. Brenta Davis
Chair, Department of Clinical Laboratory Sciences
University of Tennessee Memphis

Dr. Brenta Davis reported on the Coordinating Council for Clinical Laboratory Workforce (CCCLW) meeting [Addendum A], a followup to the previous ASCLS Summit on the Shortage of Clinical Laboratory Personnel. She explained the function and purpose of the CCCLW, delineating the organizations involved in the effort. She described the status of the increasing shortage of laboratory personnel (currently the highest vacancy rate in laboratories in 12 years), and its impact on healthcare. Dr. Davis then explained the components of the CCCLW strategic plan to address the shortage (e.g., data collection, marketing the profession, field guide, recruitment, and financing education), the lead roles to be taken by participating organizations,

and concluded by explaining how CLIAC could provide assistance in the effort. She stressed that CLIAC's presence at the CCCLW meeting was met with great enthusiasm.

Committee Discussion

The Committee agreed the shortage is significant and broadly impacts the quality of laboratory testing in the United States. The members suggested CLIAC could offer support in a number of ways, including: requesting that federal agencies contribute data which may be helpful in understanding the impact of the shortage, as well as how to alleviate the shortage; raising the issue of laboratory shortages with other relevant organizations; and lending support to the efforts of the National Research Council to improve high school science teaching.

Concern was expressed that at a local level, hospital administrators do not recognize that a problem exists. It was suggested that laboratory inspectors carefully look at staffing levels to determine whether there are adequate numbers of trained individuals performing testing. Perhaps hospital administrators would take action if deficiencies are cited during laboratory inspections.

Some members cautioned that personnel shortages are not restricted to the clinical laboratory community, but are evident in the scientific community in general. It was suggested the pool of students entering laboratory professions is becoming smaller due to poor or disconnected high school science teaching, and that individual CLIAC members could offer assistance to their respective Boards of Education seeking to improve high school science teaching.

Summarizing the views of the Committee, Dr. Merlin concluded that:

- The Committee should request HHS to look carefully at what is needed to assist in addressing the shortage;
- Representatives from organizations that might have leverage on these activities, such as Human Resources Service Administration and the Joint Commission on Accreditation of Healthcare Organizations, should be invited to speak to the Committee during future meetings about steps they are taking to address the issue; and
- Dr. Davis should continue to work with the CCCLW and CDC staff to keep the CLIAC informed on this critical issue [which Dr. Davis agreed to do].

Addendum B:
Polio Eradication Project

Dr. Walter Dowdle
Director of Programs
Task Force for Child Survival and Development

Dr. Walter Dowdle presented [Addendum B] his efforts with the Task Force for Child Survival and Development, and the World Health Organization's Global Polio Eradication Initiative. He explained the Initiative and asked for CLIAC's support for this major global program for appropriate containment of wild poliovirus, to prevent transmission from the laboratory to the anticipated increasingly non-immune global community.

Dr. Dowdle explained while it is fairly simple to contain known sources of poliovirus in the laboratory, it is a more difficult task to identify potentially infectious materials which could contain wild poliovirus. He said of greatest concern are fecal and throat specimens for which poliovirus is not suspected, particularly from specimens collected in countries where poliovirus is endemic. In an effort to address this problem, Dr. Dowdle described laboratory surveys to be conducted to identify and inventory material potentially containing poliovirus. Laboratories identified which retain such material will be notified to implement biosafety measures consistent with the risks, i.e. inventory, containment, and disposal procedures. Dr. Dowdle stressed since the U.S. is behind other countries in containment of poliovirus, all U.S. laboratories should be surveyed. In conclusion, he said the CLIAC could be extremely effective in encouraging cooperation on such an inventory by creating a letter of endorsement. To exemplify, he read a sample letter.

Committee Discussion

Dr. Merlin expressed CLIAC's support for CDC, and the CDC's role in viral disease surveillance and eradication. He suggested the Committee adopt a version of the letter proposed by Dr. Dowdle, appropriately revised for the CLIAC. After reviewing the revised draft letter, the Committee recommended its adoption [Addendum B].

Addenda C-J:
Clinical Laboratory Improvement Amendments (CLIA) Updates

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) UPDATE

Waiver Overview

Ms. Rhonda Whalen, M.S.
Chief, Laboratory Practice Standards Branch (LPSB)
DLS, PHPPO, CDC

To introduce the topic of waiver, and provide background information for CLIAC discussion, Ms. Rhonda Whalen gave a brief overview [Addendum C]. She reviewed the waiver criteria specified in the CLIA law and the requirements for waived laboratories published in the 1992 CLIA regulations, including the tests waived via the regulations. Ms. Whalen then described the test complexity model on which the CLIA regulations are based, and the difference in requirements for waived versus moderate complexity tests. She mentioned the proposed rule of September, 1995, which clarified the waiver criteria, and the FDA Modernization Act (FDAMA) of November, 1997, and the changes therein. She noted at this meeting, CLIAC was being asked to provide input on the FDA Draft Guidance for CLIA Criteria for Waiver, currently available for public comment, and concluded by summarizing the current status of waived tests.

Committee Discussion

An inquiry was posed as to whether there are personnel standards for a laboratory director of waived testing, to which Ms. Whalen replied that there are no personnel requirements (including qualification recruitments for laboratory director) for waived testing. She stressed that regardless of where waived testing is performed, the only regulatory requirement is the laboratory must follow the manufacturer's test system instructions.

Concern was expressed that the statutory language for waiver implies a moderate or high complexity test could be waived if there is not a risk of harm. Ms. Whalen pointed out tests must be both simple and low-risk, or be approved by the FDA for home use, to meet the waiver criteria.

An inquiry was posed as to what extent states or accrediting organizations have requirements that affect laboratories conducting only waived testing. Ms. Whalen indicated some states and accrediting organizations do not exempt waived testing from regulation. States and accrediting organizations could apply higher standards than the federal requirements, but they may not apply standards lower than federal requirements.

An inquiry was posed as to whether a waived test could be used in *any* location, including tests waived based on FDA approval for home use. Ms. Whalen said waived testing could be performed at any location. Dr. Merlin questioned whether a laboratory holding a certificate could bill Medicare for reimbursement of waived tests. Ms. Yost responded that tests must be ordered by a physician, and local medical review policies determine a laboratory's Medicare reimbursement.

Introduction to the Laboratory Medicine Sentinel Monitoring Network Reports

Steven Steindel, Ph.D.
Supervisory Health Scientist
Laboratory Practice Assessment Branch (LPAB)
DLS, PHPPO, CDC

Dr. Steven Steindel introduced the representatives from the Laboratory Medicine Sentinel Monitoring Network (LMSMN), who would be reporting on their studies of waived testing practices [Addendum D]. He described the role of a sentinel network, and explained that the LMSMN includes three sites. After considering the proposed changes to the waiver criteria and the resulting changes that might occur in waived testing, Dr. Steindel explained the LMSMN decided to gather information on waived testing practices in both traditional and waived-only laboratories. He indicated that two of the states in the Network, Arkansas and Washington, used a survey-based approach to their studies, collecting data from laboratories which volunteered to provide information. However, New York was using an on-site survey program, noting that as of September 2000 this program was in the pilot stage with information gathered from more than 100 pilot laboratories.

Pacific Northwest Sentinel Network Report

Kathy LaBeau
Network Director
Pacific Northwest Laboratory Medicine
Sentinel Monitoring Network

Ms. Kathy LaBeau presented the Pacific Northwest Sentinel Network's findings on quality assessment of waived test systems [Addendum E]. She described the background of the Pacific Northwest Network, created in 1995, indicating there are 633 test sites in four states.
Ms. LaBeau briefly reviewed the findings of a January 1998 Network study on quality control (QC) of waived testing, conducted on moderate and high complexity laboratories in the Network. She noted the overwhelming finding was a misunderstanding about the QC actually needed for waived test systems. As a result, most testing sites were determining their own QC protocols. She then described the October 2000 Network study of waived testing for which she developed

two questionnaires – one targeted for waived and provider-performed microscopy procedures (PPMP) laboratories, and one targeted for moderate and high complexity laboratories. In both questionnaires, laboratories were asked to list the waived tests they performed by manufacturer and brand names, and describe their quality assessment activities for those specific waived test systems.

Committee Discussion

An inquiry was posed as to what percentage of the total number of CLIA-licensed laboratories in the states covered by the Pacific Northwest Sentinel Network was represented by the 633 voluntary participants, given the concern that the data collected might be skewed by the voluntary participation. Ms. LaBeau said that she could not answer for the other three states; however, Washington is a CLIA-exempt state program, which made that state unique. She said Washington has 2,600 laboratories in its database, of which about 75% were waived and PPMP, while the other 25% were laboratories that would be inspected by the state or were accredited laboratories. She acknowledged the data may be skewed to some extent, but she stressed the percentage of waived/PPMP laboratories who volunteered to participate correlated with the percentage of moderate/high complexity laboratories.

An inquiry was posed as to whether personnel in the waived laboratories might have been confused about the QC specified in test system instructions. Ms. LaBeau indicated that concern about possible lack of understanding was the reason the Network used different questionnaires, which included definitions, for waived/PPMP and moderate/high complexity laboratories.

Some Committee members asked Ms. LaBeau to clarify how, on one hand, laboratories noted that failure on procedural controls was the indicator of a questionable erroneous test result, while, on the other hand, very low numbers of procedural control failures were reported. She said it indicated to her those laboratories did not believe controls are necessary to assess the quality of test results, and the laboratories did not know how to use information from QC testing.

New York Sentinel Network Report

Loraine M. Clarke, Ph.D.
Network Director
New York State Department of Health

Dr. Lorraine Clarke presented information on the New York Sentinel Network [Addendum F]. She indicated that in July 1965 New York State became the first state to initiate a certification program for clinical laboratories operating in selected areas of patient testing. The data she presented to the CLIAC was obtained through the integration of the Network studies with the Clinical Evaluation Program, which currently issues permits to 950 comprehensive laboratories,

and has 2400 registered limited test sites. The comprehensive laboratories include those that offer a wide range of laboratory testing and include primarily hospital and independent laboratories, while the 2400 limited tests sites are those that restrict their testing either to using waived devices or PPMP. Dr. Clarke estimated when they complete the registration process for the limited test sites, the number should increase from 2400 to about 4000 sites.

Dr. Clarke said New York is a partially exempt state in that their physician office laboratories receive oversite from the Physician Office Laboratory Program, which contracts with HCFA to provide these services. She said they developed questionnaires for each of the test methodologies for waived tests and PPMP, which were designed to capture information relating to the types of facilities in New York State performing waived and PPMP testing, the personnel conducting the tests, and the testing and quality assurance practices in place.

Dr. Clarke then discussed the five most frequently performed waived tests in New York State, the types of sites included in the limited test site facilities, and the personnel working in the sites. Dr. Clarke also reviewed data pertaining to the percentage of sites having citations relating to different aspects of the testing process identified during the on-site visits by their surveyors. She noted the data had been further separated for the limited sites based on whether a site was affiliated with a comprehensive site that might be providing guidance and oversight, and then reviewed the conclusions thus far from their analyses of the data.

Dr. Clarke mentioned that New York looked at proficiency testing (PT) failure rates for waived tests performed in moderate/high complexity laboratories participating in the New York State Program, and they plan to initiate an on-site PT program for limited testing sites.

Arkansas Sentinel Network Report

Jason Lee, Ph.D.
Network Director
Arkansas Department of Health
Division of Public Health Laboratories

Dr. Jason Lee made the presentation on the Arkansas Sentinel Network [Addendum G]. He indicated as of January 2001 Arkansas had 1760 laboratories with CLIA certificates, of which 411 (23%) were in the moderate/high complexity category. He said there had been a shift to waived laboratories, which now consisted of 77% of the laboratories in Arkansas. Dr. Lee indicated that the data he was describing was derived from their fourth survey for the Sentinel Network Project. He reviewed the Network's study design, described the types of certificates in the Arkansas laboratories surveyed, and explained the limitations of the survey. Dr. Lee noted public health laboratories included some bordering states (e.g., Tennessee, Louisiana, and Texas). He described the significant test classifications and the types of test kits, and reviewed the standard types of QC

testing they found laboratories were performing, including electronic controls, and "other" QC. He also described the tests reported for which no QC testing was performed. He said the Network was interested in answering the question, "Are waived/PPMP laboratories less likely to perform QC?"

Based on the results of the survey, the Arkansas Network concluded QC testing was performed in waived laboratories, but inconsistently; explicit guidelines for CLIA compliance for each test would be appropriate; types of tests with high rates of non-performance of QC were primarily those which had a non-automated option (e.g., dipstick tests, ESR, $CuSO_4$ hemoglobin, etc.); and waived and PPMP laboratories were less likely to use available QC measures than higher level laboratories, which may impact the quality of patient test results.

Committee Discussion

With regard to the laboratories performing no QC (liquid, reference, clinical, or electronic) and relying on the clinical correlation, it was felt clinical correlation could not entirely substitute for QC.

Noting that New York seemed to show many more QC problems than the other two networks, it was suggested that follow-up in the Pacific Network and/or Arkansas with some sort of on-site validation might be beneficial. Data from the accredited and non-accredited laboratories in Arkansas were somewhat equivalent to the New York data for affiliated and non-affiliated laboratories. Dr. Lee said that in the QC areas that Arkansas measured, a large portion of the QC was identified as clinical correlation.

HEALTH CARE FINANCING ADMINISTRATION (HCFA) UPDATE

Judith Yost, M.A., M.T. (ASCP)
Director, Division of Outcomes and Improvement
Center for Medicaid and State Operations
Health Care Financing Administration (HCFA)

Ms. Yost delivered the HCFA update [Addendum H]. She shared national data on trends in the CLIA program which agreed with information presented by the Sentinel Networks. She noted there are approximately 170,000 laboratories enrolled in CLIA, and the majority of CLIA laboratories are not traditional laboratories. She also reviewed the number of laboratories by certificate type, noting that the percentage of laboratories not inspected (waived, PPMP) has increased since 1997. She clarified that PPMP laboratories are moderate complexity laboratories,

which are subject to patient test management, and certain QC, personnel and PT standards, but are not routinely inspected.

Ms. Yost reviewed the number of CLIA accredited laboratories enrolled by accrediting organizations, and described the annual test volumes and certificate fees for physicians office laboratories, hospitals, and independent laboratories. She went over the top four CLIA deficiencies cited during three HCFA survey cycles, and the total number of substantiated complaints. While the deficiencies remained pretty much the same, over time, fewer laboratories had those deficiencies once they were inspected.

She indicated that in December 2000 a regulation was published extending the phase-in QC requirements applicable to unmodified, moderate complexity tests, and qualifications for high complexity laboratory directors.

Ms. Yost then shared the Certificate of Waiver(COW)/PPMP project findings [Addendum I], describing the history of the project (initially evaluating laboratories in Ohio and Colorado), and shared preliminary findings from the expanded pilot study. She reminded the CLIAC she had previously presented the preliminary results of the pilot study, and because of concerns regarding the extent and scope of findings in the initial pilot, HCFA extended the study to an additional eight states. She said she would share further findings at the May CLIAC meeting.

Committee Discussion

A comment was made that while data from the COW/PPMP studies suggest there might be problems with the quality of testing, the data do not indicate the clinical impact that may be associated with these issues of test quality. Ms. Yost responded HCFA does not have data correlating test results and clinical outcomes, except for unique areas such as pap smears for which there are some outcome studies. In some cases, large laboratories conduct their own outcome studies, but do not share their data given the liability issues involved.

Based on the data presented, it appeared 75% of waived laboratories are not following the test system instructions. That raised issues about how laboratories performing waived testing are monitored. Dr. Statland suggested three key evaluation steps which include evaluating process, output, and outcome. He noted the data presented pertained to the evaluation of process. He said process deficiencies need to be linked to output deficiencies, and output deficiencies could be assessed to some extent by proficiency testing. The next step would be to relate output deficiencies to impact on clinical outcome.

Dr. Hearn acknowledged it is difficult to do ultimate outcome correlates, particularly using health as a measure. Those who have been involved in CLIA research began by looking at the types of methodologies to use. If the assumption is that errors don't occur very often, then the number of

observations required to get meaningful data would be very high and quite costly. He indicated CDC conducted one small study, published in the *Journal of the American Medical Association* with the Ambulatory Sentinel Practitioners Network where, prospectively, practitioners in the network agreed over a small interval of time to record each time they encountered a laboratory test result that appeared to be wrong and led to an adverse outcome. The outcome measure was dependent on the physician, who documented each error; however, there was no documentation of the errors they did not detect. Therefore, the clinical correlate was based on the physician's bias. While the number of observed errors are fairly small, they do occur and have some clinical impact. He said CDC had also compared proficiency testing scores among previously regulated laboratories with newly regulated laboratories. For all analytes evaluated, the proficiency test scores were always statistically better in those laboratories which had more regulatory experience, and consequently, good process control.

One member agreed outcome measures are hard to obtain, but one could assume that physicians ordered laboratory tests because they expect test results to have some impact on patient care. Therefore, good laboratory testing is better than poor laboratory testing.

FOOD AND DRUG ADMINISTRATION (FDA) UPDATE

Draft Waiver Guidance

Steven Gutman, M.D.
Director, Division of Clinical Laboratory Devices
ODE, FDA

Dr. Steven Gutman discussed the FDA Draft Waiver Guidance [Addendum J]. He indicated the draft, recently developed by the FDA to provide guidance for manufacturers requesting waiver approval, was largely derivative of the model previously used by the CDC. However, he added there were some important design and statistical differences between FDA's guidance document and the waiver proposed rule, and he said FDA, CDC, and HCFA were anxious to receive CLIAC's input on the Draft Guidance. Dr. Gutman reviewed the statutory basis for waiver approvals, including explanatory information from the legislative preamble. He highlighted the elements in the Draft Guidance, and stressed the document is non-binding even after it has been vetted by the FDA.

Bernard Statland, M.D., Ph.D.
Director, ODE, FDA

Dr. Bernard Statland began by acknowledging the waiver issues are challenging. He indicated two general goals of the FDA are to protect the public health, and to promote new technology. He said the FDA is concerned that products on the market be safe and effective, and at the same time,

the agency strives to encourage industry to develop innovative and improved products. Two driving forces which may sometimes be in conflict with regard to laboratory testing are *access* and *quality,* because as access to testing is increased, there are concerns about quality being diminished. As a greater emphasis is placed on achieving quality testing, there is concern that access could be limited. Ultimately, the goal is to have both.

Dr. Statland next mentioned postmarket surveillance of waived tests, and pointed out the FDA is proposing total product lifecycle. The FDA is trying to facilitate the entry of improved products into the marketplace, but to carefully evaluate them after they have been approved. The FDA is also trying to encourage manufacturers to make devices more robust and resistant to user error and subjectivity.

Dr. Statland emphasized the FDA is seeking CLIAC's input on all aspects of the Draft Guidance. He said in addition to commenting during the meeting, there were approximately 90 days for additional public comments. He encouraged CLIAC members not only to make comments as a Committee, but also as individuals and on behalf of their organizations. Dr. Gutman added the FDA would particularly welcome alternative models, language, and suggestions with respect to the Draft Guidance.

Committee Discussion

The Committee discussion focused on specific topic areas pertaining to the FDA Draft Waiver Guidance as follows:

Home Use Approval

CLIAC members questioned whether the criteria for automatic waiver based on approval for home use are equivalent to the waiver criteria in the FDA Draft Guidance, and expressed concern that different criteria may be used to obtain waiver. Dr. Gutman said the home use criteria are not the same, and reviewed the steps for home use approval: 1) the test must provide the same information for the lay user as for the professional user; 2) a risk assessment must show that the test can be performed by lay users; and 3) the benefits of home use must outweigh the risks. Studies for home use approval require comparison of untrained to trained users, but do not require accuracy or precision studies.

Accuracy

Concern was expressed about using "accuracy" as a surrogate for "precision" in the Draft Guidance, noting that accuracy is not "precision." One member suggested the dictionary definitions be used to define "accuracy," "precision," and "comparability." Other CLIAC members suggested "accuracy," as used in the Draft Guidance referred to "accuracy" in the hands

of untrained users at clinical decision points. Dr. Gutman acknowledged there is disagreement about what is needed to demonstrate "accuracy" for waived tests. Dr. Statland also noted "accuracy" is at the heart of the controversy concerning waived tests. He said manufacturers demonstrate accuracy through the 510(k) clearance process when a test is compared to a well-credentialed working method, and for waiver approval, manufacturers should compare equivalence between lay user performance and professional performance. He indicated the FDA would consider defining terms, perhaps by adding a footnote to the Guidance. However, he stressed in the Draft Guidance, FDA used the words in FDAMA to ensure the deviation of the lay user versus the professional user was not so significant as to make a difference in waived test performance.

The manufacturer liaison pointed out manufacturers submit a substantial amount of data showing accuracy *and* precision, as part of the 510(k)/PMA process, which was separate from data submitted for waiver. Moreover, she stated probably 99% of tests in use didn't have a reference method or reference material. Others disagreed and thought that there were references for accepted methods.

Concern was expressed about using the 510(k) process as proof of accuracy of the test in a waived situation, particularly when applied to untrained users. Even if studies demonstrated the analytical performance between trained and untrained users was the same, that didn't mean performance was clinically the same.

One member noted the data previously presented indicated waived tests were being performed by users who were not following the manufacturer's instructions for test performance. Others agreed that the issue was not "analytical accuracy" so much as whether it made a difference to the patient who wanted the test result to be "the truth".

Postmarket Follow-up

CLIAC members supported the use of post-approval surveillance of waived test performance. However, several members expressed concern about the voluntary nature of follow-up as described in the Draft Guidance, and the fact that the word "should" was used throughout the document as opposed to "must." Others did not agree that mandatory reporting was useful since, for example, there are data suggesting that less than 10 percent of adverse drug reactions are reported, although by law they are to be reported to the FDA. The manufacturer liaison indicated there is already a regulation requiring manufacturers to report any adverse events with their products to the FDA.

A suggestion was made to follow the Consumer Products Safety Commission method of reporting, and to use education and public information notices requesting the public, physicians, and others who may have information to use a formal or informal incident reporting system.

Perhaps a

widespread educational effort combined with the inclusion of information (websites, 800 numbers, etc.) in product labeling would increase the reporting effort.

Although data on postmarket performance of waived tests could be obtained from physician office laboratories affiliated with hospital laboratories, several CLIAC members stressed it is not always possible to release internal data to the public domain. It was suggested that HHS draft and attempt to get sponsorship of a statute that would make it possible to make this data public in a way that it could not be used in liability proceedings in either state or federal jurisdictions. Access to the data could facilitate intelligent decision making.

Dr. Statland noted his concern with postmarket performance of waived tests, and changes over time as products are used. He suggested manufacturers should document the performance of their tests after they have been waived, and the FDA should not rely solely upon pre-market applications. He concluded by indicating the need for industry, government, and users of laboratory tests to jointly consider these issues from industry, public health, and patient perspectives.

Other Issues

Concern was expressed regarding the issue of balancing access with protection/quality. There was some agreement that this issue would continue to arise, and the Committee should keep it in mind as they consider the criteria for waiver.

An inquiry was posed as to whether the Draft Guidance is a working document already in use. Dr. Gutman responded that it was not currently being used, as it was a work in progress. He said currently the only criteria for waiver approval are the provisions in FDAMA, and pointed out there are a variety of complicated legal, scientific, medical, and regulatory issues which must be resolved before the Draft Guidance can be implemented.

Since the next official meeting of the CLIAC will not be convened until May 2001 the Committee agreed the Waiver Workgroup, previously organized at the September 2000 CLIAC meeting, should meet to review the FDA Draft Waiver Guidance in greater detail. The Waiver Workgroup could identify substantive issues, and possibly the CLIAC could meet via conference call to have an opportunity to hear the Workgroup report, and respond officially before the close of the comment period. *(Note: Since it was subsequently determined the comment period for the Draft Waiver Guidance would end on May 30, 2001, the Workgroup report will be presented for CLIAC's discussion and recommendations at the May meeting on that date.)*

After concluding the waiver discussion, the CLIAC made the following recommendations pertaining to the FDA Draft Guidance, and noted that additional recommendations would be forthcoming following the Waiver Workgroup meeting.

- Use the words "accuracy," "precision," and "comparability" appropriately. "Accuracy" should be considered through the FDA 510(k)/PMA review process, and "comparability" should be used specifically in discussing the studies comparing trained and untrained user performance.
- In the QC section of the Draft Guidance, change the word "should" to "must," and state "When QC is required, the following principles apply..."
- To document the ability of an untrained user to follow the package insert and perform the test properly, the manufacturer must test the ability of the user to understand quality control and test patient samples.
- Waiver studies should include a representative sample of intended users (e.g. nurses) to provide a valid comparison of comparability between trained users and users untrained in laboratory practice.

In addition, the CLIAC considered two other proposed motions and decided not to include them as recommendations. The first was that Section 6 of the FDA Draft Guidance, "Voluntary Safeguard for Waived Tests," be made a separate document, since it is voluntary. Some members also noted the safeguards would be appropriate for all tests, and should not be limited to waived tests. Dr. Gutman felt strongly this section should remain in the guidance document, explaining that if contained in a separate document, an important part of the waiver process could be missed. Many CLIAC members agreed that users of the document would be more inclined to accept consolidated concepts than to have two documents containing criteria for waiver approval. The second motion proposed, but not recommended, by CLIAC was a suggestion that there be some type of oversight of waived laboratories, given that essentially 75% of all laboratories are now unregulated, with 50% of those having problems with of testing. It was mentioned that since additional information on waived laboratory performance would be presented at the May 2001 CLIAC meeting, this motion should be deferred until after the May meeting.

Addenda K-N:
Public Comments

Joeline Davidson
American Society for Clinical Laboratory Science (ASCLS)

Ms. Joeline Davidson, ASCLS representative, presented several comments on the FDA Draft Waiver Guidance [Addendum K]. In addition, she said ASCLS is continuing to study the document and planned to make written comments during the comment period.

Robert Bray, Ph.D.
Professor, Emory University
President-Elect, American Society for Histocompatibility and Immunogenetics (ASHI)

Dr. Robert Bray indicated he was representing ASHI and the Histocompatibility Committee at the United Network of Organ Sharing. In making his comment, Dr. Bray requested that at a future meeting, the CLIAC consider an issue specific to the CLIA requirements for histocompatibility testing related to solid organ transplantation [Addendum L].

Committee Discussion

A CLIAC member said this was an appropriate issue for CLIAC to consider, and if it was to be addressed at a future meeting, ASHI and their colleagues would have time to gather information for presentation to CLIAC. ASHI could present data on the success rates for liver and heart transplants, including information on transplants with HLA-matched histocompatibility donors and recipients versus those that were not. Dr. Bray acknowledged it was a complicated issue, not just in the HLA testing but in the pre-sensitization, even when a patient has antibodies, it may be preferable to administer drugs and perform the transplant. The data would be helpful because in many cases these people would use more blood products post-transplant, and they have a high incidence of needing re-transplantation as well.

A CLIAC member suggested it would be useful to hear from other organizations, as well as HHS, concerning organ allocation. This member was concerned that it would take substantial time for the CLIAC to consider this issue in its entirety, and noted it is a topic which might need the formation of a Workgroup to focus the issues before bringing the topic to CLIAC for discussion. Dr. Merlin requested that CDC determine the best way to develop the issue for CLIAC discussion.

Joel Slomoff
Consultant, Hemocue

Mr. Joel Slomoff noted that Hemocue had obtained waiver approval, and stressed waiver is a privilege – not a right. He briefly discussed data provided to the FDA as part of the 510(k) clearance or waiver approval processes, and suggested such data be provided to the public when a test system is cleared or approved for waiver. This information is currently available to the public through the Freedom of Information Act. By automatically releasing these data, the public would have an opportunity to comment on or evaluate the data in a timely manner.

Robin Weiner
Vice President
Clinical and Regulatory Affairs
Quidel Corporation

Ms. Robin Weiner, of the Quidel Corporation, expressed several concerns regarding waiver. [Addendum M]. She stressed that no data had been presented to show that lack of compliance with QC requirements for waived tests affects patient outcome. Therefore, she noted the need to determine the effect of not performing QC testing on patient results and patient outcomes. She also suggested the need for data on whether moderate complexity laboratories follow manufacturer's instructions.

Committee Discussion

A CLIAC member stated the FDA clearance process and the CLIA regulations are irrevocably intertwined and can not be separated. While CLIA does not regulate manufacturers, those who advise the program should consider related issues as they provide advice to HHS. Dr. Merlin clarified the purpose of CLIAC is to advise HHS on matters pertaining to the quality of laboratory testing, which does include the quality of testing devices and the waiver process.

Alan Cohen
Editor, Physician Office Laboratory News

Mr. Alan Cohen asked for clarification on whether the FDA Draft Guidance was currently being used as a mechanism to obtain CLIA waiver using valid scientific evidence. Mr. Cohen said he'd been told previously that the criteria used in the draft were the ones used to approve the two new influenza tests [Addendum N]. He also noted the readers of *Physician Office Laboratory News* follow the CLIAC meetings and the issues discussed, and distributed copies of the latest edition which included an article on CLIAC.

Committee Discussion

Dr. Gutman responded that waiver decisions are based on scientific principles, and the FDA is considering a more expansive set of criteria for approval than those in the 1995 proposed rule. He said the Draft Guidance was derived from the FDA review of products since the August 2000 meeting. He stressed the Draft Guidance is a non-binding document, and there are other potential paths to waiver approval.

Quality Institute

Joe Boone, Ph.D.
Assistant Director for Science
DLS, PHPPO, CDC

Dr. Joe Boone introduced the concept of a Quality Institute to focus on the future of laboratory testing. Dr. Robert Martin noted that beginning in the early 1980s, CDC hosted a number of Critical Institutes to address major issues associated with laboratory testing. He suggested the timing was right to begin to address some of the issues that would arise over the course of the coming three to five years. He stressed due to rapidly changing technology and science, there is a need to reconsider the optimal methods to ensure that quality testing is available to the public and the clinical community. Dr. Martin added HHS has been working with CLIA since 1967, and while it is unlikely there will be a change completely away from a regulatory model, it would be appropriate, in collaboration with professional organizations and manufacturers, to consider how much regulation is necessary, and alternative mechanisms to assure quality testing.

Committee Discussion

The Committee was in favor of convening the proposed Quality Institute and made the following suggestions:

- The Institute include significant representation by laboratorians, consumers, users of laboratory testing, manufacturers, health insurance industry, legal community, members of the research community and nursing community, clinical laboratory and medical school educators, and special populations (e.g., military, Veteran's Administration, under-served populations such as Native Americans).
- The format for the Institute should be one that facilitates problem solving and focus on the long-term, best interest of the public. It should not be a forum for position papers, or one that encourages participation based on elected, vested, or corporate interests.
- Individuals are changing dramatically in terms of their own sense of responsibility for health care. The public now uses the Internet extensively, and is clearly interested in health information and its reliability. Perhaps there could be a specific educational component aimed toward the public regarding basic laboratory issues (e.g., error, specificity, sensitivity and legal issues).
- Because access to laboratory tests is changing, the Institute should share information regarding available tests, their quality, and where testing may be obtained; how to work with industry to ensure quality performance; and how laboratory information should be shared with providers and the public.

- Attention should be paid to evaluation of laboratory performance, using mechanisms such as postmarket surveillance, proficiency testing, etc.
- Focus should be on a program of active data gathering concerning problems with laboratory tests and their results, with some emphasis on the sources of this information (e.g., consumers, test performers, test certifiers).
- The Institute should consider mechanisms for assessing the competency of those who perform testing.
- The Quality Institute should be an on-going process, not just a one-time meeting. It was suggested strategies be considered to garner financial support to sustain the Quality Institute effort.

Addendum O:
Secretary's Advisory Committee on Genetic Testing (SACGT) Meeting Report

Patricia Charache, M.D.
Professor of Pathology and Medical Oncology
Johns Hopkins Medical Institute

Dr. Patricia Charache reported on the recent SACGT activities [Addendum O], including a summary of the November 2-3, 2000, SACGT meeting; revisions to the previously proposed two-scrutiny level algorithm for reviewing genetic tests; progress in areas of Institutional Review Board (IRB) approval and informed consent, data elements and data collection, rare disease and low-volume tests, access to testing, and education of health care providers and the public; and the former HHS Secretary, Dr. Donna Shalala's, response to SACGT regarding the oversight of genetic testing by HHS agencies, i.e., HCFA, FDA, and CDC. Dr. Charache pointed out there were interfaces and overlapping interests between CLIAC and SACGT, and because of its expertise in laboratory practice, the CLIAC should continue to contribute to the SACGT discussions.

Committee Discussion

Several Committee members commented the revised scrutiny model was an improvement over the previous one, however, there were additional considerations and problems in applying this model to actual tests. The Committee members expressed the following concerns:

- The terms "disease prevalence" and "incidence" were not clearly defined, and the cut-off values were confusing and inconsistent with each other.
- It was not likely the same scrutiny level could be applied to the general population, since disease prevalence varies among different subpopulations and ethnic backgrounds.

- Laboratories should not report test results without clinical validity; however, the revised model removed considerations for clinical validity as well as ethical, legal, social issues and primarily relies on disease frequency for test evaluation.
- It is difficult to apply the revised model to pharmacogenetic tests or tests that detect normal genetic variations.
- It would be necessary to assess the practicality and the cost of implementing the proposed test review mechanism. One member commented increased funding should be considered not only for FDA but also for the laboratory community to support this effort.

Dr. Charache responded that the Access Working Group of the SACGT had been addressing cost issues, as well as access to testing in minority populations. She also pointed out surveillance of scrutiny level I tests had implications for *all* laboratory tests, not just genetic tests. One member suggested the proposed Quality Institute assess both the current practice of genetic testing and the impact of technology on test development in the near future.

Dr. Steve Gutman, commented the FDA is using a gradual approach in establishing its oversight of genetic testing. He noted currently, the FDA is making progress in certain areas, such as establishing requirements and a database for registering genetics testing laboratories, initiating round-table discussions on the test classification system, and further evaluation of several novel approaches in test classification. He stressed the FDA is trying to develop user-friendly mechanisms that will not inhibit access to testing or technology advancement.

Addenda P-R:
CDC Genetic Testing Activities/Introduction to Genetics Workgroup/CLIAC Genetics Workgroup Report/CLIAC Discussion Regarding Genetic Testing

Dr. Joe Boone, Assistant Director for Science, DLS, PHPPO, CDC, briefly described some of the ongoing genetic projects at the CDC [Addendum P]. He then outlined the formation and purpose of the CLIAC Genetics Workgroup, the need to move forward in establishing specific requirements for genetic testing, and the expectations and charge to the Workgroup.

Dr. Lawrence Silverman, CLIAC Genetics Workgroup Chair, reported on the meeting of December 7-8, 2000 [Addendum Q]. He indicated the purpose of the meeting was to review public comments received to the Notice of Intent published in the *Federal Register* on May 3, 2000, and to evaluate the proposed revisions to the CLIA regulations to include specific requirements for genetic testing previously recommended by the CLIAC. He summarized the Workgroup recommendations on definitions of genetic tests, the laboratory role in documenting clinical validity, the person authorized to order a genetic test, informed consent, confidentiality, genetic counseling and consultation, and issues related to specific phases of genetic testing. He

stressed it will be crucial to determine whether acquired or somatic mutation testing should be included in the genetics specialty, considering the view that genetic testing consists primarily of tests for heritable mutations. He also pointed out many molecular testing laboratories perform tests for both acquired and heritable conditions, which have similar considerations for the analytical phase but different considerations for the pre- and post-analytical phases. Finally, he noted many recommendations made for genetic tests could have implications for other testing specialties.

Committee Discussion

Dr. Boone guided the Committee discussion with slides summarizing the Workgroup recommendations into a series of discussion topics: 1) definitions and subspecialties of genetic testing; 2) general requirements including clinical validity, person authorized to order a genetic test, confidentiality, informed consent, and re-use of tested specimens; and 3) requirements for specific testing phases [Addendum R]. He asked the Committee to comment on the Workgroup recommendations and provide additional input on each specific issue. The Committee reviewed each recommendation of the Workgroup, and generally supported the recommendations with the additions or modifications discussed below. The following summarizes the topics and issues that received specific comments and suggestions from the CLIAC.

Definitions and Subspecialties of Genetic Testing

Regarding the proposed subspecialty of biochemical genetics, one member questioned how measuring normal proteins would differ from measuring protein products of genetic variants. Dr. Silverman pointed out the definition was intended to include tests for proteins associated with specific genetic disorders, such as some of the tests used for newborn screening, and the purpose of the test would be important in making the distinction. Several members expressed concern about how proteomic analyses, when available clinically, should be placed under the proposed genetic testing specialty. One member indicated this might be an important issue in defining personnel qualifications related to board certification requirements. For example, the definition used by the American Board of Medical Genetics for its biochemical genetics certification examination is different from this proposed definition.

One member indicated requirements for pharmacogenetic tests might be challenging to establish because it could be difficult to determine the strength of genetic influence on a particular analyte. Another member commented some of these tests might be submitted to the FDA for waiver approval during the process of the genetic test rulemaking. Several members concurred with this comment and suggested consideration be given to hand-held chip devices, which might be developed in the near future for physicians to assist in prescribing individualized medicine, instead of for use in genetic testing laboratories. Dr. Silverman commented when pharmacogenetic tests are performed for patient care, a CLIA certificate is required and the pre-

and post-analytical issues related to these tests should be addressed.

Several members felt specific examples or lists of tests should be provided under each subspecialty, i.e., molecular genetics, cytogenetics, and biochemical genetics. One member suggested tests currently performed in immunohistochemistry and general chemistry laboratories be excluded from the genetics specialty. Dr. Boone responded the proposed framework was one of several options the Workgroup discussed, and it would be necessary to obtain consultation from professional organizations to define the types of tests to be included in each subspecialty. One member commented the intent was not to exclude technology but to stress that genetic tests are currently covered under CLIA and not every test requires expanded oversight. Dr. Merlin summarized the discussion by saying the Committee agreed with establishing the three subspecialties under the specialty of genetics, and recommended caution be used in determining the tests to be included or excluded from each subspecialty.

Documentation of Clinical Validity

Several members expressed concern about the laboratory role in validating the methodology selected for a test, because laboratories usually adopt tests that have been developed elsewhere with slight or no modifications. Dr. Boone clarified under CLIA, the laboratory director is responsible for selecting test methods that provide the quality of results required for patient care; however, there is no specific requirement for establishing clinical validity, and laboratories may not be consistently documenting clinical validity. It was suggested laboratories verify test performance specifications as documented in literature references or by test developers, and demonstrate the test results are comparable for the same patient populations.

Person Authorized to Order a Genetic Test

Several members expressed concern about the self-referral issue and felt while it is important not to obviate people's opportunity to make their own healthcare decisions, the laboratory director should decide which tests to offer and whether additional assistance associated with self-referral would be needed. It was also suggested the term "patient self-ordering" be used instead of "self-referral," which has a legal meaning related to Medicare reimbursement.

Informed Consent

Several members expressed concern about the laboratory burden associated with requiring informed consent. One member indicated that requiring informed consent for cancer-related tests would be difficult. Another member inquired whether tests, such as hemoglobin electrophoresis, performed in non-genetic laboratories, would require informed consent for diagnosis of heritable conditions. Some members noted obtaining informed consent when patients self-order tests might be problematic, particularly if testing could be ordered over the Internet. One member suggested

the laboratory have a system for self-ordering, perhaps using a separate form, if the laboratory is allowed to accept such ordering. It was also suggested some tests might need to be screened by health care providers. Dr. Silverman pointed out the intent was not to create unmanageable laboratory requirements, but to require the *appropriate level* of informed consent. It was also clarified that the laboratory should be *available to* assist in determining the appropriate level of informed consent.

Re-use of Tested Specimens

One member pointed out specimen re-use should be an overall laboratory issue and not be restricted to genetic tests, and suggested specimen re-use be included in the general CLIA requirements. Another member indicated the genetics community has emphasized the need to re-use specimens for quality assurance (QA) and QC purposes through SACGT and other discussions, and suggested requirements for specimen re-use be included within the genetics specialty to prevent conflicting policies. It was suggested the recommendation "If subsequently desired for research testing under IRB, then new consent is needed" be deleted, since CLIA does not apply to research testing.

Test Requisition and Clinical Information

One member raised concern about the practicality of the proposed components of the test requisition, since laboratories do not always receive all the required information. Another member commented that while about 70% of laboratories performing genetic testing currently require information such as age and ethnicity, fewer than 10% of the laboratories are enforcing the requirement, and suggested the following requirement be added: "Reports should not be sent out until appropriate clinical information critical for interpreting test results is received by the laboratory." One member commented the suggested requirement might be an attempt to correct operational problems by regulation, and it might be more appropriate to rely on professional societies and accrediting agencies to develop guidelines to improve collection of information required by laboratories.

Personnel Qualifications and Responsibilities

It was noted that determining appropriate personnel qualifications would depend on which tests were included in the genetics specialty. Dr. Boone acknowledged the need to assess the credentials currently possessed by laboratory personnel and the impact of the proposed qualification requirements on these individuals. Several members suggested the requirement for the technical supervisor to "be certified in medical genetics" be modified to "certified in an appropriate medical genetic subspecialty."

Genetic Counseling

One member pointed out patients might need to be referred to medical services other than genetic counseling. Another member suggested "when appropriate" be added to the second recommendation, i.e., "laboratories should facilitate access to genetic services when appropriate." In addition, the member suggested deleting the third and fourth recommendations, i.e., "laboratory should not be required to have a documented relationship with genetic counseling resources because the laboratory cannot direct patient care," and "laboratory should be required to recommend genetic counseling for family members when indicated." One member suggested the third recommendation be reworded to "the laboratory should not be required to provide genetic counseling." Dr. Silverman clarified the fourth recommendation meant the laboratory should recommend genetic counseling to health care providers, not to the patient or family members directly.

Proficiency Testing (PT)

One member felt the two-tiered system (regular PT and inter-laboratory comparison programs) recommended by the Workgroup would be difficult to develop or carry out, and urged the CDC to continue its vigorous efforts to enhance QC programs and to develop QC materials. Another member expressed concern about research laboratories performing patient testing for rare diseases as a courtesy to their colleagues and suggested professional societies would be helpful in providing advice in this area. Dr. Boone noted the recommendation "The requirements should not be less stringent for low volume tests and rare disease testing, but alternative PT may be needed" was an attempt to address this issue.

Result Reporting

One member suggested "date of birth" be required for all laboratory tests, not just genetic tests. With regard to qualifications of the individuals signing the report, several members suggested "highest qualification" be changed to "appropriate qualification" or "equivalent certification."

Retention of Records

It was indicated record retention requirements might depend on the type of testing performed; for example, records of newborn screening testing might need to be retained for a timeframe longer than 10 years or for 25 years as required by some States. One member suggested requirements for retention of genetic testing records be comparable to the requirement for retention of pathology reports, which must be retained for at least 10 years under the current CLIA requirements. It was also clarified that electronic records are allowed and must be retained for the same timeframe as hard copies.

Retention of Specimens

One member inquired how patient refusal for specimen re-use should affect retention of the specimen. Dr. Boone clarified the laboratory might need to perform confirmatory tests and should not discard the specimen prematurely. Another member suggested the specimen retention policy should be different from the requirements for re-use of tested specimens for QC purposes. The Committee supported using the Notice of Proposed Rulemaking to solicit public comments on this issue.

Summary and Next Steps

In summary, the Committee reviewed the recommendations by the CLIAC Genetics Workgroup and generally endorsed the proposed requirements for genetic testing, with comments provided (as discussed above) for suggested revisions to the Workgroup recommendations. The Committee recommended moving forward with development of a Notice of Proposed Rulemaking to contain the CLIAC suggested requirements for genetic testing under CLIA.

Dr. Martin indicated the next step would be to begin developing the proposed rule for genetic testing, based on the revised CLIAC recommendations and noted there will be additional opportunities for CLIAC involvement as the proposed rule is developed. In addition, Dr. Charache will represent the CLIAC and present the genetic testing recommendations in her report at the next SACGT meeting.

Closing Remarks

With no further business, Dr. Merlin officially adjourned the February 2001 CLIAC meeting.

Date for the next CLIAC meeting: May 30-31, 2001

I certify that this summary report of the February 7-8, 2001, meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting:

/S/ Toby L. Merlin, M.D., CLIAC Chair